# Causality in Biomedicine
# Lecture Series: Lecture 3

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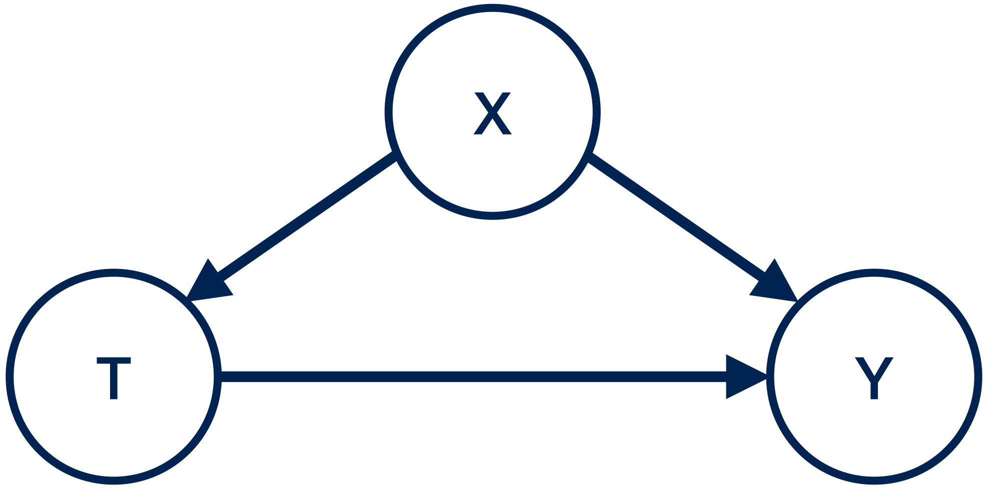
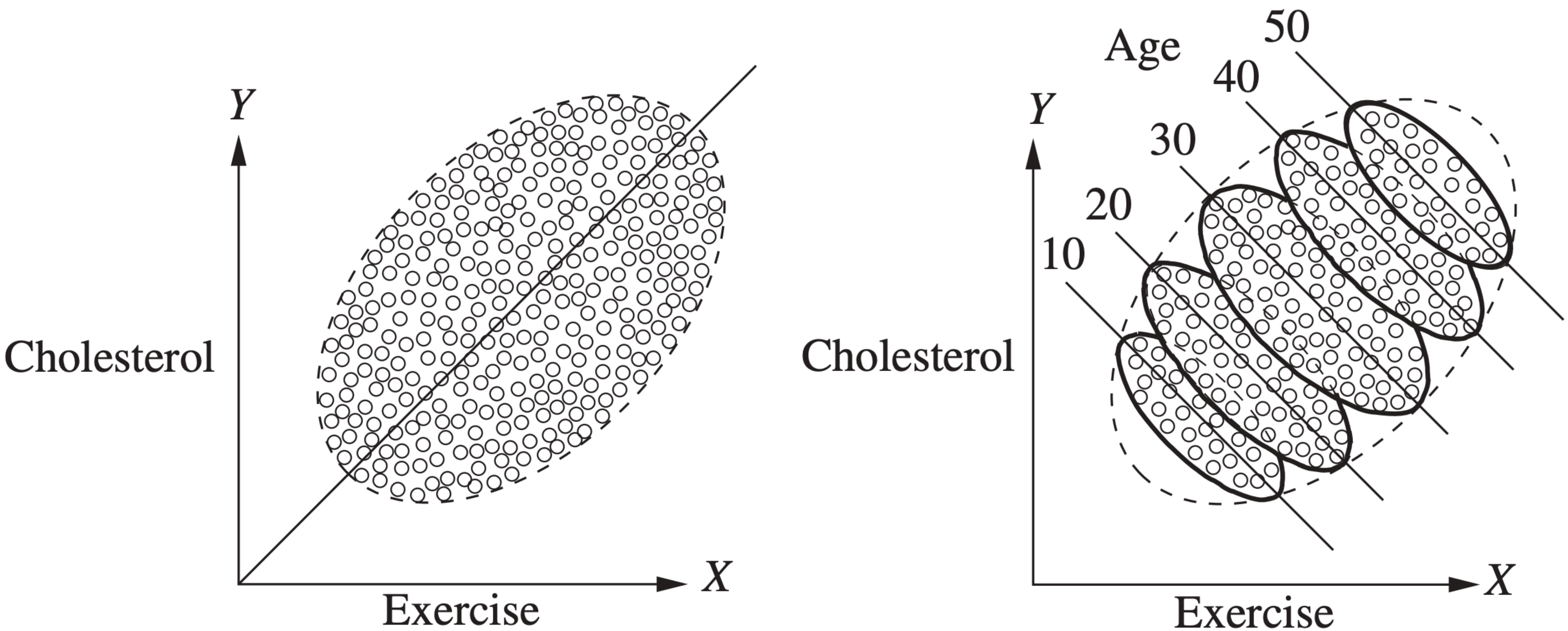
# Causal inference with observed confounders



# Simpson’s Paradox

- Why concluding causality from purely associational measures, i.e. correlation, can be **very wrong** (not just neutral): “It would have better not to make any statements!”




Causal Inference in Statistics, Pearl (2016)

# So Far …

- **Matching:** Stratification, balancing (propensity) score, IPTW, …

$$x \perp\!\!\!\perp t | b(x)$$

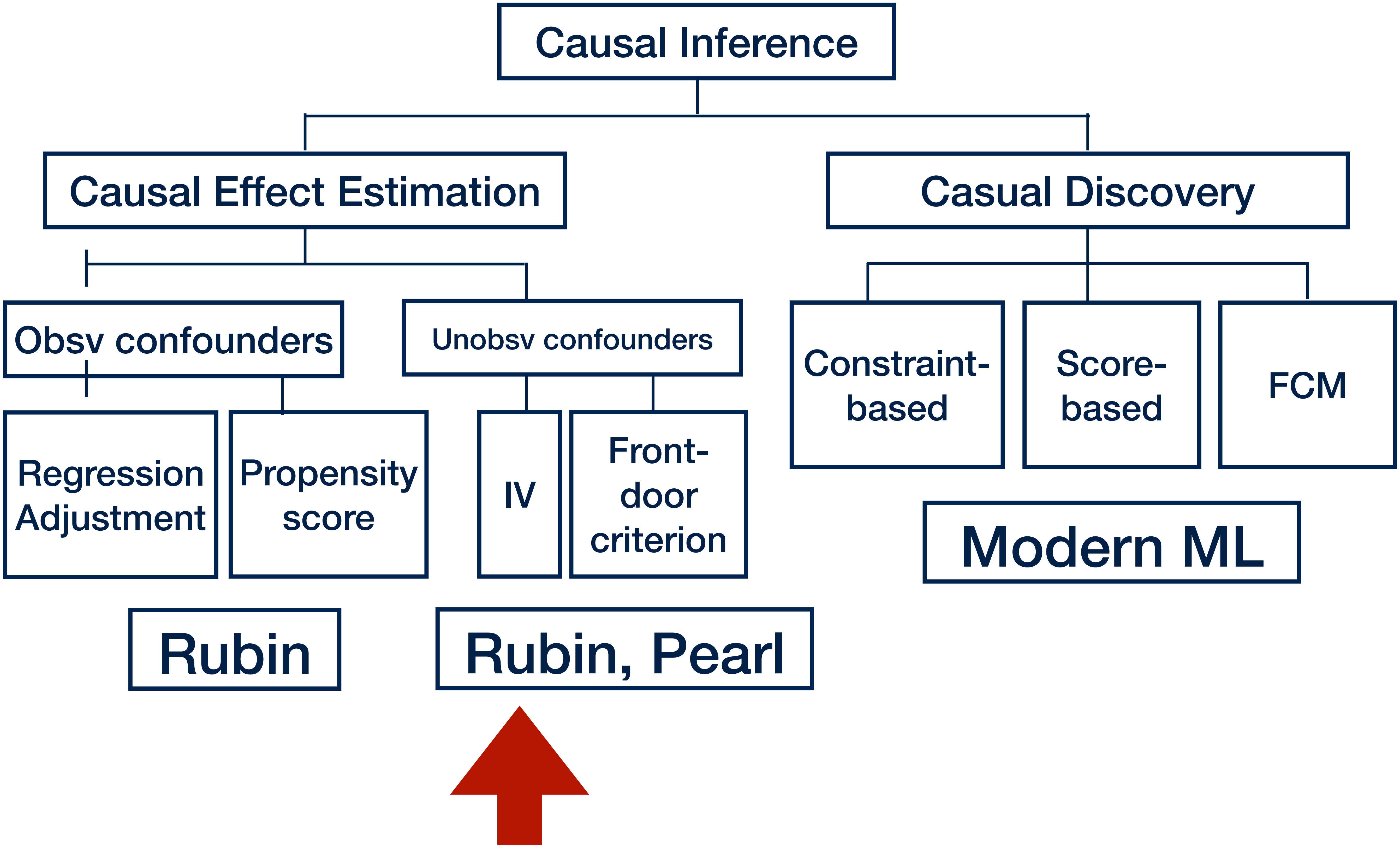
- Estimation of propensity scores directly from the data & algorithms

$$e(x) = p(t = 1 | x)$$

- **Sensitivity analysis:** No guarantee that matching leads to balance on variables we did not match for, people who look comparable may differ. If there is hidden bias, how severe is it:
  - Does the conclusion change from statistically significant to not?
  - Does it change the direction of effect?

**Notice:** There are **two sources of uncertainty**:
1) Due to the (causal) statistical estimates
2) Due to sensitivity analysis (of unobserved variables, bias)

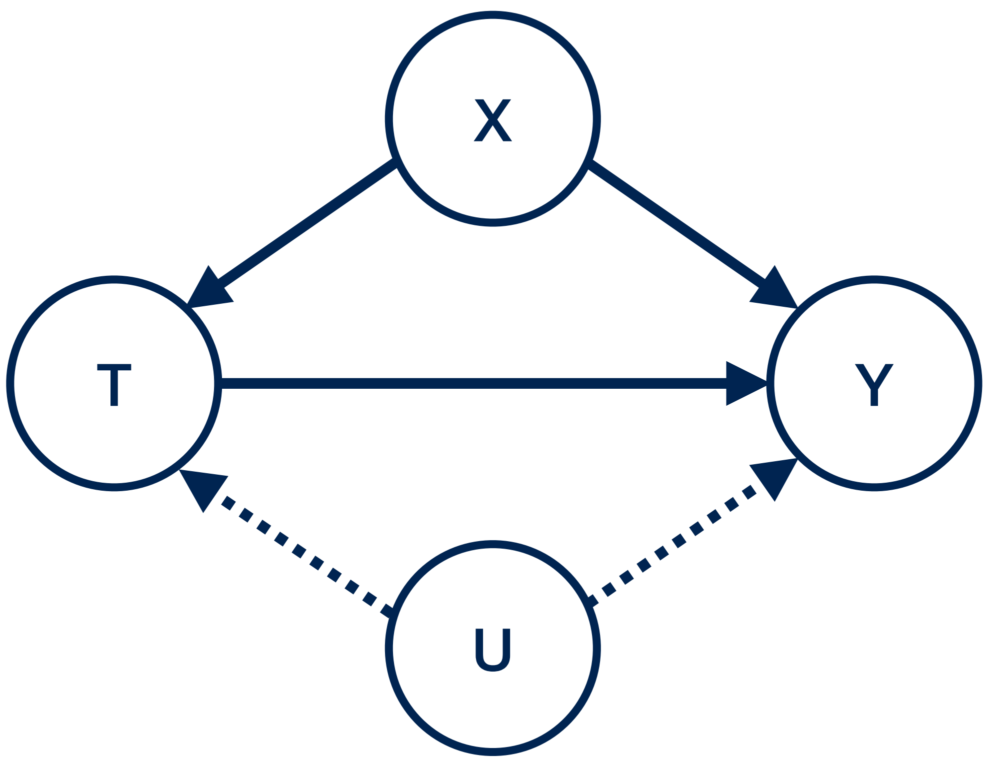
# Overview of the course



# **Instrumental Variable** (Originally due to Rubin)

- Unobserved confounders (U), **violates unconfoundedness,** i.e. conditioning on X alone, would not results in a randomised treatment assignment

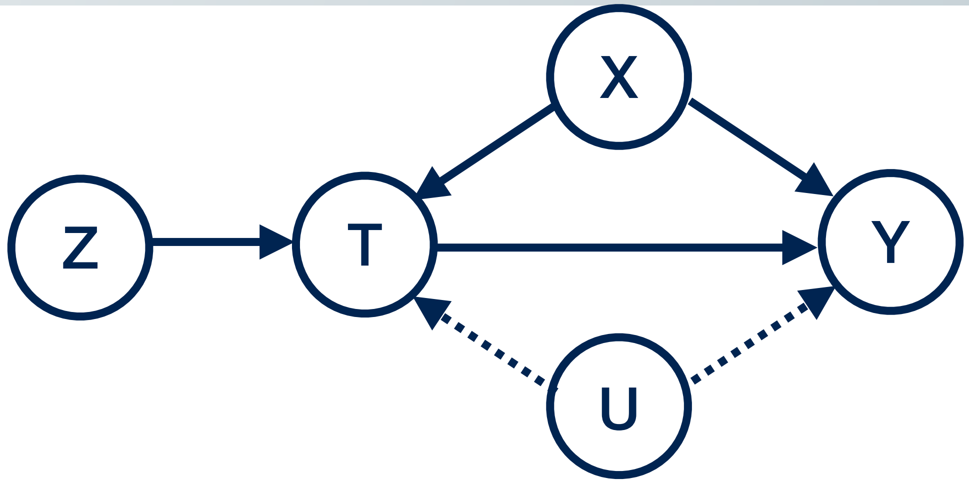
- Unconfoundedness is fundamentally unverifiable




Rubin 1996

# Instrumental Variable example

- Example 1:
  - T: smoking during pregnancy
  - Y: birthweight
  - X: parity, mother's age, weight, …
  - U: Other unmeasured confounders




- Randomise Z (intention-to-treat): either receive encouragement to stop smoking (Z=1), or receive usual care (Z=0)
- Intention-to-treat analysis gives causal effect estimator of encouragement z on outcome y:

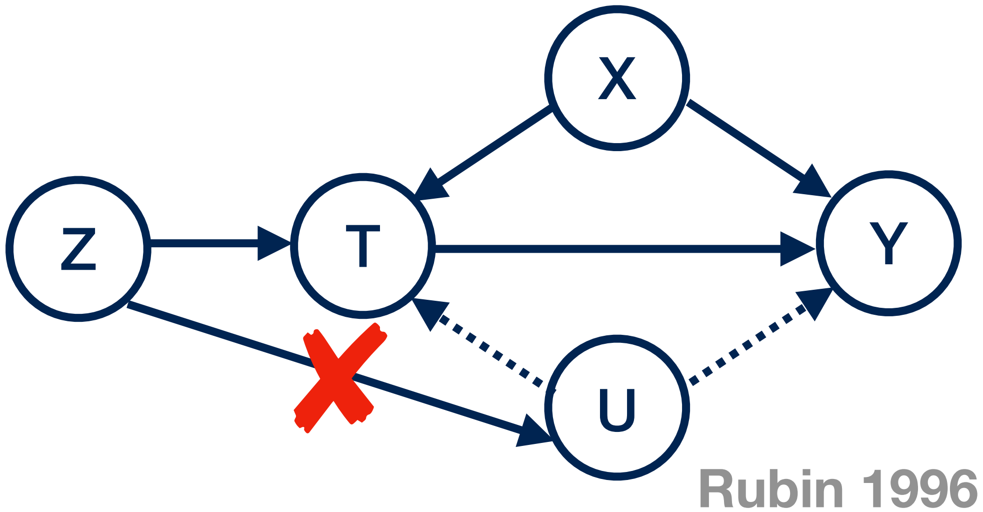
$$\mathbb{E}(y|z=1) - \mathbb{E}(y|z=0)$$

- What can we say about the causal effect of smoking itself?

# Instrumental Variable assumptions

- **SUTVA**: Potential outcomes for each individual i are unrelated to the treatment status of other individuals:

$$Y^{(i)}(\mathbf{Z}, \mathbf{T}) = Y^{(i)}(Z^{(i)}, T^{(i)}) \ , \ |\mathbf{Z}| = |\mathbf{T}| = N \text{ individuals}$$




Rubin 1996

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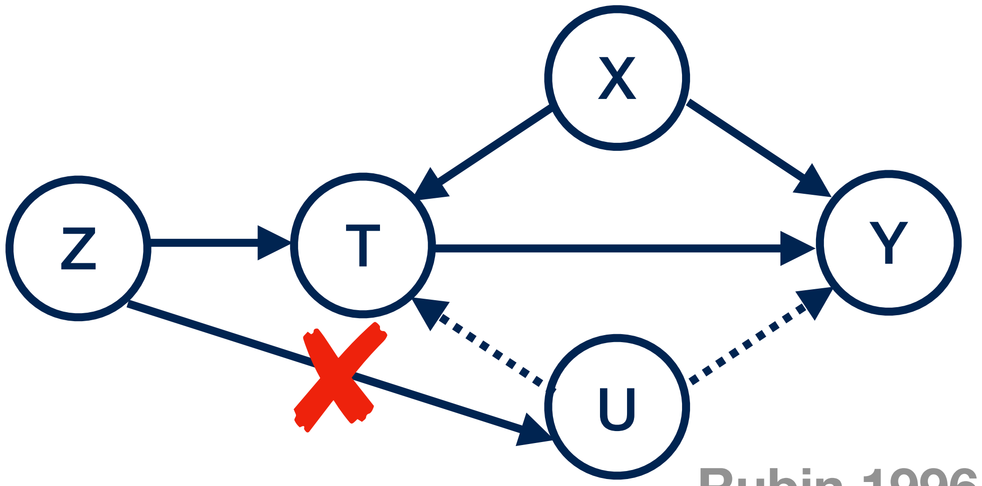
- Treatment assignment Z (**associated** with the treatment) is **random**:

$$P(Z^{(i)} = 0) = P(Z^{(i)} = 1) \ , \ \forall i$$

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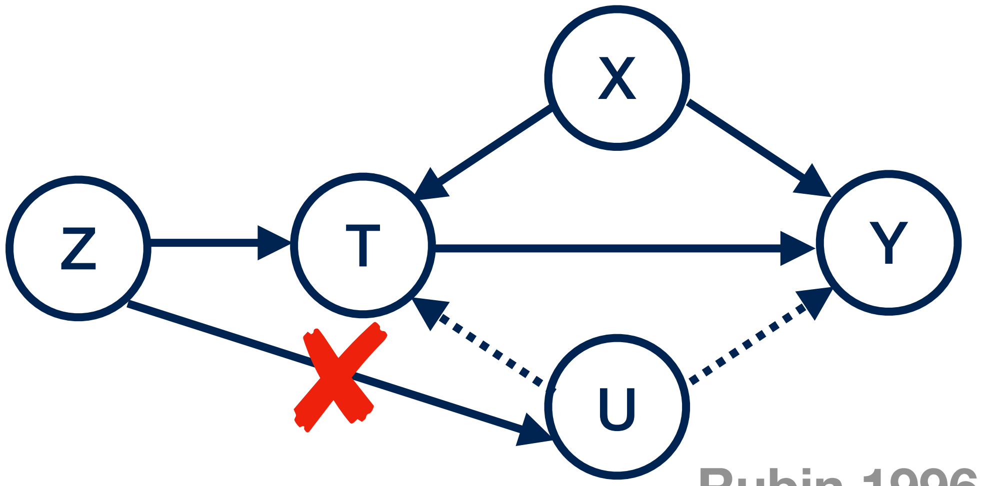
- **Exclusion Restriction**: Any effect of Z on Y is via an effect of Z on T, i.e., Z should not affect Y when T is held constant $\left(Y^{(i)}|z = 1, t\right) = \left(Y^{(i)}|z = 0, t\right)$

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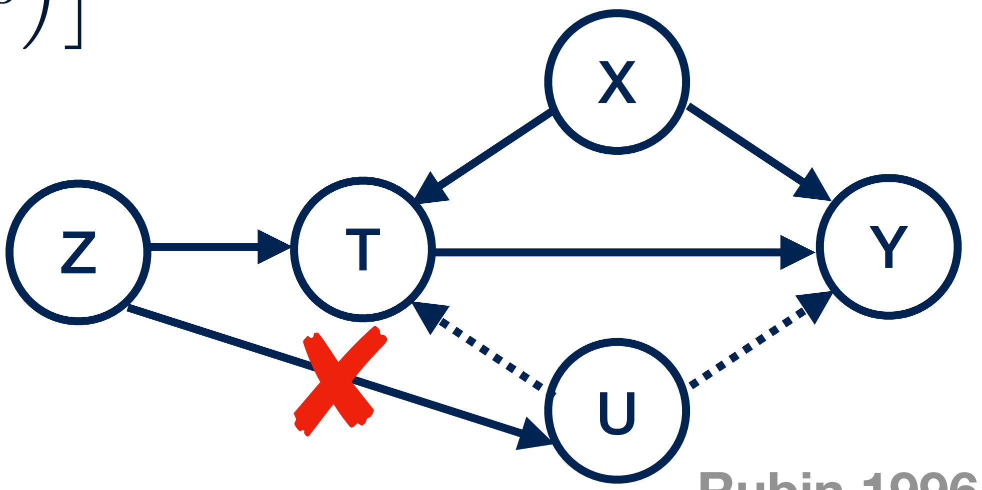
- **Non-zero Average:** $\mathbb{E}\left[\left(T^{(i)}|z=1\right) - \left(T^{(i)}|z=0\right)\right]$




Rubin 1996

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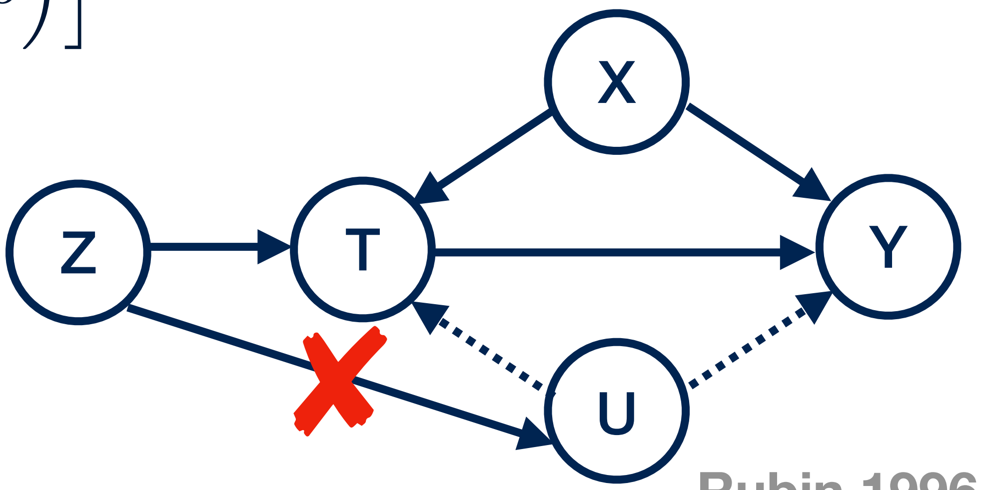
- **Non-zero Average:** $\mathbb{E}\left[\left(T^{(i)}|z=1\right) - \left(T^{(i)}|z=0\right)\right]$

- **Monotonicity** (increasing encouragement "dose" increases probability of treatment, no defiers)**:**

$$\left(T^{(i)}|z=1\right) \geq \left(T^{(i)}|z=0\right)$$




Rubin 1996

# Instrumental Variable: Potential values of T

| Population | T\|z=0 | T\|z=1 | Description |
|---|---|---|---|
| Never-takers | 0 | 0 | Causal effect of Z on T is zero, since $\left(T^{(i)}\|z=1\right)-\left(T^{(i)}\|z=0\right)=0$ |
| Compliers | 0 | 1 | $\left(T^{(i)}\|z=1\right)-\left(T^{(i)}\|z=0\right)=1$ Treatment received is randomised **causal effect inference**: $\left(Y^{(i)}\|T^{(i)}=1\right)-\left(Y^{(i)}\|T^{(i)}=0\right)$ |
| Defiers | 1 | 0 | Rule out by **monotonicity**, since $\left(T^{(i)}\|z=1\right)-\left(T^{(i)}\|z=0\right)=-1$ |
| Always-takers | 1 | 1 | Causal effect of Z on Y is zero, since $\left(T^{(i)}\|z=1\right)-\left(T^{(i)}\|z=0\right)=0$ |

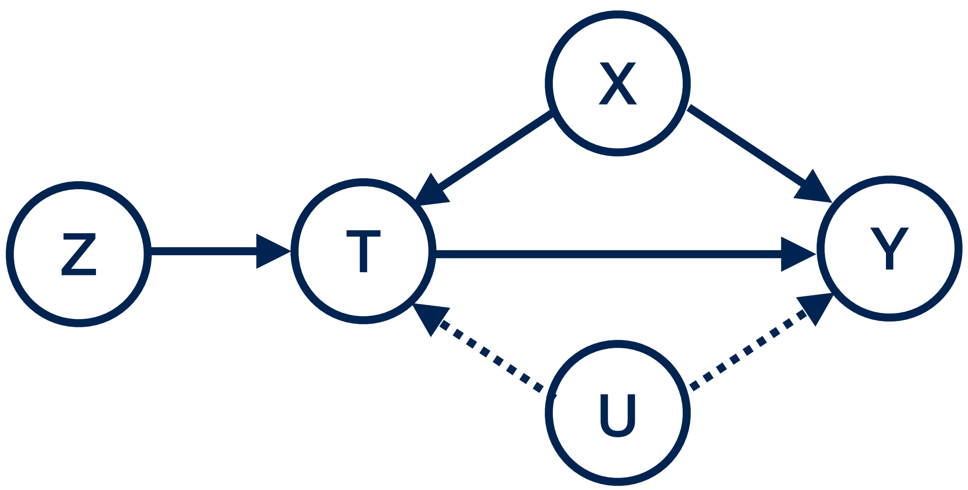
**Notation: T=1 is not smoking**

Rubin 1996

# Instrumental Variable: The estimand

**Want ATE:**

$$\mathbb{E}\left[\left(Y^{(i)}|t^{(i)}=1\right)-\left(Y^{(i)}|t^{(i)}=0\right)\right]$$




**"Almost"**

**Will estimate:**

$$\hat{\tau}=\frac{\mathbb{E}\left[\left(Y^{(i)}|z=1\right)-\left(Y^{(i)}|z=0\right)\right]}{\mathbb{E}\left[\left(T^{(i)}|z=1\right)-\left(T^{(i)}|z=0\right)\right]}$$

Rubin 1996

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**Derivation:**

$$\left(Y^{(i)}|T^{(i)}(z=1)\right)-\left(Y^{(i)}|T^{(i)}(z=0)\right)$$

t is either t=0 or t=1, and exclusion restriction

$$=\left[Y^{(i)}\left(t^{(i)}=1\right)\cdot\left(t^{(i)}|z=1\right)+Y^{(i)}\left(t^{(i)}=0\right)\cdot\left(1-\left(t^{(i)}|z=1\right)\right)\right]$$

$$-\left[Y^{(i)}\left(t^{(i)}=1\right)\cdot\left(t^{(i)}|z=0\right)+Y^{(i)}\left(t^{(i)}=0\right)\cdot\left(1-\left(t^{(i)}|z=0\right)\right)\right]$$

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Hence, the causal effect of Z on Y for individual i, is the product of the causal effect of Z on T, and, the casual effect of T on Y.

Rubin 1996

# Instrumental Variable: The estimand

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Rubin 1996

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Rubin 1996

# Instrumental Variable: The estimand

To continue the derivation, we use the fact that:

$$\mathbb{E}[XY] = \int\int xy\ p(x,y)dxdy = \int dy\ y\ p(y)\int dx\ x\ p(x|y) = \int dy\ y\ p(y)\mathbb{E}[x|y]$$

and write,

$$\mathbb{E}\left[\left(Y^{(i)}|T^{(i)}(z=1)\right) - \left(Y^{(i)}|T^{(i)}(z=0)\right)\right]$$

$$= \mathbb{E}\left[\left(Y^{(i)}\left(t^{(i)}=1\right) - Y^{(i)}\left(t^{(i)}=0\right)\right)\cdot\left(\left(t^{(i)}|z=1\right) - \left(t^{(i)}|z=0\right)\right)\right]$$

→ 0, 1, -1

Rubin 1996

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$$= \mathbb{E}\left[\left(Y^{(i)}\left(t^{(i)}=1\right) - Y^{(i)}\left(t^{(i)}=0\right)\right) | \left(\left(t^{(i)}|z=1\right) - \left(t^{(i)}|z=0\right)\right) = 1\right] \cdot$$

$$P\left(\left(t^{(i)}|z=1\right) - \left(t^{(i)}|z=0\right) = 1\right)$$

$$-\mathbb{E}\left[\left(Y^{(i)}\left(t^{(i)}=1\right) - Y^{(i)}\left(t^{(i)}=0\right)\right) | \left(\left(t^{(i)}|z=1\right) - \left(t^{(i)}|z=0\right)\right) = -1\right] \cdot$$

$$P\left(\left(t^{(i)}|z=1\right) - \left(t^{(i)}|z=0\right) = -1\right)$$

0, by monotonicity

Rubin 1996

# Instrumental Variable: The estimand

$$\frac{\mathbb{E}\left[\left(Y^{(i)}|T^{(i)}(z=1)\right)-\left(Y^{(i)}|T^{(i)}(z=0)\right)\right]}{\mathbb{E}\left[\left(t^{(i)}|z=1\right)-\left(t^{(i)}|z=0\right)\right]}$$

$$=\mathbb{E}\left[\left(Y^{(i)}\left(t^{(i)}=1\right)-Y^{(i)}\left(t^{(i)}=0\right)\right)\Big|\left(\left(t^{(i)}|z=1\right)-\left(t^{(i)}|z=0\right)\right)=1\right]$$

i.e. restricting to *compliers*, the average casual effect of Z on Y is proportional to the average causal effect of T on Y.

Rubin 1996

$$\hat{\tau}=\frac{\mathbb{E}\left[\left(Y^{(i)}|z=1\right)-\left(Y^{(i)}|z=0\right)\right]}{\mathbb{E}\left[\left(T^{(i)}|z=1\right)-\left(T^{(i)}|z=0\right)\right]}$$

- In this example, Z was randomly assigned as part of the study
- IV can also be randomised in nature (nature randomiser):
  - Mendelian randomisation
  - Quarter of birth (T=education, Y=earning)

## **Pearl's framework**

Graphical models & Do-calculus

# Causal Inference

- **Model** a causal inference problem with assumptions manifest in Causal Graphical Models **[Pearl]**
- **Identify** an expression for the causal effect under these assumptions ("causal estimand"), [**Pearl**]
- **Estimate** the expression using statistical methods such as matching or instrumental variables, [**Rubin**'s Potential Outcomes]
- **Verify** the validity of the estimate using a variety of robustness checks.

# Pearl’s Model of Causality

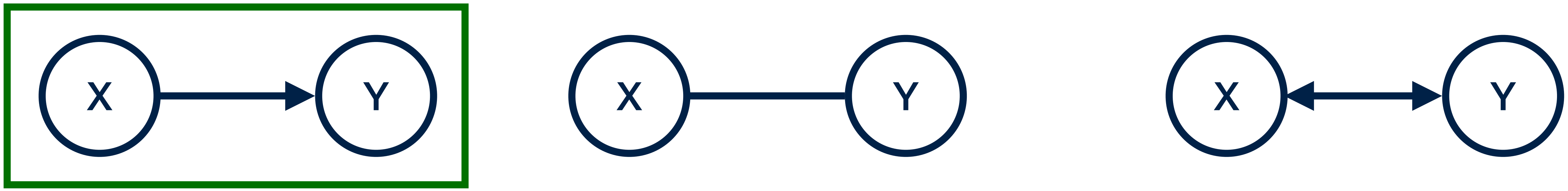
- Ladder of causation:
  - **Association:** What does a symptom tell me about a disease?
  - **Intervention (perturbation):** If I take aspirin will my headache be cured?
  - **Counterfactual:** Was it the aspirin that stopped the headache? (alternative versions of past events, strongest causal statements e.g. **physical laws**)

- Aim: To **model** and **identify** the causal estimand

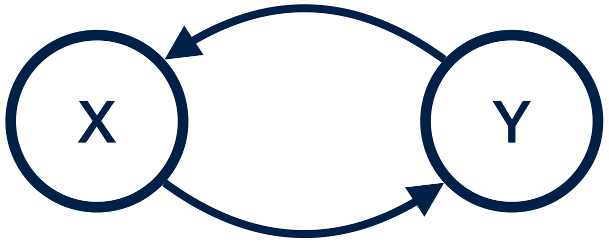
- Causal graphical models + structural equations

# Causal Graphical Models

- Diagrammatic representation of probability distributions + **causal info**
- **Graph:** Consists of a set of **vertices** V (nodes), **edges** E
- V are the variables and E contains information between the variables
- Graphs can be directed, undirected and bidirectional (confounder?)



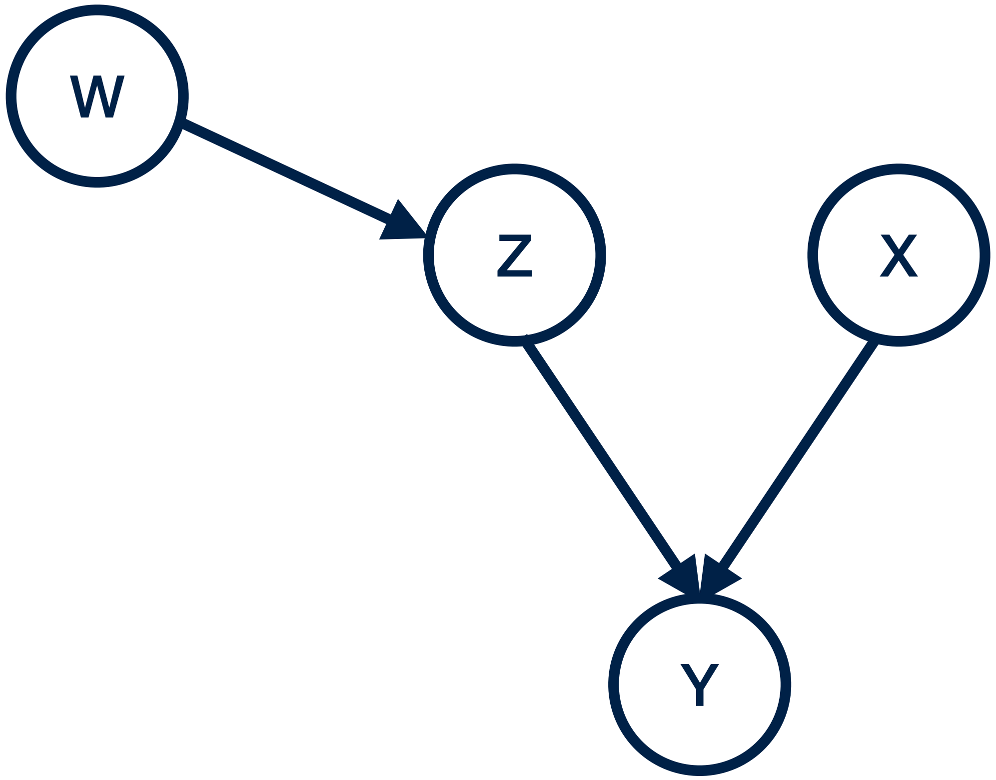

- Directed graphs may include directed cycles, i.e., mutual causation/feed-back process.




- A graph with no directed cycles is an **acyclic** graph.

Causality, Pearl (2009)

# Directed Acyclic Graphs (DAGs)



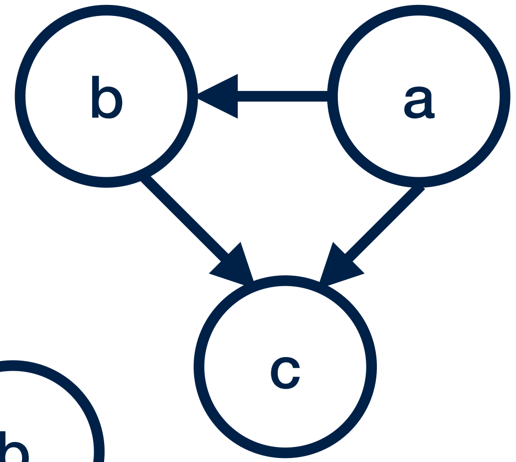

Z, X are parents of Y
Z, X, W are ancestors of Y
Y has no children
X has no parents

- DAG in which every node has at most one parent is a **tree**
- A tree in which every node has at most one child is a **chain**
- **DAG:**
    - Expresses **model assumptions** explicitly
    - Represents **joint probability** functions
    - Provides **efficient inference** of observations

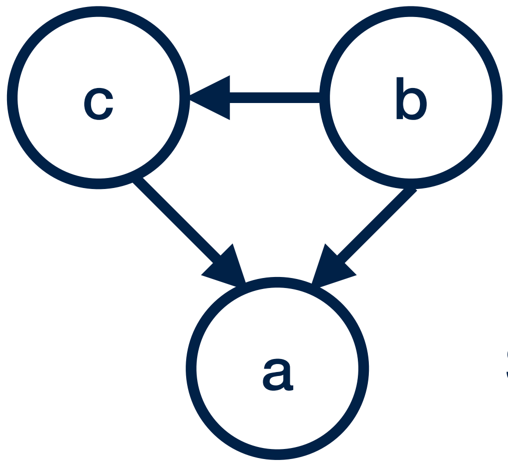
Causality, Pearl (2009)

# DAG contains more info than joint probability

$$p(a,b,c) = p(c|a,b)p(a,b) = p(c|a,b)p(b|a)p(a)$$




$$p(a,b,c) = p(a|b,c)p(b,c) = p(a|b,c)p(c|b)p(b)$$




**Symmetric in a, b, c**

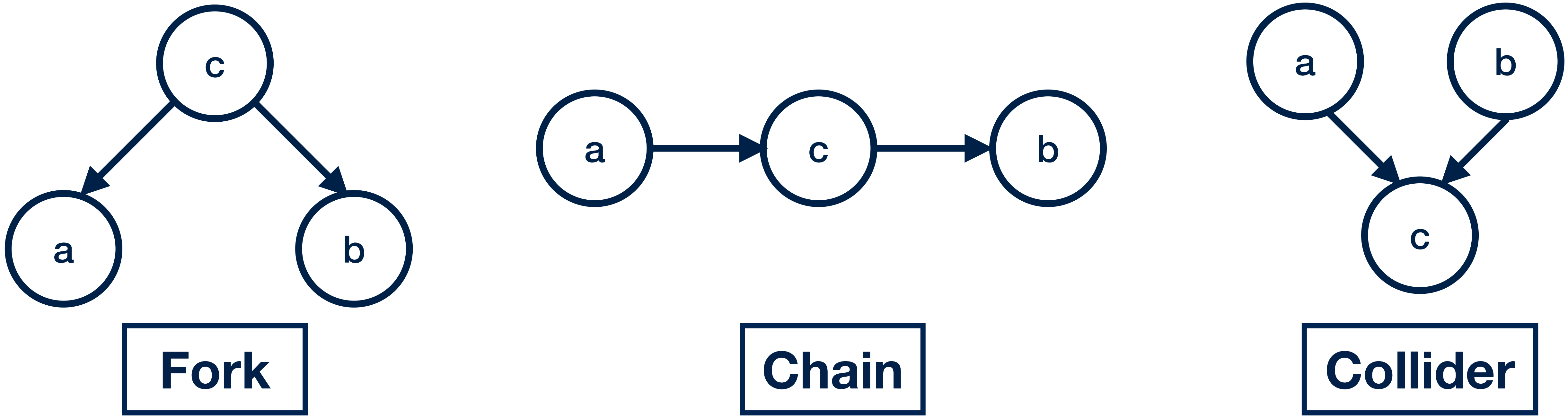
**NOT symmetric**

- Probabilistic notations are not enough to describe causal aspects
- Using repeated application of Bayes' rule, one can write any joint probability distribution in terms of its marginals and conditionals
- A graph is **fully connected** if there is a link between every pair of nodes
- The interest lies in the **absence** of a link and link **direction**.

Bishop, Pattern Recognition and Machine Learning, Chapter 8

# Basic DAG structures:

- Conditional independence via graphs and **D-separation**
- 3 main graph structures:




- Next Lecture: **Do-calculus** and **causal identification**

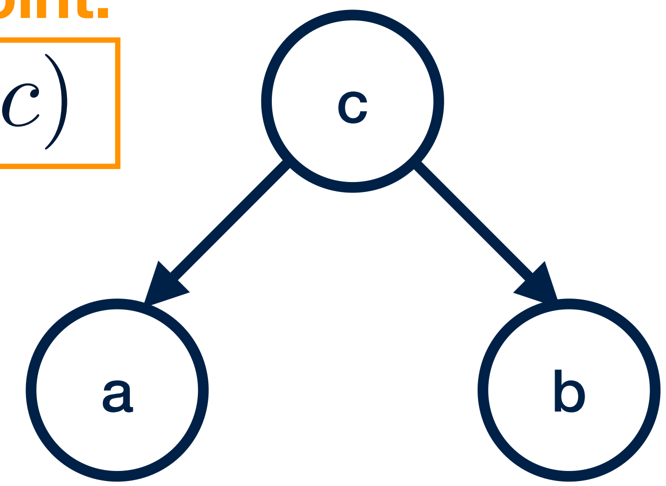
Pearl, Causality (2009)

# Fork

$$p(a, b, c) = p(a|c)p(b|c)p(c)$$

In contrast to the full joint:

$$p(a|b, c)p(b|c)p(c)$$




Fork

**Case 1: No conditioning**

$$p(a, b) = \sum_c p(a, b, c) = \sum_c p(a|c)p(b|c)p(c) \neq p(a)p(b) \text{ in general}$$

$$\Rightarrow a \not\perp\!\!\!\perp b | \emptyset$$

**Case 2: Conditioning on c**

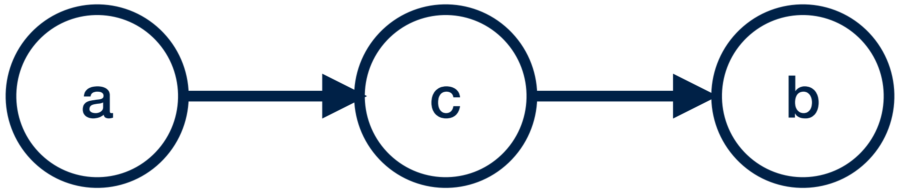
$$p(a, b|c) = \frac{p(a, b, c)}{p(c)} = \frac{p(a|c)p(b|c)p(c)}{p(c)} = p(a|c)p(b|c)$$

$$\Rightarrow a \perp\!\!\!\perp b | c$$

**c blocks (d-separates) the path from a to b**

# Chain

$$p(a,b,c) = p(a)p(c|a)p(b|c)$$




**Chain**

**Case 1: No conditioning**

$$p(a,b) = \sum_c p(a)p(c|a)p(b|c) = p(a)\sum_c p(b|c)p(c|a) = p(a)p(b|a) \neq p(a)p(b)$$

$$\Rightarrow a \not\perp\!\!\!\perp b | \emptyset$$

**Case 2: Conditioning on c**

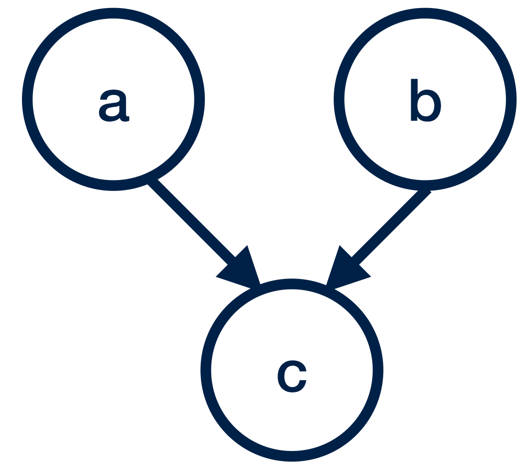
$$p(a,b|c) = \frac{p(a,b,c)}{p(c)} = \frac{p(a)p(c|a)p(b|c)}{p(c)} = \frac{p(a)p(b|c)}{p(c)}\frac{p(a|c)p(c)}{p(a)} = p(a|c)p(b|c)$$

$$\Rightarrow a \perp\!\!\!\perp b | c$$

**c blocks (d-separates) the path from a to b**

# Collider

$$p(a,b,c) = p(a)p(b)p(c|a,b)$$




**Case 1: No conditioning**

$$p(a,b) = \sum_c p(a)p(b)p(c|a,b) = p(a)p(b)\sum_c p(c|a,b) = p(a)p(b)$$

**Collider**

$\Rightarrow a \perp\!\!\!\perp b|\emptyset$ **with no conditioning, a and b are independent**

**Case 2: Conditioning on c**

$$p(a,b|c) = \frac{p(a,b,c)}{p(c)} = \frac{p(a)p(b)p(c|a,b)}{p(c)} \neq p(a|c)p(b|c) \text{ in general}$$

$\Rightarrow a \not\perp\!\!\!\perp b|c$ **c unblocks the path from a to b**

# Causality in Biomedicine Lecture Series: Lecture 3

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