Correlation does not imply causation

- What does this mean in the context of randomized experiments and observational studies?

  - By the end of this presentation, the goals are to:
    - describe causal effects using directed acyclic graphs
    - describe the importance of randomization prcoedures
    - compare intention-to-treat analysis with per-protocol analysis

Causal effects in randomized trials and observational studies

Sumeet Kalia

UTOPIAN clinical trials group

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Causality at individual level

- Hernan and Robins (2020) defines "causality at individual level" as:

Definition

- Consider binary exposure A (1: smoker; 0: non-smoker) and binary outcome Y (1: lung cancer; 0: No lung cancer).
- Let $Y^{a=1} = Y^1$ be the observed outcome for smoker; likewise $Y^{a=0} = Y^0$ be the observed outcome for non-smoker.
- The causal effect at the individual level is described as the difference between Y^1 and Y^0.

- Together, Y^1 and Y^0 are referred to as potential (or counterfactual) outcomes.

Causality at population level (average causal effect)

- Hernan and Robins (2020) defines "causality at population level" as:

Definition

- An average causal effect is present if the risk of developing lung cancer among smokers is different from the risk of developing lung cancer among non-smokers:

$$Pr(Y^1 = 1) \neq Pr(Y^0 = 1)$$

- Alternatively, average causal effect may not exist in the population if risk of death is the same in treatment and control group: $Pr(Y^1 = 1) = Pr(Y^0 = 1)$.

Randomized trials

- Prospective randomized experiments are often conducted to assess the effectiveness of a treatment.
- *Ideal* **randomized experiments** with following properties allow researchers to estimate causal relationships using associations:
  - No loss to follow-up
  - No non-compliance of assigned treatment
  - Single version of treatment
  - Double-blinded treatment assignment
- Causal inference becomes difficult in some randomized trials with:
  - Informed drop-out (e.g. systematic loss to follow-up for patients with severe conditions)
  - Non-compliance (e.g. participants do not receive intervention to which they were randomized).

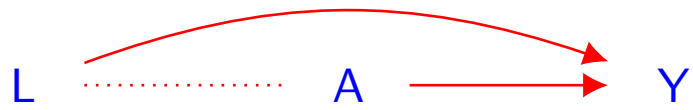
Components of randomized trials

Table 1. A Summary of the Protocol of a Target Trial to Estimate the Effect of Postmenopausal Hormone Therapy on the 5-Year Risk of Breast Cancer

Protocol Component	Description
Eligibility criteria	Postmenopausal women within 5 years of menopause between the years 2005 and 2010 and with no history of cancer and no use of hormone therapy in the past 2 years.
Treatment strategies	Refrain from taking hormone therapy during the follow-up. Initiate estrogen plus progestin hormone therapy at baseline and remain on it during the follow-up unless you are diagnosed with deep vein thrombosis, pulmonary embolism, myocardial infarction, or cancer.
Assignment procedures	Participants will be randomly assigned to either strategy at baseline and will be aware of the strategy to which they have been assigned.
Follow-up period	Starts at randomization and ends at diagnosis of breast cancer, death, loss to follow-up, or 5 years after baseline, whichever occurs first.
Outcome	Breast cancer diagnosed by an oncologist within 5 years of baseline.
Causal contrasts of interest	Intention-to-treat effect, per-protocol effect
Analysis plan	Intention-to-treat effect estimated via comparison of 5-year cancer risks among individuals assigned to each treatment strategy. Per-protocol effect estimation requires adjustments for pre- and postbaseline prognostic factors associated with adherence to the strategies of interest. All analyses will be adjusted for pre- and postbaseline prognostic factors associated with loss to follow-up (57). This analysis plan implies that the investigators prespecify and collect data on the adjustment factors.

$\sim$ Hernán and Robins (2016), AJE 183(8).

Treatment assignment using randomization



How does randomization ensure causal effect of treatment A on outcome Y for baseline confounder L?

- Randomization ensures balance in both measured and unmeasured confounders across treated and untreated group.
- Randomization ensures that the treatment groups are exchangeable (i.e. same effect measures are expected if the labels for treated and untreated groups are switched).
- Randomization ensures that the missing values of potential (or counterfactual) outcome Y^a occur only due to chance (i.e. missing at random). This allows the causal effect measures to be consistently estimated.

Randomization procedures to achieve balance

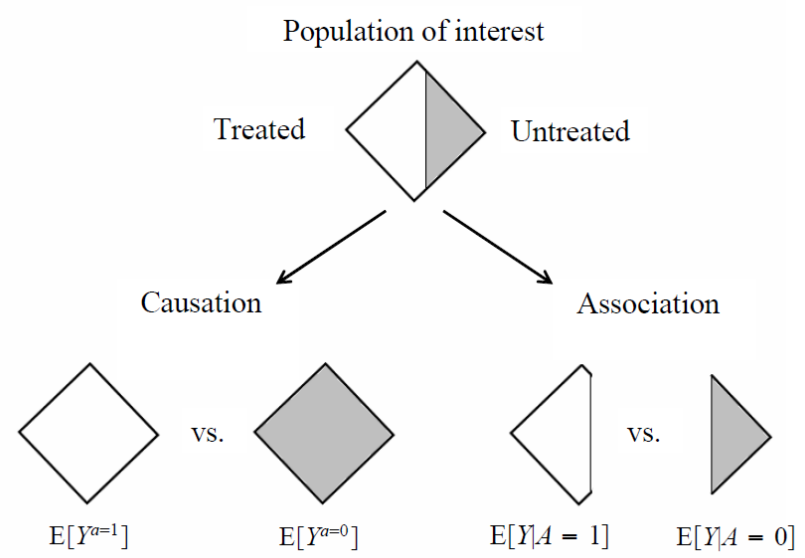
- **Simple cluster randomization**
- **Pairwise or stratified cluster randomization**
- **Crossover or step-wedge cluster randomization***
- **Adaptive cluster randomization**

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Total (N=199)	Lopinavir–Ritonavir (N=99)	Standard Care (N=100)
Age, median (IQR) — yr	58.0 (49.0–68.0)	58.0 (50.0–68.0)	58.0 (48.0–68.0)
Male sex — no. (%)	120 (60.3)	61 (61.6)	59 (59.0)
Coexisting conditions — no. (%)			
Diabetes	23 (11.6)	10 (10.1)	13 (13.0)
Cerebrovascular disease	13 (6.5)	5 (5.1)	8 (8.0)
Cancer	6 (3.0)	5 (5.1)	1 (1.0)
Body temperature, median (IQR) — °C	36.5 (36.4–36.8)	36.5 (36.4–37.0)	36.5 (36.5–36.8)
Fever — no. (%)	182 (91.5)	89 (89.9)	93 (93.0)
Respiratory rate >24/min — no. (%)	37 (18.8)	21 (21.6)	16 (16.0)
Systolic blood pressure <90 mm Hg — no. (%)	2 (1.0)	2 (2.0)	0
White-cell count ($\times 10^{-9}$/liter) — median (IQR)	7.0 (5.1–9.4)	7.3 (5.3–9.6)	6.9 (4.9–9.1)
4–10 $\times 10^{-9}$/liter — no. (%)	137 (70.3)	64 (67.4)	73 (73.0)

Causality in observational studies

- In some instances, randomized experiments may not always be feasible due to high-cost, time-commitment and ethical concerns. As a result, observational data may be used to emulate randomized experiments.
- Causal effect can only be defined for observational studies with prospective design (since the cause must precede the effect).

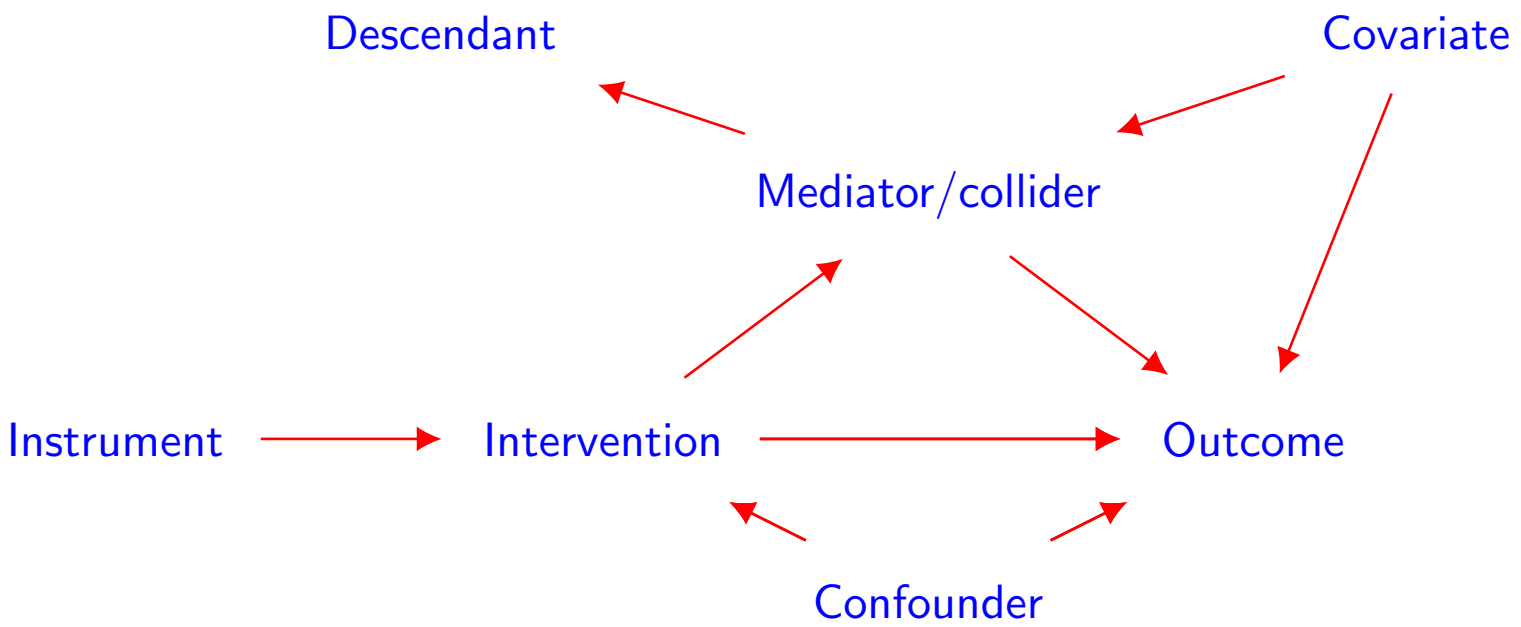


Identifiability assumptions for causal effects

- Conditional exchangability (No unmeasured confounding) assumption :
  - Potential outcomes are independent of treatment assignment given confounders:
    - Violated for infectious disease (e.g. COVID-19, influenza).
- Positivity assumption:
  - Each subject has positive conditional probability of receiving the treatment given confounders:
    - Violated when clinicians are obligated to prescribe treatment based on underlying symptoms.
- Consistency assumption:
  - Observed outcome is equal to potential outcome under observed treatment:
    - Violated when intervention is different among patients.

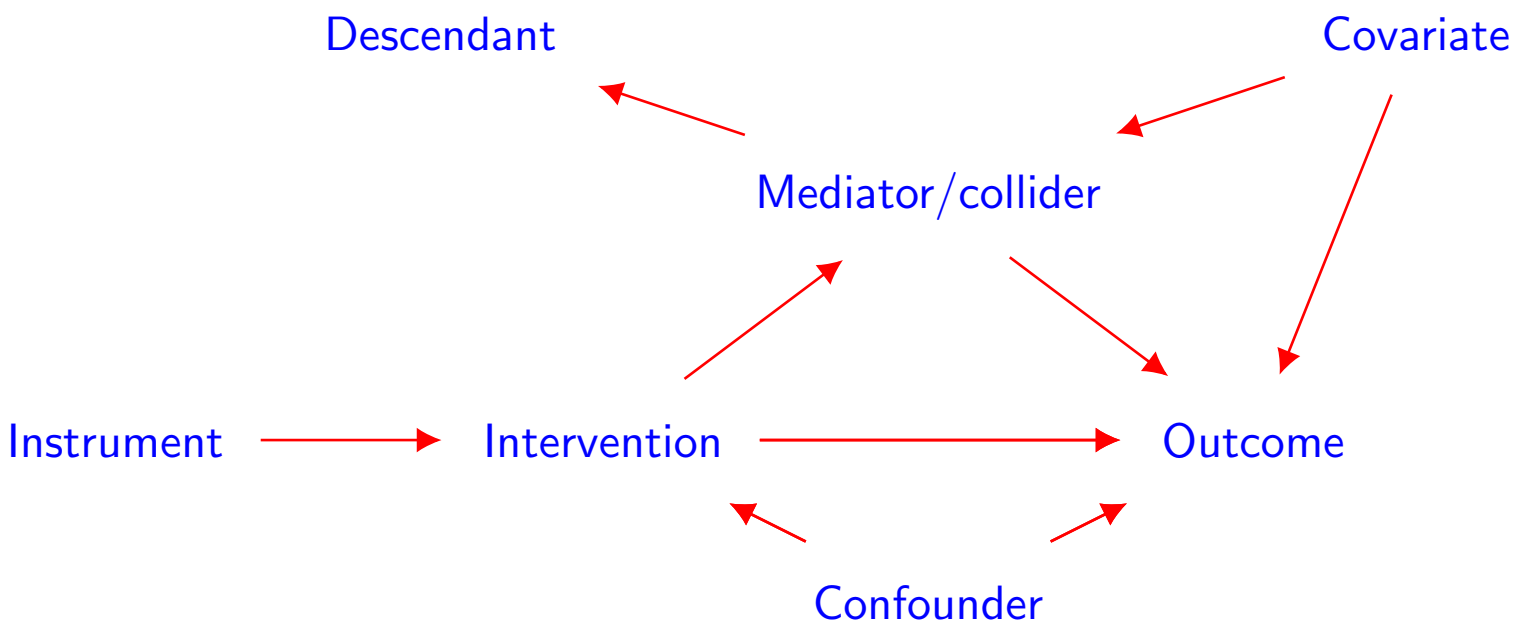
Directed acyclic graphs (i)

- DAGs are graphical representation of causal effects in which the treatment, outcome, confounders and other factors are linked together in a causal network:



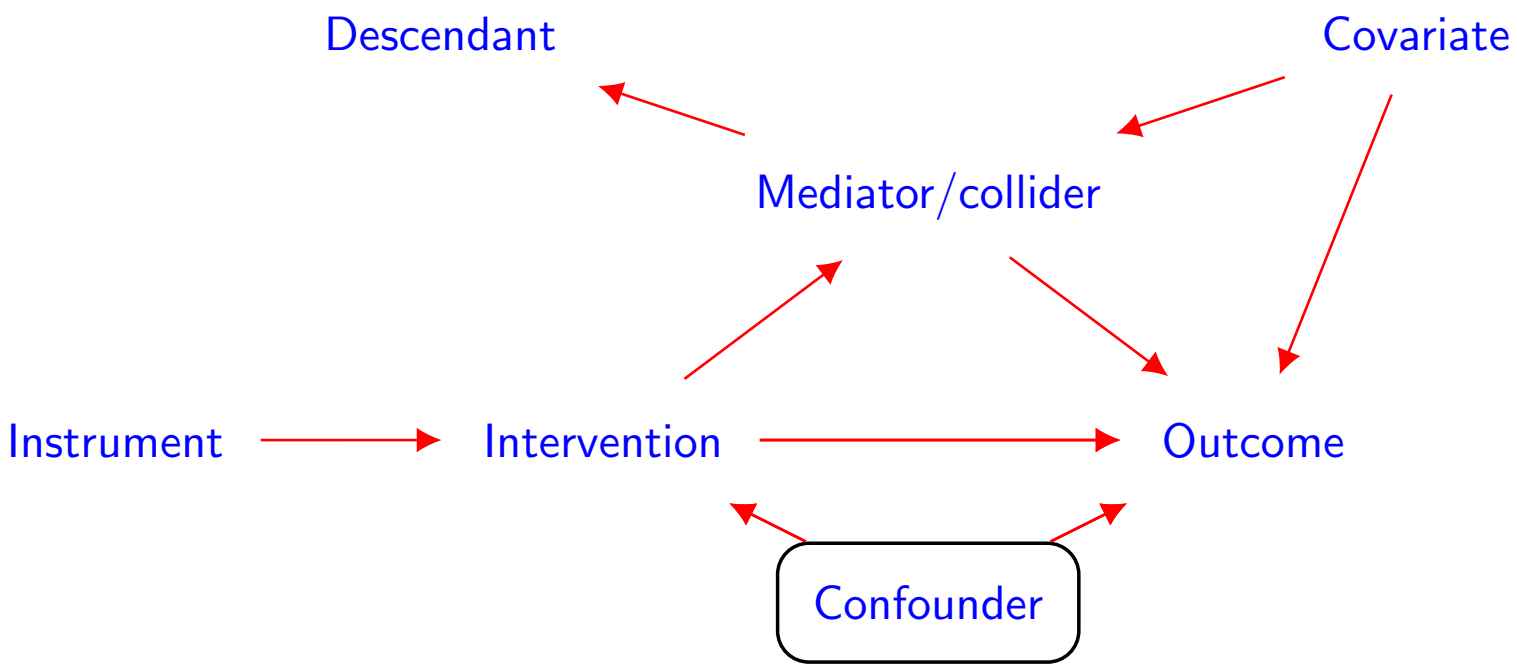
Directed acyclic graphs (ii)

- Rule 1: If no variables are conditioned, then the path is blocked if and only if there exist a collider in the path.



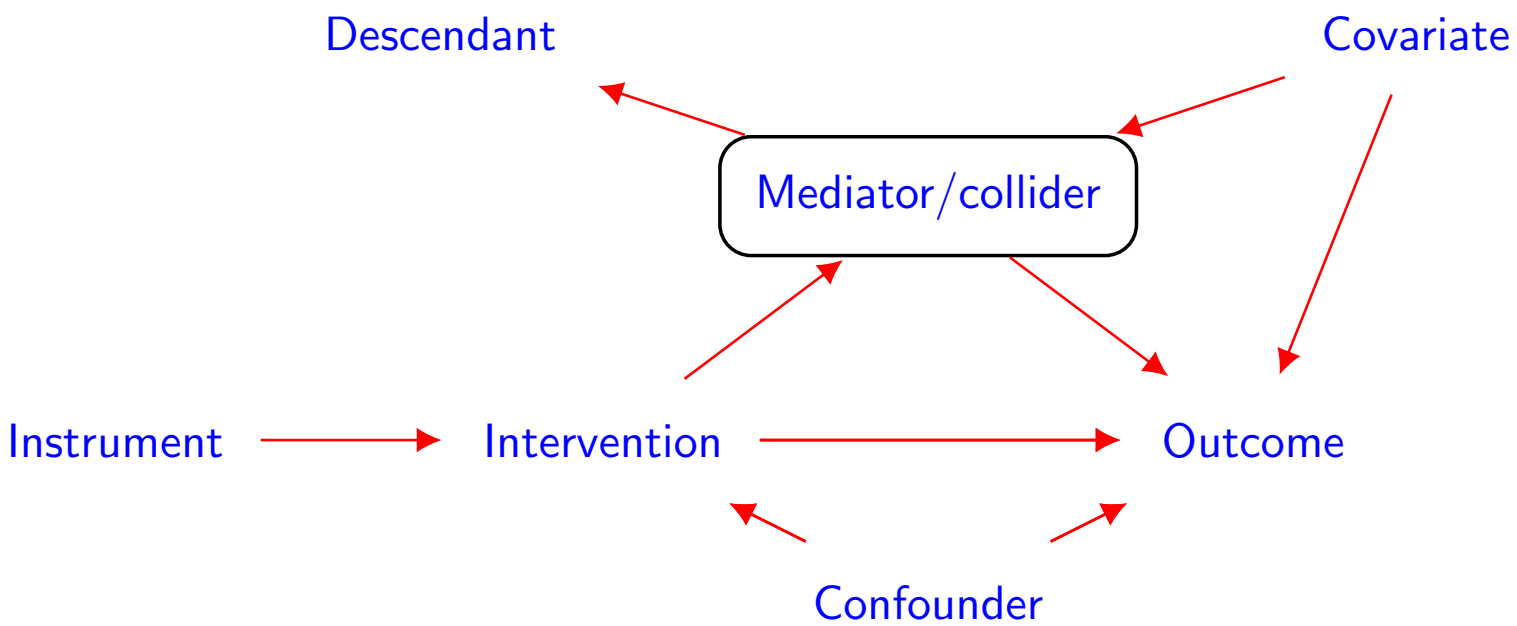
Directed acyclic graphs (iii)

- Rule 2: A path without a collider is blocked if a variable is conditioned in the path



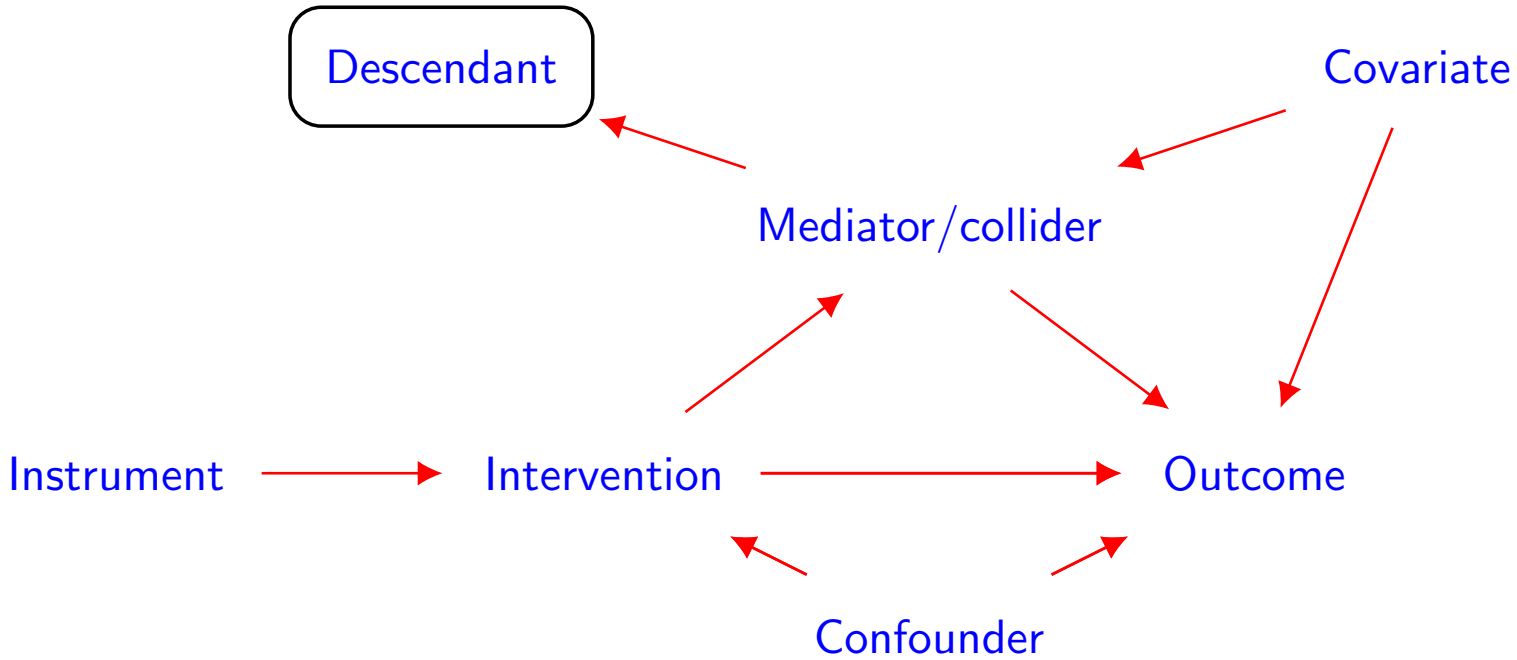
Directed acyclic graphs (iv)

- Rule 3: If a collider is conditioned in the path, then it does not block the path



Directed acyclic graphs (v)

- Rule 4: If a collider has a descendant that has been conditioned then the collider does not block the path



- Extensions of DAGs using potential outcomes include single world intervention graphs (SWIGs).

Understanding causal effects using DAGs (i)

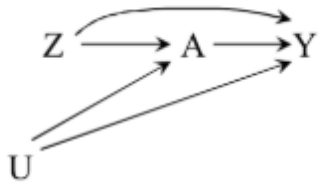


Figure 9.11

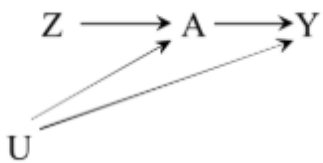


Figure 9.12

Z: Assigned treatment

A: Heart Transplant

Y: 5-year Mortality

(Ignore **U** here)

Figure 9.11 is an example of an **intention-to-treat** RCT.

ITT RCT's can be almost thought of as an RCT with a potentially *misclassified treatment*. However, unlike a misclassifed treatment, the treatment assignment Z has a causal effect on the outcome Y, both
(a) by influencing the actual treatment A, and
(b) by influencing study participants who know what Z is and change their behavior accordingly.
Hence, the causal effect of Z on Y depends on the strength of the arrow $Z \to Y$, the arrow $Z \to A$, and the arrow $A \to Y$.

Double-blinding attempts to remove $Z \to Y$ (Figure 9.12).

Understanding causal effects using DAGs (ii)

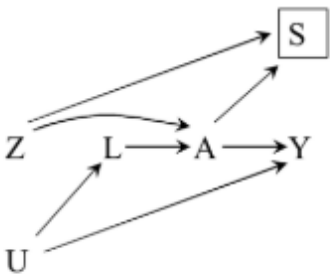


Figure 9.14

Z: Assigned treatment

A: Heart Transplant

Y: 5-year Mortality

U: Illness Severity (unmeasured)

L: Measured factors that mediate U

S: Selection filter (A=Z)

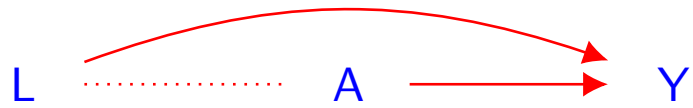
This example is of a **conventional per-protocol analysis**, a second method to measure per-protocol effect.

Conventional per-protocol analyses limit the population to those who adhered to the study protocol, subsetting to those for whom $A = Z$.

This method induces a *selection bias* on $A = Z$, and thus still requires adjustment on L.

Marginal Structural models

- Marginal structural models use counterfactual outcomes, rather than observed outcomes, to specify the causal effect of an exposure.
- These are "marginal" models because they model the marginal distribution of the counterfactual outcome and "structural" models because they model the probabilities of counterfactual outcomes.
- Create pseudo-population where the relationship between the confounder and the exposure is broken:



Why randomization is preferred?

- Identifiability conditions of causal inference are enforced in the design of randomized trials and thus causal relationships can be estimated using associations.
- Identifiability conditions of causal inference are needed to be assumed in observational studies and thus causal relationship can not be estimated using associations.
  - "No unmeasured confounding" and "consistency" assumptions are untestable in observational studies;
  - Violation of "positivity" assumption can be determined by data exploration;
  - The validity of DAGs can not be tested to explain the real-life phenomena. We assume DAG holds to estimate the causal effects.

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