Berkeley School of Public Health

Confounding in depth

PHW250B

Outline

- Review: 3 criteria for confounding
- Exceptions to the traditional rules of confounding
- Implications of a confounder that is strongly correlated with the exposure
- Identify confounding by assessing non-collapsibility
- Define negative, positive, and qualitative confounding
- Role of statistical significance in assessing confounding
- Connection to counterfactuals

3 Criteria for a confounder

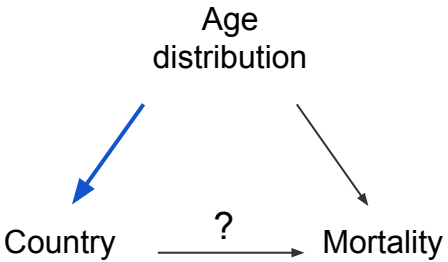
A confounder:

1. Must be associated with exposure
2. Must be an independent cause or predictor of disease
3. Cannot be an intermediate between exposure and disease

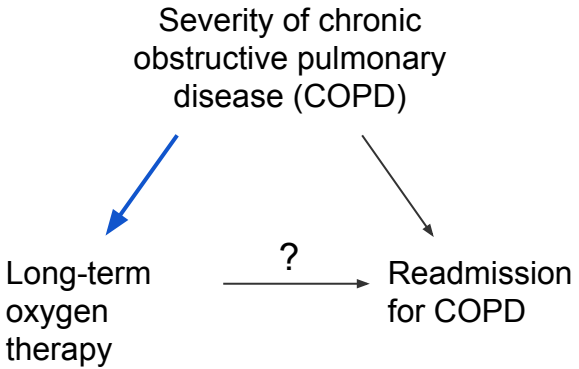
Confounding criterion #1

A confounder must be associated with the exposure.

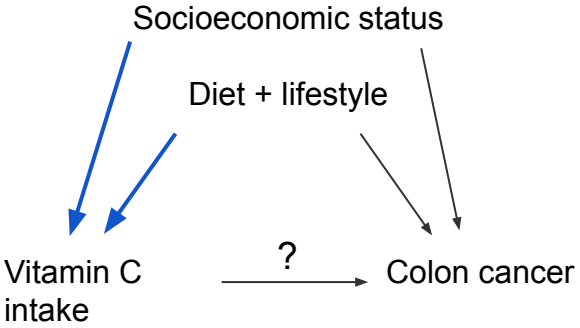
- Can be casually or non-causally associated



Noncausal association



Causal association



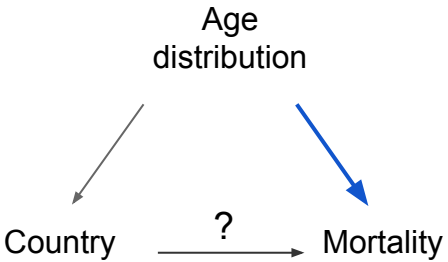
SES: Causal association
Diet + lifestyle: could be noncausal

Szklo & Nieto, 3rd Ed.

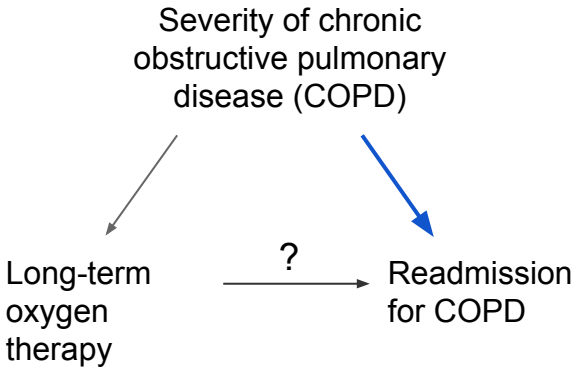
Confounding criterion #2

A confounder must be an independent cause or predictor of disease.

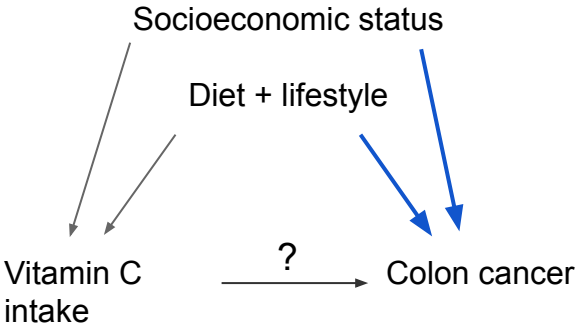
- Must be a causal association.



Causal association



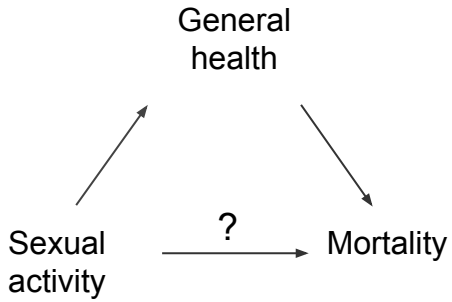
Causal association

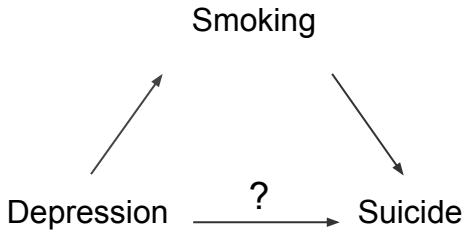


Causal association

Confounding criterion #3

A confounder cannot be an intermediate between exposure and disease





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Exceptions to the traditional rules of confounding

1. “Confounding” due to random associations
2. The “confounder” does not cause the outcome, but it is a marker of another unmeasured causal risk factor
3. The “confounder” is an intermediate variable in the causal pathway of the relationship between exposure and outcome

Szklo & Nieto, 3rd Ed.

"Confounding" due to random associations

- Sometimes a random statistical association results in confounding even when the confounder does not cause the outcome
- For example, in **case-control studies** random variability due to sampling may create an imbalance between cases and controls on a variable associated with the exposure and outcome.
- This can also occur in **randomized trials** - random differences in variables associated with the exposure and outcome can occur between groups when the sample size is small.
  - In trials it is always important to compare potential confounders between intervention and control groups after randomization to assess the possibility of confounding.

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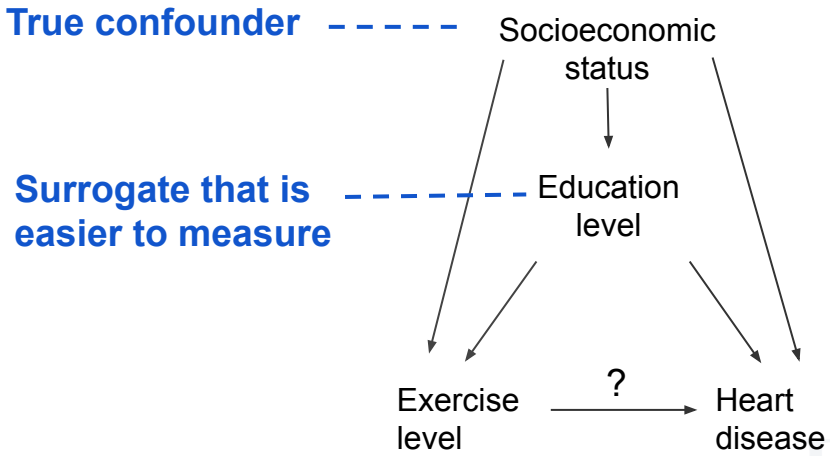
The "confounder" does not cause the outcome, but it is a marker of another unmeasured causal risk factor

- A "confounder" may be a surrogate for a true confounder.
- Education level and gender are often surrogates of confounders.
- (More on this in the video on DAGs and confounding.)



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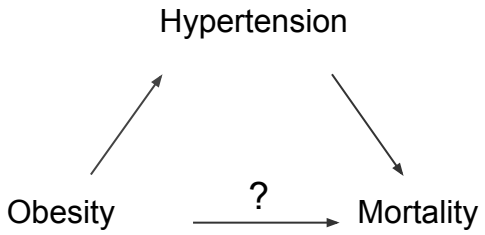
The “confounder” is an intermediate variable

- There are some uncommon cases when it is acceptable to define an intermediate as a confounder.
- The Szklo & Nieto textbook discusses how you can control for an intermediate if interested in the effect of an exposure on the outcome other than through that pathway.
  - Example: If you’re interested in the effect of obesity on mortality through pathways other than hypertension, you could control for hypertension.
- More recent epidemiologic articles have argued against this. This is related to a more advanced topic of direct vs. indirect effects.
- For this course, it’s important to know that controlling for an intermediate is something that should be done with caution and careful thought because it affects the quantity you are estimating.



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Implications of a confounder that is strongly correlated with the exposure

- A confounding variable that is strongly correlated with the exposure of interest may be difficult to adjust for
  - This is called **collinearity.**
- **Example:** the exposure is air pollution and the confounder is area of residence.
  - It would be difficult and potentially impossible to control for area of residence because there is no variation left once controlling for it
- Ideally, there is variation so that when stratifying the confounder and the exposure (and outcome), all cells in a 2x2 table have data

	Confounder present	**Confounder absent**
Exposure present	A	(no data)
Exposure absent	(no data)	D

	Areas near freeway	**Areas far from freeway**
High level air pollution	A	(no data)
Low level air pollution	(no data)	D

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Assessing confounding by non-collapsibility of strata

- Does the crude exposure-outcome association have the same direction and similar magnitude as **confounder stratified associations**?

Exhibit 5–4 Stratified Analyses of the Association Between Gender and Malaria (from Exhibit 5–2), According to Whether Individuals Work Mainly Outdoors or Indoors

Mostly outdoor occupation

	Cases	Controls
Males	53	15
Females	10	3
Total	63	18

Odds ratio = 1.06

Mostly indoor occupation

	Cases	Controls
Males	35	53
Females	52	79
Total	87	132

Odds ratio = 1.00

Stratified ORs

The Crude OR = 1.71, which is different from the confounder stratified ORs.

The apparent increase in malaria risk associated with male gender disappeared when accounting for the location of occupation.

Szklo & Nieto, 3rd Ed.

Assessing confounding by non-collapsibility of strata

- Does the crude exposure-outcome association have the same direction and similar magnitude as the **confounder adjusted associations**?
- This is the most common method
- Can compare crude estimate to Mantel-Haenszel adjusted estimate or to an estimate from an adjusted regression model.

Table 5–1 Association between medical interventions and risk of readmission to a hospital in chronic obstructive pulmonary disease (COPD) patients: estimating the proportion of risk explained by markers of COPD severity (FEV_1, PO_2, and previous admission to a hospital)

	Crude Hazard Ratio	*Adjusted Hazard Ratio**	*Excess Risk Explained by Covariates†*
Long-term oxygen therapy	2.36‡	1.38	72%
Respiratory rehabilitation	1.77‡	1.28	64%
Anticholinergics	3.52‡	2.10‡	56%
Under the care of pulmonologist¶	2.16‡	1.73‡	37%

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Define negative, positive, and qualitative confounding

- **Positive confounding:** confounding leads to an overestimate of the true strength of association
  - Example for a harmful exposure
    - True RR=2.0
    - 1.0 > Crude RR > 2.0
- **Negative confounding:** confounding leads to an underestimate of the true strength of association
  - Example for a harmful exposure
    - True RR=2.0
    - 1.0 > Crude RR < 2.0
- **Qualitative confounding:** confounding results in an inversion of the direction of association
  - Example for a harmful exposure
    - True RR=2.0
    - Crude RR < 1.0

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Define negative, positive, and qualitative confounding

TABLE 5-8 Directions of the associations of the confounder with the exposure and the outcome and expectation of change of estimate with adjustment; assume a direct relationship between exposure and outcome, i.e., for exposed/unexposed, relative risk, or odds ratio > 1.0.

Association of confounder with exposure is	Association of confounder with outcome is	Type of confounding	Expectation of change from unadjusted to adjusted estimate
Direct*	Direct*	Positive‡	Unadjusted > Adjusted
Direct*	Inverse†	Negative§	Unadjusted < Adjusted
Inverse†	Inverse†	Positive‡	Unadjusted > Adjusted
Inverse†	Direct*	Negative§	Unadjusted < Adjusted

Szklo & Nieto, 4th Ed.

Examples of negative, positive, and qualitative confounding

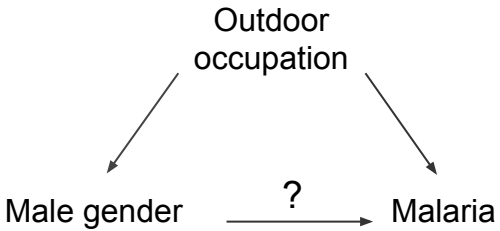
Table 5–7 Hypothetical Examples of Unadjusted and Adjusted Relative Risks According to Type of Confounding (Positive or Negative)

Example No.	*Type of Confounding*	*Unadjusted Relative Risk*	*Adjusted Relative Risk*
1	Positive	3.5	1.0
2	Positive	3.5	2.1
3	Positive	0.3	0.7
4	Negative	1.0	3.2
5	Negative	1.5	3.2
6	Negative	0.8	0.2
7	Qualitative	2.0	0.7
8	Qualitative	0.6	1.8

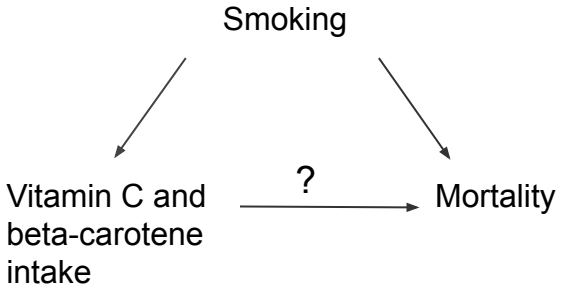
Szklo & Nieto, 3rd Ed.

Confounding is not an “all or none” phenomenon

- Sometimes a confounding variable is responsible for the **entire relationship** between the exposure and outcome
- Assuming no other confounders, adjusting for this confounder will have a **large effect** on the estimated measure of association — it may cause it to be null.



- Sometimes it is only responsible for **part of the relationship**.
- Assuming no other confounders, adjusting for this confounder will have a **small effect** on the estimated measure of association.



Szklo & Nieto, 3rd Ed.

Confounding is not an "all or none" phenomenon
Example: strong confounder

Exhibit 5–4 Stratified Analyses of the Association Between Gender and Malaria (from Exhibit 5–2), According to Whether Individuals Work Mainly Outdoors or Indoors

Mostly outdoor occupation

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Males	53	15
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Odds ratio = 1.06

Mostly indoor occupation

	Cases	Controls
Males	35	53
Females	52	79
Total	87	132

Odds ratio = 1.00

Crude OR = 1.71

The association is does not differ greatly when stratifying by the confounder.

The stratum-specific estimates are very different from the crude estimate.

The pooled OR would be close to 1.00 based on these stratified estimates.

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Confounding is not an "all or none" phenomenon
Example: weak confounder

Table 5–6 Unadjusted and Smoking-Adjusted All-Cause Mortality Ratios Rate in the Western Electric Company Study

	Vitamin C/Beta Carotene Intake Index Rate Ratios		
Rate Ratios	*Low*	*Moderate*	*High*
Unadjusted	1.00	0.82	0.79
Adjusted*	1.00	0.85	0.81

There are very small differences between unadjusted and adjusted rate ratios (and no difference for the low intake category). This suggests that smoking was a weak confounder.

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Role of statistical significance in assessing confounding

- It is inappropriate to rely solely on statistical significance to identify a confounder, especially when the exposure or outcome is strongly associated with the confounder.
- If using a p-value for the strength of association with a confounder, it is recommended to use a cutoff of 0.2 instead of 0.05 to reduce the chance of a Type II error (and err on the side of detecting a confounder).
- However, generally it is best to focus on the magnitude of the association of the confounder with the exposure and outcome.

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Connection to counterfactuals

- In the causal inference unit, we learned that our goal is to create exchangeability between the exposed and unexposed.
- When there is confounding:
  - The exposed and unexposed are not exchangeable because they have differing distributions of a variable that causes disease (i.e., the confounder).
  - The unexposed do not serve as a good counterfactual and will produce a biased estimate of the measure of association.

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Summary of key points

- The traditional definition of confounding is based on 3 criteria, though there are a few exceptions to these rules.
- Confounding may also be assessed by comparing:
  - Crude vs. confounder stratified measures of association
  - Crude vs. confounder adjusted measures of association
- A confounding variable that is strongly correlated with the exposure of interest may be difficult to adjust for due to collinearity.
- It is best to focus confounding assessment on the strength of the confounder's association with the exposure and disease rather than on statistical significance.

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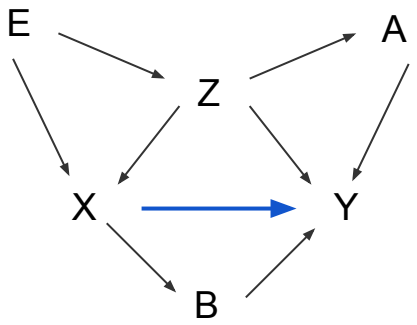
Using DAGs to detect confounding

PHW250B

Intuition behind using DAGs to assess confounding

- We are only interested in directed paths from X to Y.
- Any other unblocked paths between X and Y imply statistical dependence due to reasons other than the causal relationship between X and Y (e.g., confounding).
- DAGs help us:
  - 1) Identify confounders
  - 2) Assess the implications of restriction, stratification, and multivariate adjustment.



Using DAGs to detect confounding

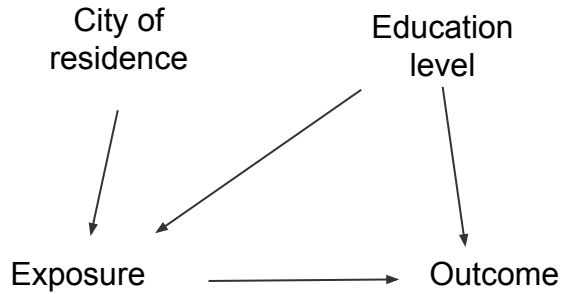
- Most real DAGs are complex and include many different potential pathways between the exposure and outcome.
- We can use a process called **d-separation** to predict dependencies between nodes in a DAG.
- The “d” stands for “directional”

Pearl, Glymour & Jewell 2016

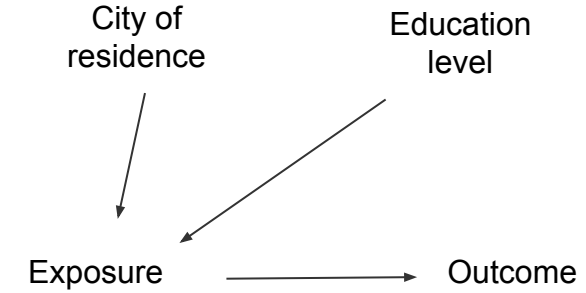
Using DAGs to detect confounding

- **d-connected**: a path exists between two nodes, and the two nodes are likely to be statistically dependent
- **d-separated**: no path exists between two nodes or all paths between them are blocked, and the two nodes are statistically independent
- **If the nodes for exposure and outcome are d-separated except for directed paths from exposure to outcome, there is no confounding.**

Exposure and outcome are d-connected



Exposure and outcome are d-separated



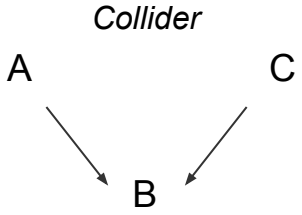
Pearl, Glymour & Jewell 2016

Blocking a directed path

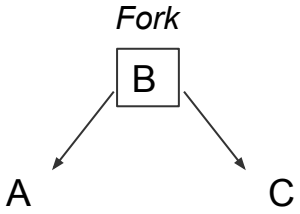
- There are two ways a directed path can be blocked:

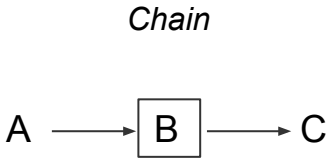
1. The presence of a collider along the path
2. Conditioning on a node along the path (through adjustment, stratification, restriction)

- This is regardless of the direction of the arrows between nodes along the pathways between nodes.



Path from A to C is blocked

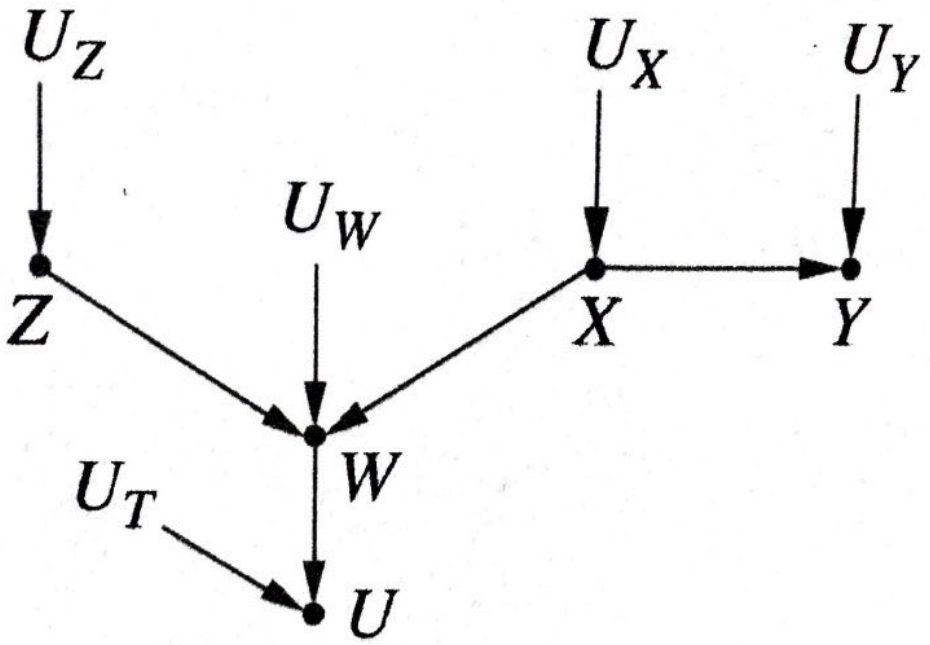




Path from A to C is blocked

Pearl, Glymour & Jewell 2016

Example #1: Are Z and Y d-separated?



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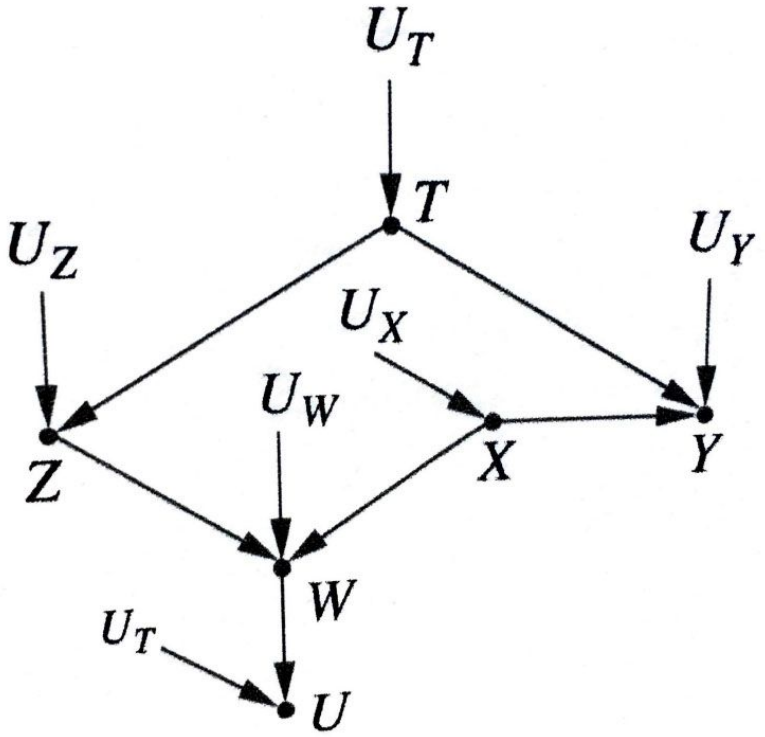
Example #2: Are Z and Y d-separated?



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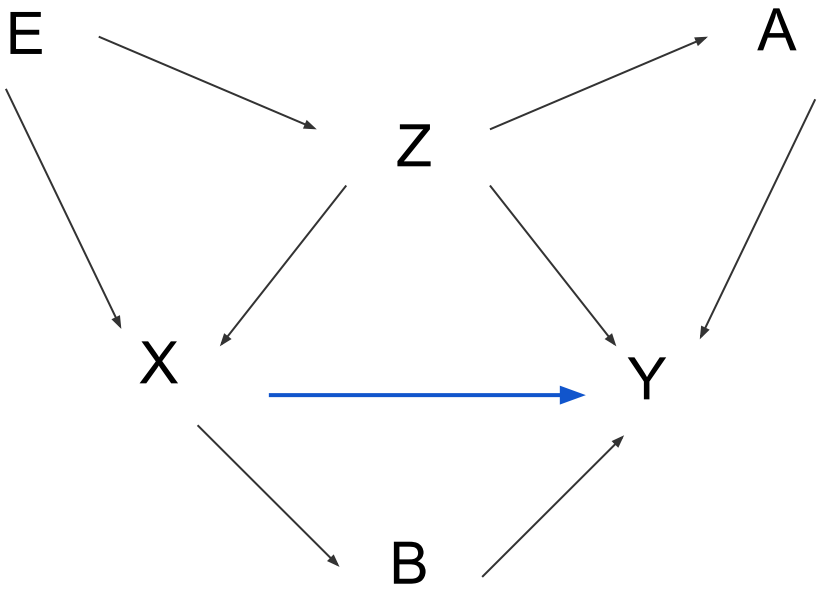
Example #3: Are X and Y d-separated?



The Backdoor Criterion

- This criterion helps us assess under what conditions is the association between exposure and outcome unconfounded. (i.e., under what conditions is there a causal effect between the exposure and outcome)
- **Formal definition:** For a pair of nodes X and Y, a set of variables Z satisfies the backdoor criterion if no node in Z is:
  a. A descendant of X, and
  b. Z blocks every path between X and Y that contains an arrow into X

Pearl, Glymour & Jewell 2016

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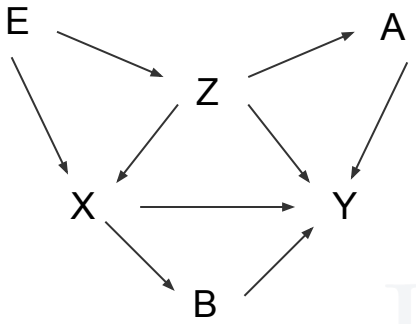
In this DAG, conditioning on the following sets could meet the criterion:

- Z,
- Z, A
- Z, E
- Z, A, E

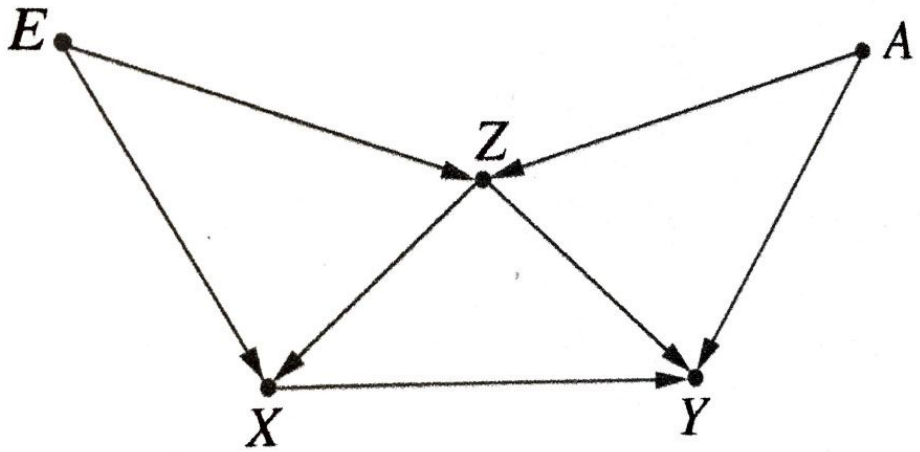


Pearl, Glymour & Jewell 2016

What variables should be adjusted for in order to remove confounding?

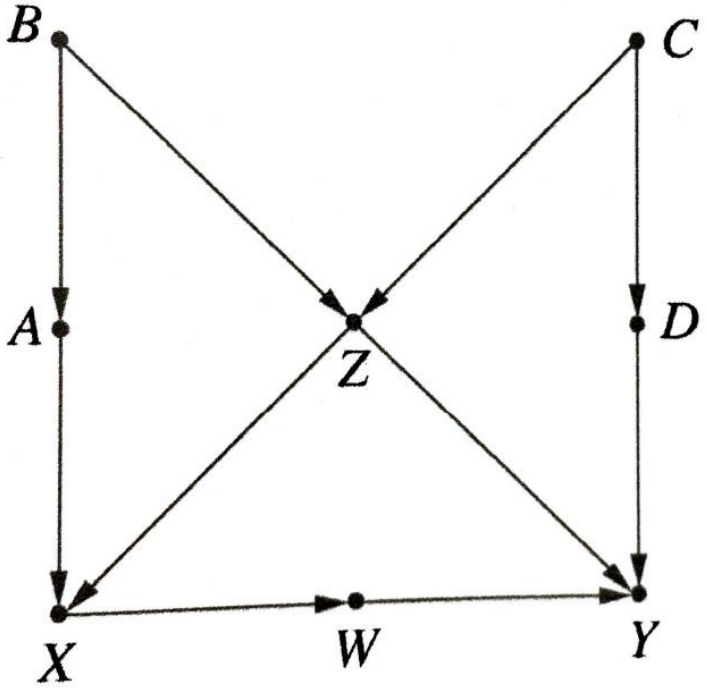
- Use the DAG to identify which node or which set of nodes could be blocked to d-separate the exposure and outcome.
- Conditioning on that node or set of nodes will d-separate exposure and outcome, and confounding will be removed.
- This is also called “blocking backdoor pathways”.
- Watch out for colliders! Conditioning on them could create new backdoor pathways between exposure and outcome, re-introducing confounding.

Example #1: which node(s) block backdoor pathways from X to Y?



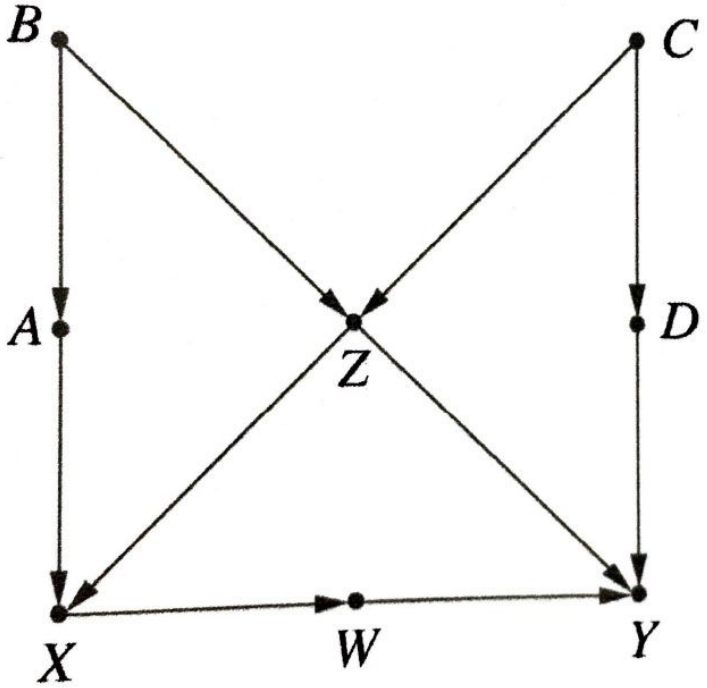
Pearl, Glymour & Jewell 2016

Example #2: which node(s) block backdoor pathways from X to Y?



Pearl, Glymour & Jewell 2016

Example #2: which node(s) block backdoor pathways from X to Y?



1. *Sets of 2 nodes:* $\{Z, A\}, \{Z, B\}, \{Z, C\}, \{Z, D\}$
2. *Sets of 3 nodes:* $\{Z, A, B\}, \{Z, A, C\}, \{Z, A, D\}, \{Z, B, C\}, \{Z, B, D\}, \{Z, C, D\}$
3. *Sets of 4 nodes:* $\{Z, A, B, C\}, \{Z, A, B, D\}, \{Z, A, C, D\}, \{Z, B, C, D\}$
4. *Sets of 5 nodes:* $\{Z, A, B, C, D\}$

Pearl, Glymour & Jewell 2016

Comparing DAG vs. traditional approach to assessing confounding

Traditional criteria:

1. Must be associated with exposure

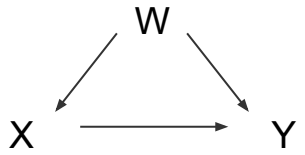
   DAG: arrow from W to X (or X and W d-connected)

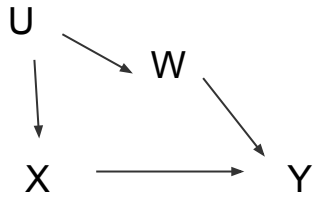
2. Must be an independent cause or predictor of disease

   DAG: arrow from W to Y

3. Cannot be an intermediate between exposure and disease

   DAG: W not on path from X to Y





- In #1, for the association to exist when one variable does not cause the other, they have to share a common cause – the common cause may be unmeasured

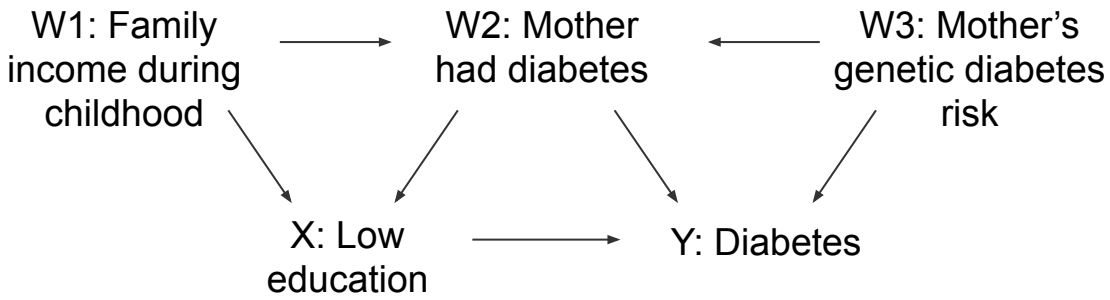
What do DAGs offer that the traditional criteria do not?

- Clear identification of colliders
- Sufficiency of confounder adjustment
- Most often, these two approaches agree.
  - When they do not, it is the three criteria that fail to detect confounding.

Example of when the traditional criteria fail to capture confounding

Using traditional criteria, should we control for W2? **Yes.**

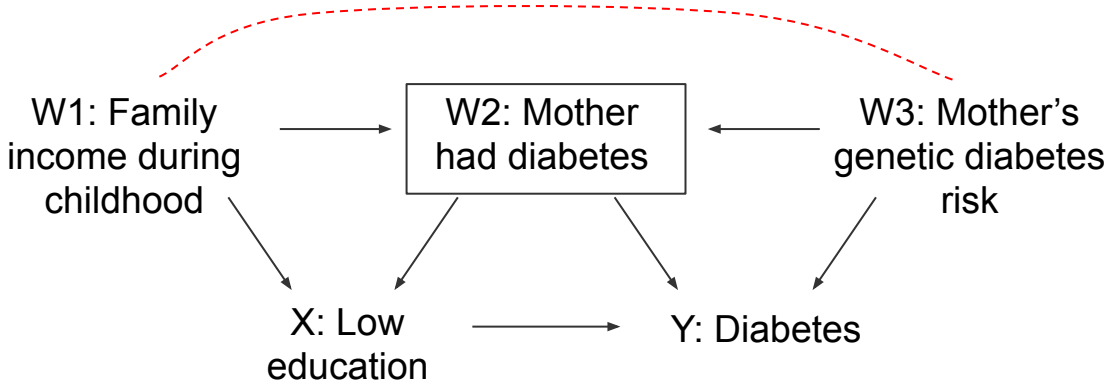
1. Must be associated with exposure ✔
2. Must be an independent cause or predictor of disease ✔
3. Cannot be an intermediate between exposure and disease ✔



Example of when the traditional criteria fail to capture confounding

Using the backdoor criterion, should we control for W2? **No.**

W2 is a collider, and controlling for it opens a backdoor pathway through W1 and W3. As a result, if we control for W2, we also have to control for W1 or W3.



Summary of key points

- To assess whether an exposure-outcome relationship is confounded, we can assess whether the two nodes are d-separated in a DAG.
- To determine which node or set of nodes needs to be adjusted for to remove confounding, we can identify the node(s) that meet the backdoor criterion.
  - Conditioning on these nodes blocks any backdoor pathways from X to Y and ensures d-separation of X and Y
- Most often, the traditional and DAG-based approaches agree, but when they do not, it is the three criteria that fail to detect confounding.

Berkeley School of Public Health

Negative controls

PHW250B

Detecting bias and confounding

- Epidemiologists' toolkit for assessing confounding include:
  - Compare crude and confounder stratified estimates
  - Compare crude and adjusted estimates
  - DAGs
- All three of these methods require us to anticipate specific potential confounders
  - Even in DAGs, we can include "U" nodes for unmeasured, but we must posit some relationship between the U nodes and other nodes.
  - But what if we don't know of a node or path that can cause confounding?
- **Negative controls** are another tool inspired by basic science experiments that can be used to detect suspected and unsuspected sources of bias and confounding.

Pearl, Glymour & Jewell 2016

Negative controls in basic science experiments

- Laboratory scientists are always aware that their experimental results may be due to something other than the hypothesized mechanism.
  - e.g., was the laboratory equipment contaminated during the experiment?
- To detect any potential sources of error, they repeat their experiment under conditions in which they do not expect to see an effect (i.e., a null result is expected). They do so by:
  - Leaving out a key ingredient
  - Using an inactive ingredient
  - Checking for an effect that would be impossible under the hypothesized mechanism
- A non-null result suggests that something other than the mechanism of interest is responsible for at least part of the observed effect.

Lipsitch et al., 2010

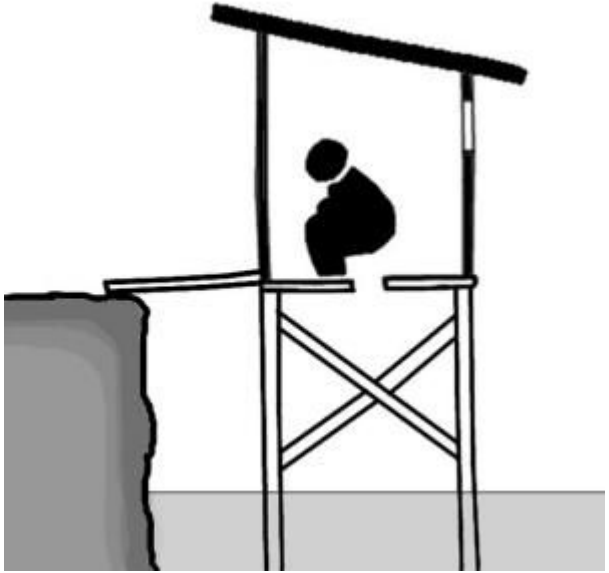
Negative controls in epidemiology

- In recent years, epidemiologists have translated this approach to epidemiologic studies. These approaches include using a:
  - **Negative control outcome** that is believed not to be affected by the exposure or intervention
  - **Negative control exposure** that is believed not to cause the outcome of interest
  - **Negative control time period** in which the exposure is believed not to be able to cause the outcome
- *"The essential purpose of a negative control is to reproduce a condition that cannot involve the hypothesized causal mechanism but is very likely to involve the same sources of bias that may have been present in the original association."*

Lipsitch et al., 2010

Example: negative control outcome

- In a trial of the effects of water and sanitation interventions on self-reported diarrhea, measure the effect of interventions on self-reported scrapes and bruises
- Both outcomes are self-reported and may involve similar sources of bias. However, scrapes and bruises are not affected by the intervention.



Lipsitch et al., 2010

Example: negative control exposure

- In a study of corticosteroids and self-reported asthma symptoms, repeat the analysis among a very low dose of the drug (so low that no effect on asthma is possible).
- An observed effect among patients who took a very low dose would suggest that there was bias in the measurement of asthma symptoms.

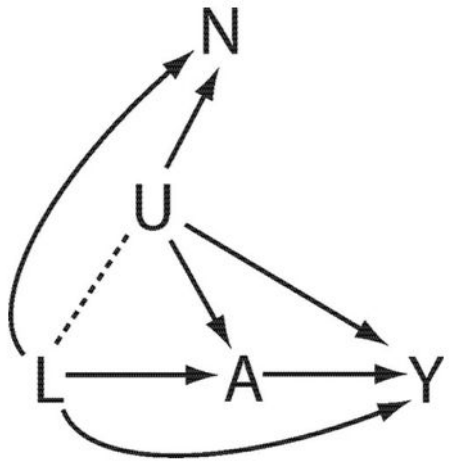
Lipsitch et al., 2010

Example: negative control time period

- In a cohort study of the effect of influenza vaccination on mortality, measure the effect in the exposed vs. unexposed group in the period after immunization but before the start of influenza season, when no influenza is circulating.
- An observed difference in mortality between the exposed and unexposed in the period when influenza was not circulating locally would suggest other systematic differences between the exposed and unexposed explained differences in mortality, not influenza vaccination.

Lipsitch et al., 2010

DAG of the ideal negative control outcome



- N is the negative control outcome
- Y is the outcome
- A is the exposure
- L is a measured confounder
- U is an unmeasured confounder

For an ideal negative control, N should have the same arrows going into it as Y except that A does not cause N.

- U leads to N and Y
- L leads to N and Y
- A does not lead to N

Lipsitch et al., 2010

Summary of key points

Strengths

- If an appropriate negative control outcome, exposure, or time period can serve as a negative control, the analysis is typically straightforward since it is the same as in the primary analysis but with the negative control.
- Negative controls can detect unanticipated, non-specific bias and confounding that is missed through the traditional epidemiologic tools.

Limitations

- *"A properly selected negative control is a sensitive, but blunt, tool to probe the credibility of a study."*
- When we find an effect that we don't expect to see in a negative control analysis, negative control analyses can't tell us the cause of the bias or confounding.
- Negative controls must be defined appropriately (ideally using DAGs) as outlined by Lipsitch et al.
- For some research questions, it is not possible to define a good negative controls.

Lipsitch et al., 2010