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

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 $S_2^{e=1}$ represent the outcome of the second pregnancy if all exposed women were exposed and $S_2^{e=0}$ represent the outcome of the second pregnancy if all exposed women had instead been unexposed. Then the causal risk ratio would be $\Pr[S_2^{e=1} = 1]/\Pr[S_2^{e=0} = 1]$. In the data, only $\Pr[S_2^{e=1} = 1]$ would be observed (indicated $\Pr[S_2 = 1|E = 1]$). $\Pr[S_2^{e=0} = 1]$ would be estimated from the experience of the unexposed group, $\Pr[S_2 = 1|E = 0]$. 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 $\Pr[S_2^{e=1} = 1]/\Pr[S_2^{e=0} = 1] = \Pr[S_2 = 1|E = 1, S_1]/\Pr[S_2 = 1|E = 0, S_1]$.
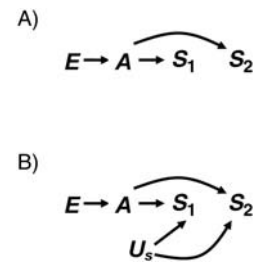
Figure 1. A) Directed acyclic graph (DAG) 1A, in which a single exposure (E) causes a single underlying abnormality (A) that causes both outcomes (S_1 and S_2). B) DAG 1B, in which a shared cause (U_s) of S_1 and S_2 is added to DAG 1A.

DAG 1A (Figure 1A) is consistent with Weinberg's assumptions and is equivalent to Figure 1b in her original paper [1]. It assumes that E causes an underlying abnormality A, which in turn affects risk of spontaneous abortion in both pregnancies (S_1 and S_2). In this DAG, there is no confounding, so $\Pr[S_2^{e=1} = 1]/\Pr[S_2^{e=0} = 1] = \Pr[S_2 = 1|E = 1]/\Pr[S_2 = 1|E = 0]$. Nevertheless, S_1 would be considered a confounder on the basis of some conventional criteria. S_1 is associated with S_2 through an open path that does not directly involve exposure ($S_1 \leftarrow A \rightarrow S_2$); S_1 is associated with E because S_1 is a descendant of E; and S_1 is not a causal intermediate or mediator between E and S_2. Given these conditions, the unadjusted effect estimate for E would be expected to differ from the estimate adjusted for S_1, but based on DAG 1A, controlling for S_1 would introduce bias (i.e., $\Pr[S_2^{e=1} = 1]/\Pr[S_2^{e=0} = 1] \neq \Pr[S_2 = 1|E = 1, S_1]/\Pr[S_2 = 1|E = 0, S_1]$) as Weinberg stated [1], because S_1 and S_2 are affected by a shared parent (A), which is an intermediate between E and S_2. In a sense, S_1 is a proxy for the intermediate A, so adjusting for S_1 is like imperfectly adjusting for an intermediate and produces a form of bias that has been called overadjustment bias [14]. The equations from the original paper are directly relevant to this DAG [1].

One of the advantages of DAG analyses is that one can easily illustrate increasingly complex situations. DAG 1B (Figure 1B) builds on DAG 1A by introducing an unmeasured risk factor for spontaneous abortion (U_s). This addition changes Weinberg's simplifying assumption that S_1 and S_2 are independent conditional on A [1] and is more realistic. Under DAG 1B, $\Pr[S_2 = 1|E = 1]/\Pr[S_2 = 1|E = 0]$ is still an unconfounded estimate of $\Pr[S_2^{e=1} = 1]/\Pr[S_2^{e=0} = 1]$, and Weinberg's conclusion that adjusting for S_1 introduces bias still holds, because adjustment for S_1 would be equivalent to adjusting for a proxy of an intermediate. There are further complications in DAG 1B, because S_1 is also a collider on a path from E to S_2 ($E \rightarrow A \rightarrow S_1 \leftarrow U_s \rightarrow S_2$), so adjusting for S_1 would open this path.

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

utero 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 $\Pr[S_2^{e_2=1} = 1]/\Pr[S_2^{e_2=0} = 1]$.

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 $S_1 \leftarrow A_1 \leftarrow U_a \rightarrow A_2 \rightarrow S_2$ and $S_1 \leftarrow A_1 \leftarrow E_1 \rightarrow E_2 \rightarrow A_2 \rightarrow S_2$. In addition, we now assume $\Pr[S_i|A_i, E_i] = \Pr[S_i|A_i]$ as an extension of the corresponding original assumption (1). This is represented by the fact that all paths from E_i to S_i go through A_i. 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, $\Pr[S_2 = 1|E_2 = 1]/\Pr[S_2 = 1|E_2 = 0]$ is an unconfounded estimate of $\Pr[S_2^{e_2=1} = 1]/\Pr[S_2^{e_2=0} = 1]$ 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 not a confounder of the estimated effect of E_2 on S_2, but some conventional criteria would still define it as such. S_1 is associated with the outcome (S_2) among the unexposed because of the open path between them that does not include E_2 ($S_1 \leftarrow A_1 \leftarrow U_a \rightarrow A_2 \rightarrow S_2$). This path exists because U_a is a shared parent of A_1 and A_2. For concreteness, we can think of U_a as a genetic factor that makes some women liable to develop the abnormality every time they become pregnant. In DAG 2A, S_1 is associated with the exposure of interest (via the open path $E_2 \leftarrow E_1 \rightarrow A_1 \rightarrow S_1$) but is not on the causal path of interest (from E_2 to S_2). The association between S_1 and E_2 is due to the assumption in DAG 2A that exposure status during the first pregnancy directly affects exposure status during the second pregnancy (e.g., smoking is addictive, and therefore smokers tend to continue smoking). That is to say, S_1 and E_2 are associated because they share E_1 as a cause.

In DAG 2A, 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., $\Pr[S_2^{e_2=1} = 1]/\Pr[S_2^{e_2=0} = 1] \neq \Pr[S_2 = 1|E_2 = 1, S_1]/\Pr[S_2 = 1|E_2 = 0, S_1]$). 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 conditioning on 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_s). This creates 2 backdoor paths from E_2 to S_2 ($E_2 \leftarrow E_1 \rightarrow A_1 \leftarrow U_a \rightarrow A_2 \rightarrow S_2$ and $E_2 \leftarrow E_1 \rightarrow A_1 \rightarrow S_1 \leftarrow U_s \rightarrow S_2$), 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 ($E_2 \leftarrow U_e \rightarrow E_1 \rightarrow A_1 \leftarrow U_a \rightarrow A_2 \rightarrow S_2$) 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
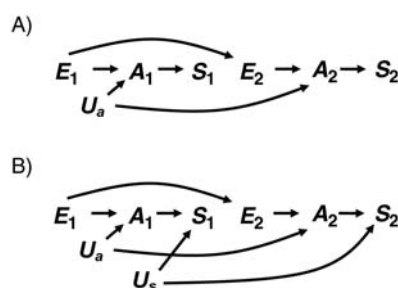

Figure 2. A) Directed acyclic graph (DAG) 2A, in which exposure during the first pregnancy (E_1) causes an underlying abnormality during the first pregnancy (A_1) and exposure during the second pregnancy (E_2). E_2 causes an underlying abnormality during the second pregnancy (A_2). In addition, an unknown covariate (U_a) causes both A_1 and A_2, and A_1 and A_2 cause the corresponding outcomes (S_1 and S_2, respectively). B) DAG 2B, in which a shared cause (U_s) of S_1 and S_2 is added to DAG 2A.
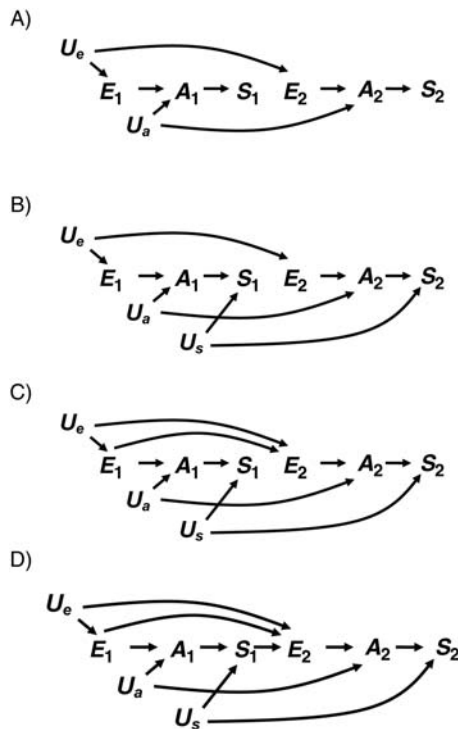
Figure 3. A) Directed acyclic graph (DAG) 3A, in which an unknown variable (U_e) causes exposure during the first (E_1) and second (E_2) pregnancies. Each exposure causes the corresponding underlying abnormality (A_1 and A_2). In addition, an unknown variable (U_a) causes both underlying abnormalities, and each underlying abnormality causes the corresponding outcome (S_1 and S_2). B) DAG 3B, in which a shared cause (U_s) 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).

Figure 4. A) Directed acyclic graph (DAG) 4A, in which exposure during the first pregnancy (E_1) causes an underlying abnormality during the first pregnancy (A_1) and exposure during the second pregnancy (E_2). E_2 causes an underlying abnormality during the second pregnancy (A_2). In addition, A_1 causes A_2. Each underlying abnormality causes the corresponding outcome (S_1 and S_2). B) DAG 4B, which removes the effect of A_1 on A_2 that was present in DAG 4A. C) DAG 4C, which alters DAG 4B so that E_1 and E_2 have a shared cause (U_e) instead of E_1 causing E_2.

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., $E_2 \leftarrow S_1 \leftarrow U_s \rightarrow S_2$). Thus, this is the first example in which the unadjusted estimate is biased (i.e., $\Pr[S_2^{e_2=1} = 1]/\Pr[S_2^{e_2=0} = 1] \neq \Pr[S_2 = 1|E_2 = 1]/\Pr[S_2 = 1|E_2 = 0]$). If U_s and U_a 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 a collider on other backdoor paths ($E_2 \leftarrow E_1 \rightarrow A_1 \rightarrow S_1 \leftarrow U_s \rightarrow S_2$ and $E_2 \leftarrow U_e \rightarrow E_1 \rightarrow A_1 \rightarrow S_1 \leftarrow U_s \rightarrow S_2$). Therefore, additional adjustment (e.g., adjusting for E_1) would be needed to block the paths opened by conditioning on S_1.

DAGS THAT FURTHER ALTER THE ORIGINAL ASSUMPTIONS

Figure 4 presents DAGs that substantially modify Weinberg's original assumptions (1) despite being similar to
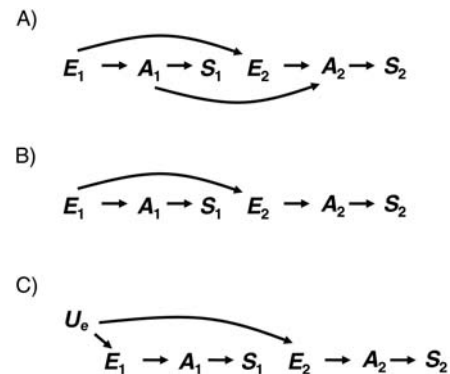
the preceding DAGs. DAG 4A is similar to DAG 2A, except that A_1 causes A_2. This modification means that A_1 is no longer a collider, so there is an open backdoor path from E_2 to S_2 ($E_2 \leftarrow E_1 \rightarrow A_1 \rightarrow A_2 \rightarrow S_2$). An unbiased estimate for the effect of E_2 on 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_i is only directly affected by E_i. 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., $\Pr[S_2^{e_2=1} = 1]/\Pr[S_2^{e_2=0} = 1] = \Pr[S_2 = 1|E_2 = 1]/\Pr[S_2 = 1|E_2 = 0] = \Pr[S_2 = 1|E_2 = 1, S_1]/\Pr[S_2 = 1|E_2 = 0, S_1]$) 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
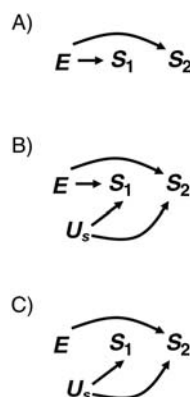
Figure 5. A) Directed acyclic graph (DAG) 5A, in which exposure (E) causes both pregnancy outcomes (S_1 and S_2). B) DAG 5B, which adds a shared cause of S_1 and S_2 (U_s) to DAG 5A. C) DAG 5C, in which E still causes S_2 but no longer causes S_1.
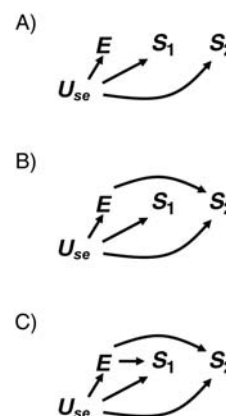

Figure 6. A) Directed acyclic graph (DAG) 6A, in which exposure (E) has no effect on the outcome (S_2). An unmeasured confounder (U_{se}) is a risk factor for both pregnancy outcomes (S_1 and S_2) and causes E. B) DAG 6B, which builds on DAG 6A by allowing E to be a risk factor for S_2. C) DAG 6C, which builds on DAG 6B by allowing E to affect both pregnancy outcomes (S_1 and S_2).

general situation where E caused 2 events that were independent given E, and the causal contrast of interest was $\Pr[S_2^{e=1} = 1]/\Pr[S_2^{e=0} = 1]$. 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 $\Pr[S_2^{e=1} = 1]/\Pr[S_2^{e=0} = 1] = \Pr[S_2 = 1|E = 1]/\Pr[S_2 = 1|E = 0]$; 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 $E \leftarrow U_{se} \rightarrow S_2$, 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 confounder, 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 pregnancy outcome, whereas in Figures 2 and 3, we considered an exposure that occurred just prior to the current pregnancy 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 conventional 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 relations between variables. They have simple rules that allow the identification of confounders, and they allow complexity 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 introduced by improper exclusion of confounders or inappropriate adjustment for nonconfounders. Quantitative analyses complement DAGs because they can be used to explore the magnitude of these biases under specific assumptions. Nevertheless, 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 assumptions. Despite their limitations, together quantitative sensitivity analyses and DAGs improve our ability to make causal inferences from observational data.

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REFERENCES

1. Weinberg CR. Toward a clearer definition of confounding. *Am J Epidemiol.* 1993;137(1):1–8.
2. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology.* 1999;10(1):37–48.
3. Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology.* 2003;14(3):300–306.
4. Hernán MA, Hernández-Díaz S, Werler MM, et al. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *Am J Epidemiol.* 2002;155(2):176–184.
5. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology.* 2004;15(5): 615–625.
6. Pearl J. Causal diagrams for empirical research. *Biometrika.* 1995;82(4):669–710.
7. Glymour MM, Greenland S. Causal diagrams. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:183–209.
8. Shpitser I, VanderWeele TJ, Robins JM. On the validity of covariate adjustment for estimating causal effects. In: *Proceedings of the 26th Conference on Uncertainty and Artificial Intelligence.* Corvallis, WA: AUAI Press; 2010:527–536.
9. Hernández-Díaz S, Schisterman EF, Hernán MA. The birth weight "paradox" uncovered? *Am J Epidemiol.* 2006; 164(11):1115–1120.
10. Pearl J. *Causality: Models, Reasoning, and Inference.* 2nd ed. New York, NY: Cambridge University Press; 2009.
11. Nelson DB, McMahon K, Joffe M, et al. The effect of depressive symptoms and optimism on the risk of spontaneous abortion among innercity women. *J Womens Health (Larchmt).* 2003;12(6):569–576.
12. Swan SH, Waller K, Hopkins B, et al. A prospective study of spontaneous abortion: relation to amount and source of drinking water consumed in early pregnancy. *Epidemiology.* 1998;9(2):126–133.
13. Weng X, Odouli R, Li DK. Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study. *Am J Obstet Gynecol.* 2008;198(3):e1–e8.
14. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology.* 2009;20(4):488–495.