THE UNIVERSITY of EDINBURGH

Methods for Causal Inference
Lecture 1: Introduction

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School of Informatics
2024-2025

References

- Causal Inference in Statistics: A Primer (Pearl, Glymour, Jewell, 2016)

- What If (Hernán and Robins, 2023)

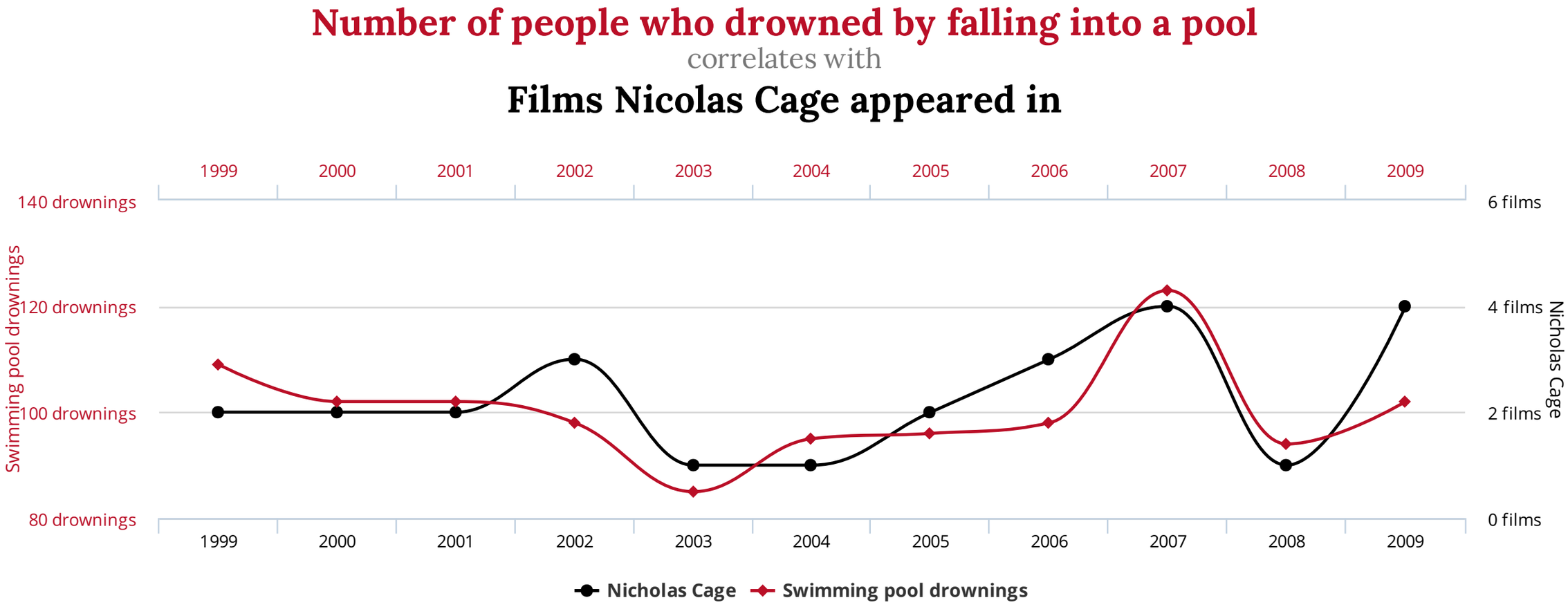
- Elements of Causal Inference: Foundations and Learning Algorithms (Peters, Janzing and Schölkopfk, 2018)

- Causality (Pearl, 2009)

- Many other papers from the literature … (will be referenced)

“Correlation does not imply causation”

Spurious correlation (random coincidence)



Correlation: 66.6%
(r=0.666)

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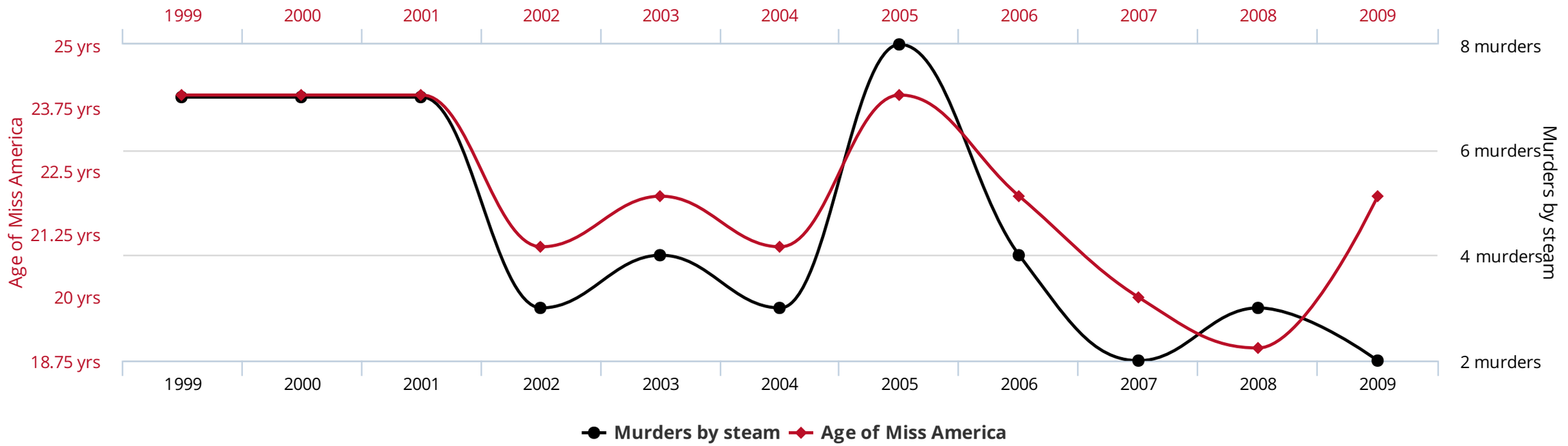
Spurious correlation (random coincidence)

Age of Miss America
correlates with
Murders by steam, hot vapours and hot objects



tylervigen.com

Correlation: 87.01%
(r=0.8701)

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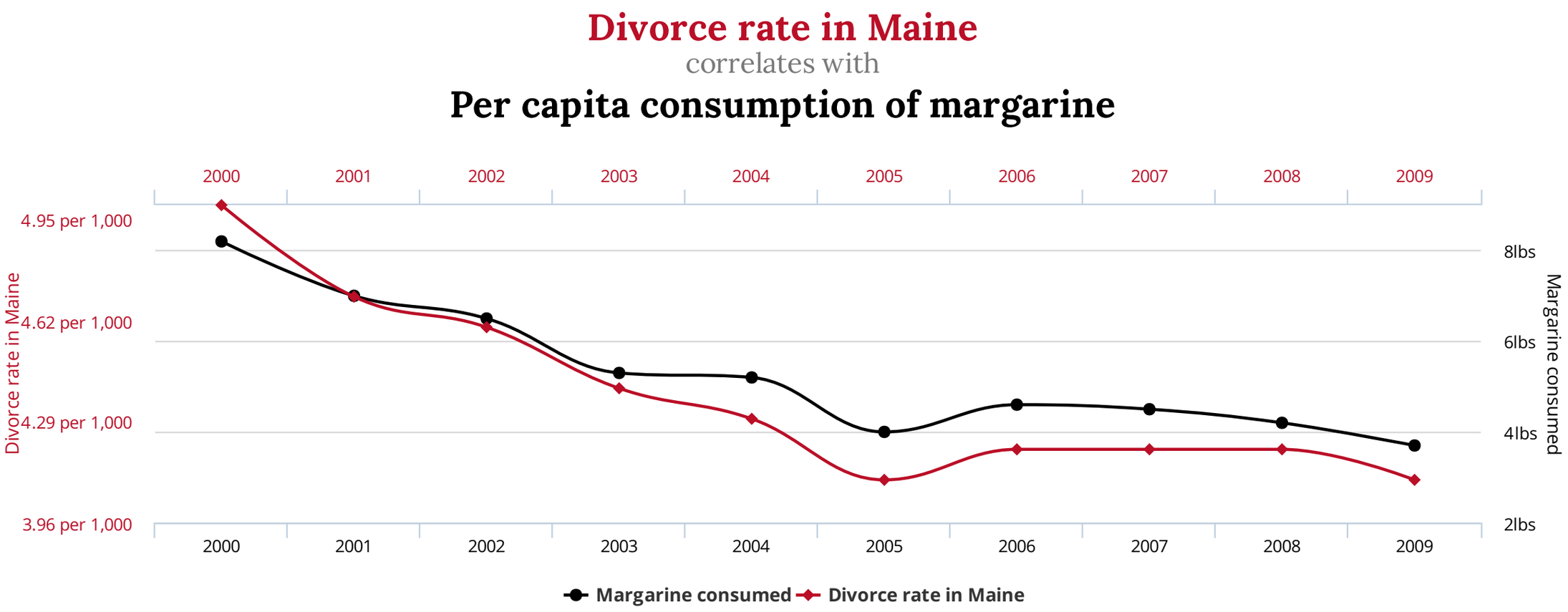
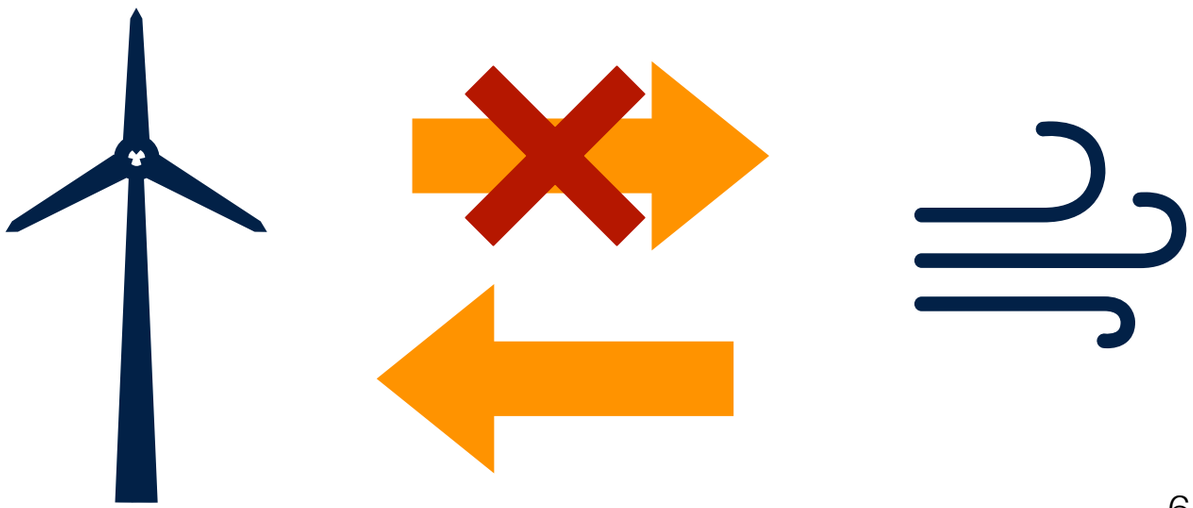


Correlation: 99.26%
(r=0.9926)

“Correlation does not imply causation”

Reverse causation:

The faster the wind-turbine rotates, the more wind is observed.
Therefore, rotation of turbines is the cause for winds!



“Correlation does not imply causation”

Circular/bidirectional cause and consequence:

Hours spent on Netflix and weight gain

<u>Scenario 1:</u>

Hours spent on Netflix → Less activity → increase in weight

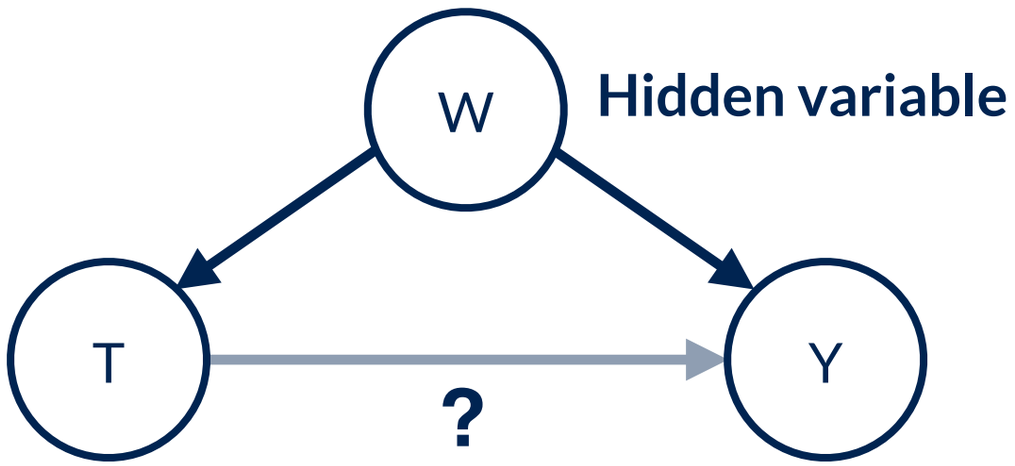
<u>Scenario 2:</u>

Weight gain → exercising gets harder → more time online as hobby

“Correlation does not imply causation”

Confounding factor:
Fever is not a cause of sneezing, they are both symptoms of flu (no arrow)

Treatment & health outcome relationship confounded by age



Why should we care about causation?

- To guide **actions** and **policies**
- To understand *how* and *why* **interventions** affect outcomes
- **Predict** what would have happened under a different intervention: "What if I were to act differently?"

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- **Biomedical**: "Vaccines lead to autism" (no scientific evidence!)

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- **Political/Economical**: "increases in minimum wage, increases unemployment (people become lazy)"

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- **Education:** People with feature X are more likely to obtain an internship in tech

More examples: Personalised medicine

An individual is diagnosed with a particular disease

Baseline covariants (‘features’) are measured, e.g., age, sex, BMI, …

Question: What treatment (A or B) is best for this individual?
What is the causal effect of A or B on the individual’s health outcome?

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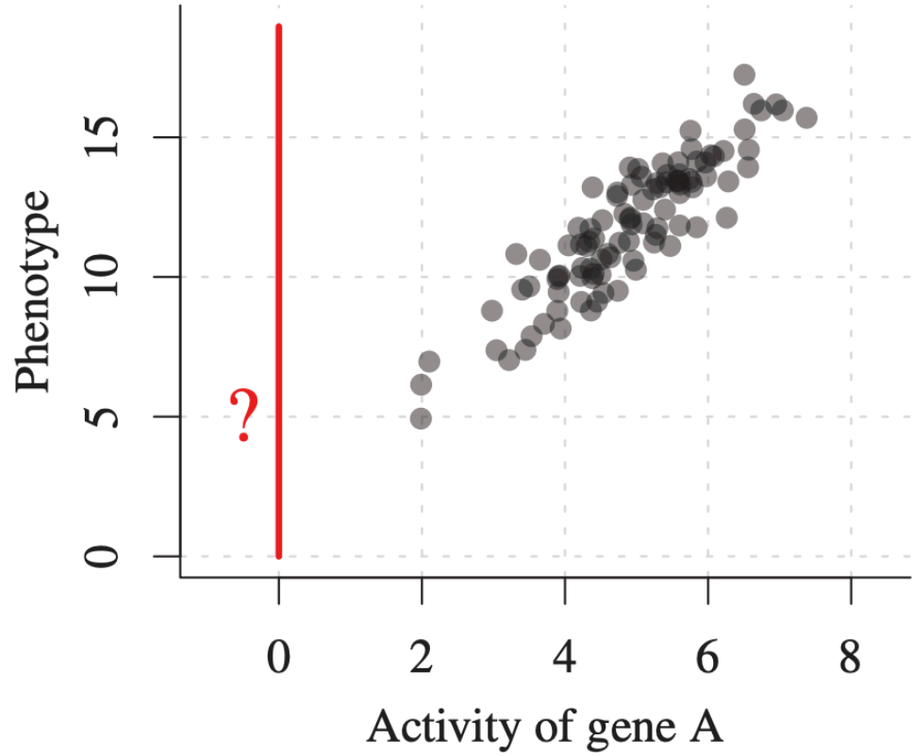
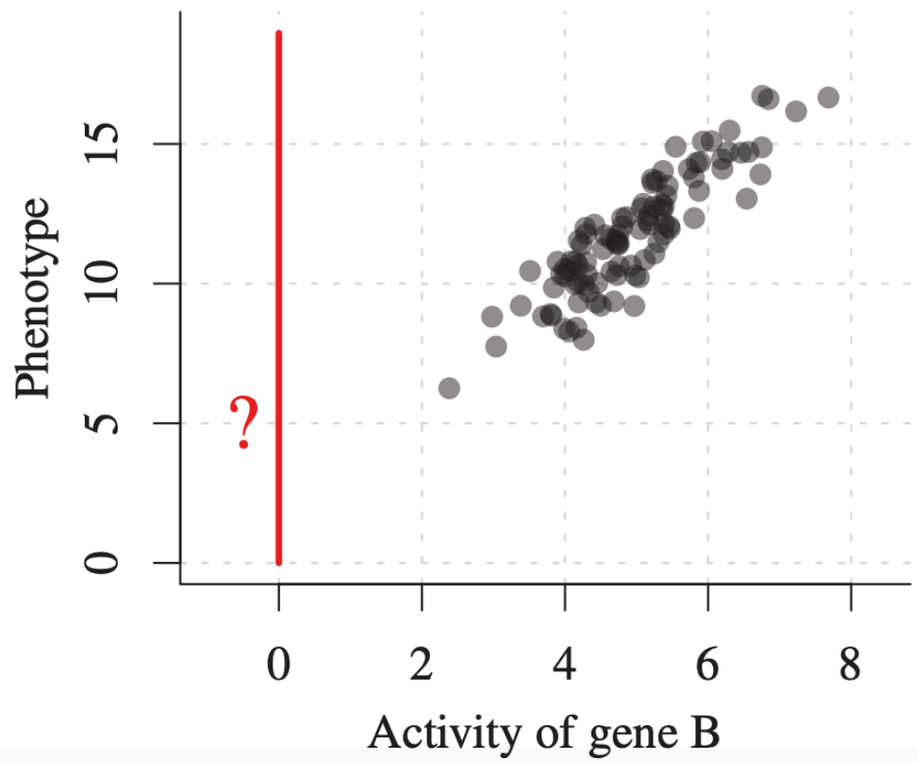
Ideally: We wish to design a policy that maps individual's:

Features → Best choice: A or B

Source of data: Biobanks (e.g. UK's Biobank, US's All-of-US, …) and electronic health records

More examples: Gene perturbation





Elements of Causal Inference, Peters et al.

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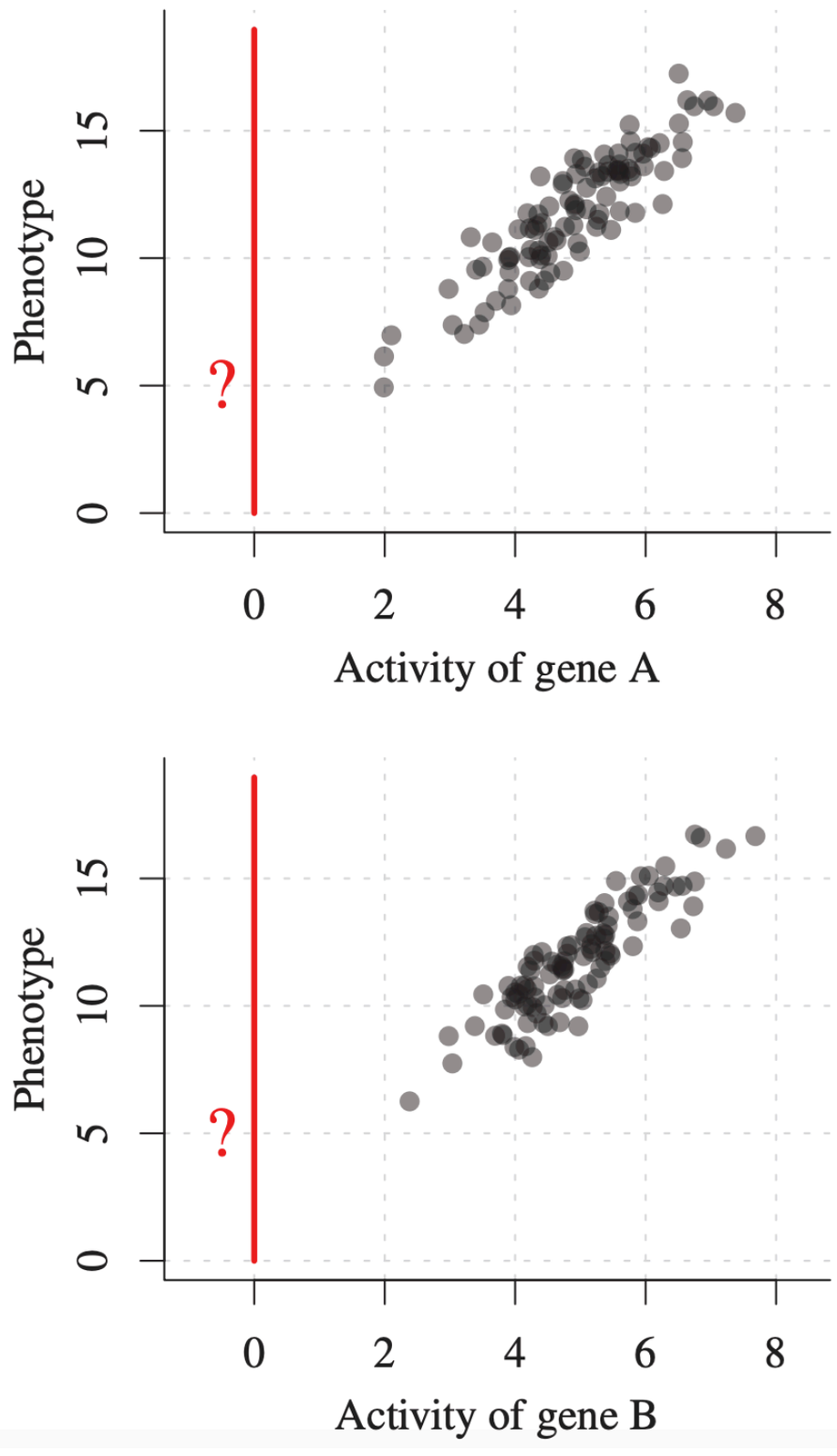
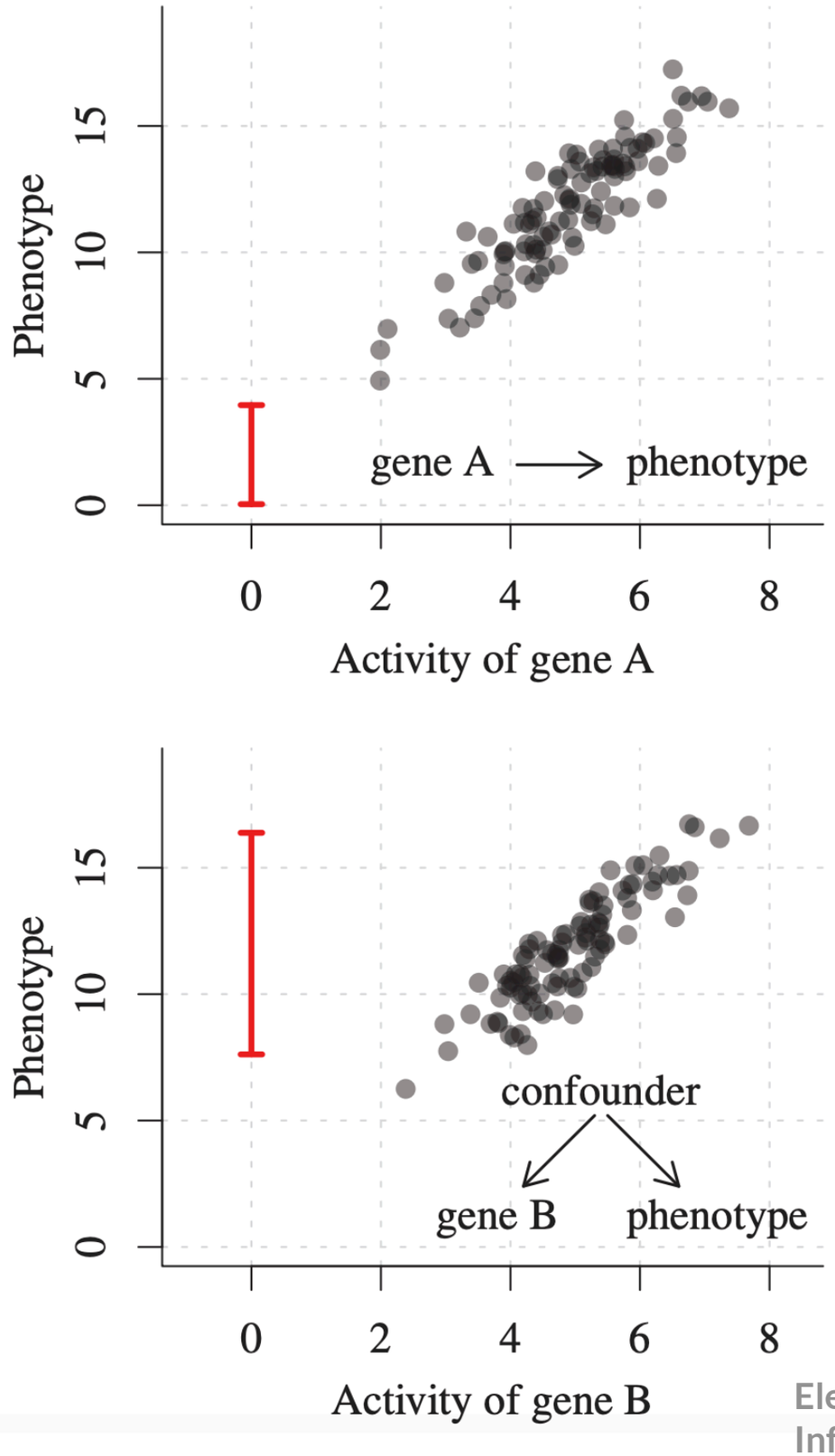
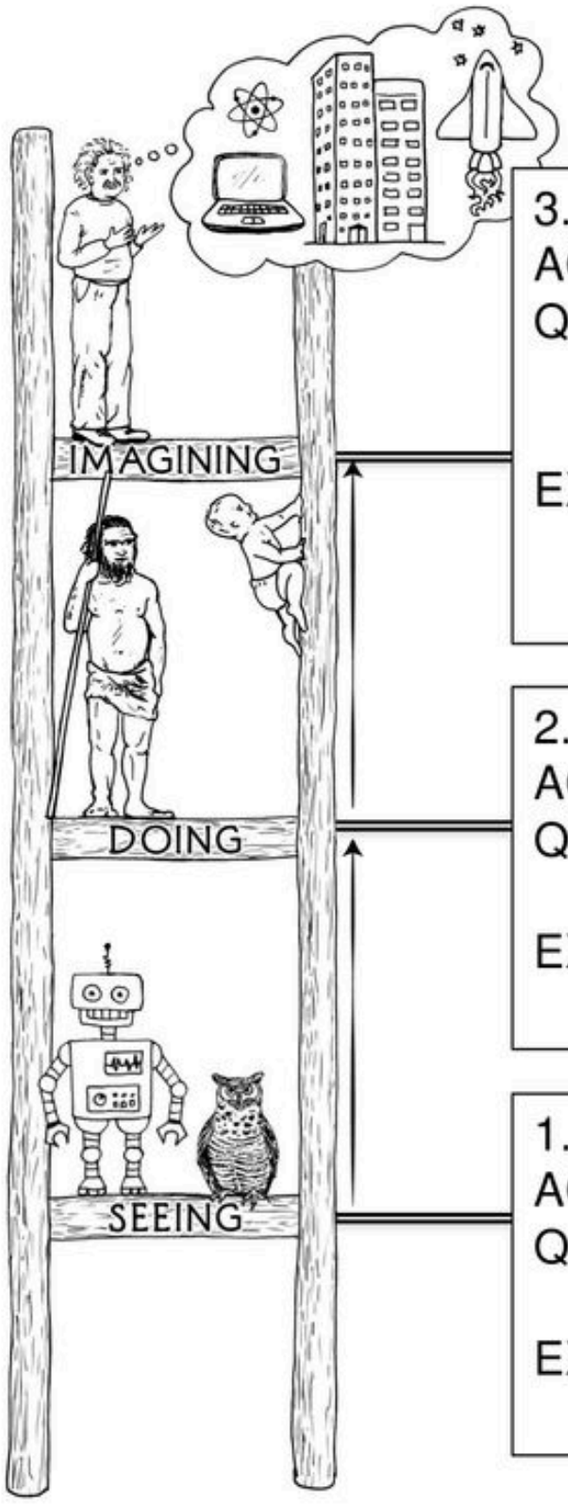




Pearl's ladder of causation



3-LEVEL HIERARCHY

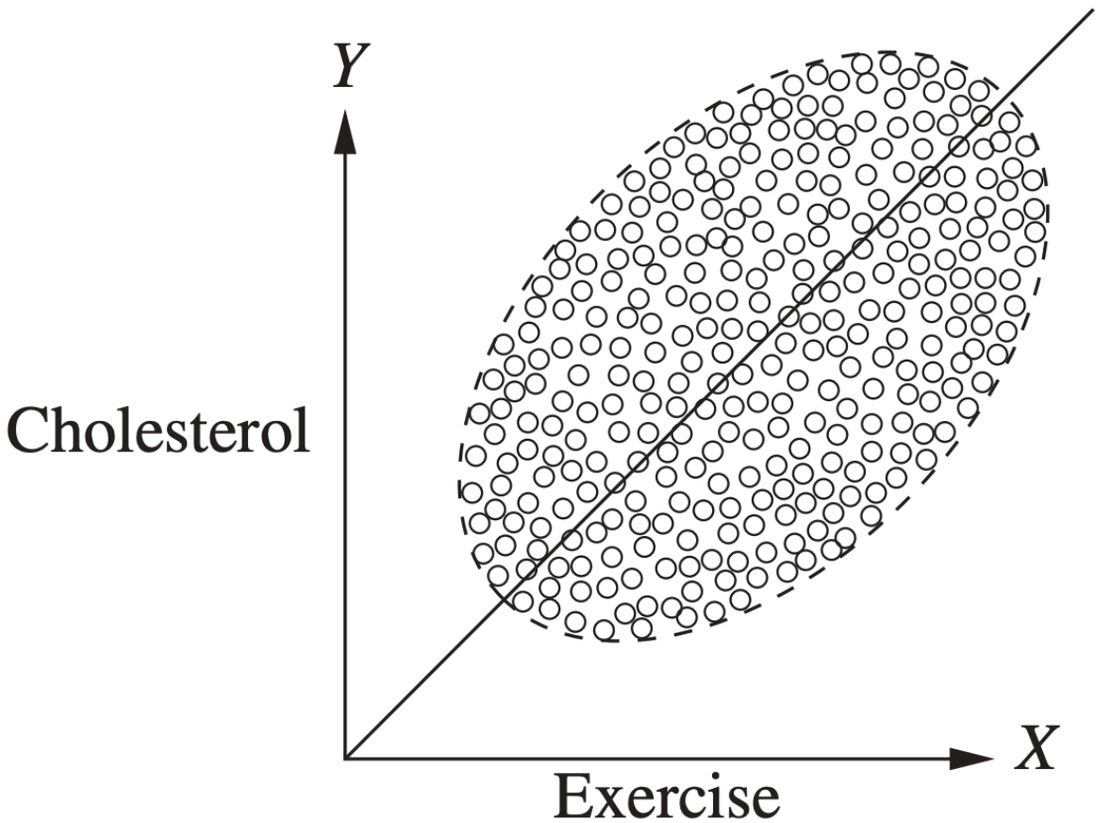
3. COUNTERFACTUALS
ACTIVITY: Imagining, Retrospection, Understanding
QUESTIONS: *What if I had done . . . ? Why?*
(Was it X that caused Y? What if X had not occurred? What if I had acted differently?)
EXAMPLES: Was it the aspirin that stopped my headache? Would Kennedy be alive if Oswald had not killed him? What if I had not smoked the last 2 years?

2. INTERVENTION
ACTIVITY: Doing, Intervening
QUESTIONS: *What if I do . . . ? How?*
(What would Y be if I do X?)
EXAMPLES: If I take aspirin, will my headache be cured? What if we ban cigarettes?

1. ASSOCIATION
ACTIVITY: Seeing, Observing
QUESTIONS: *What if I see . . . ?*
(How would seeing X change my belief in Y?)
EXAMPLES: What does a symptom tell me about a disease? What does a survey tell us about the election results?

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!"



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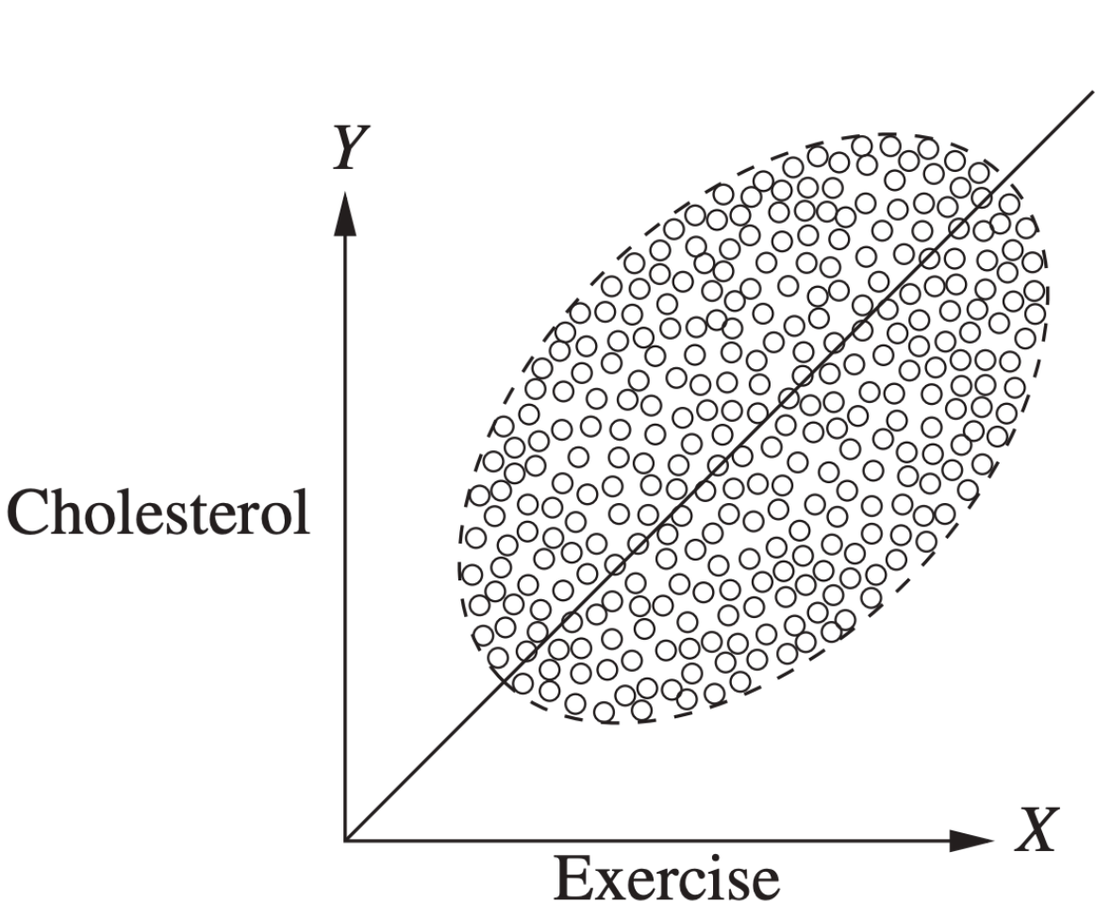
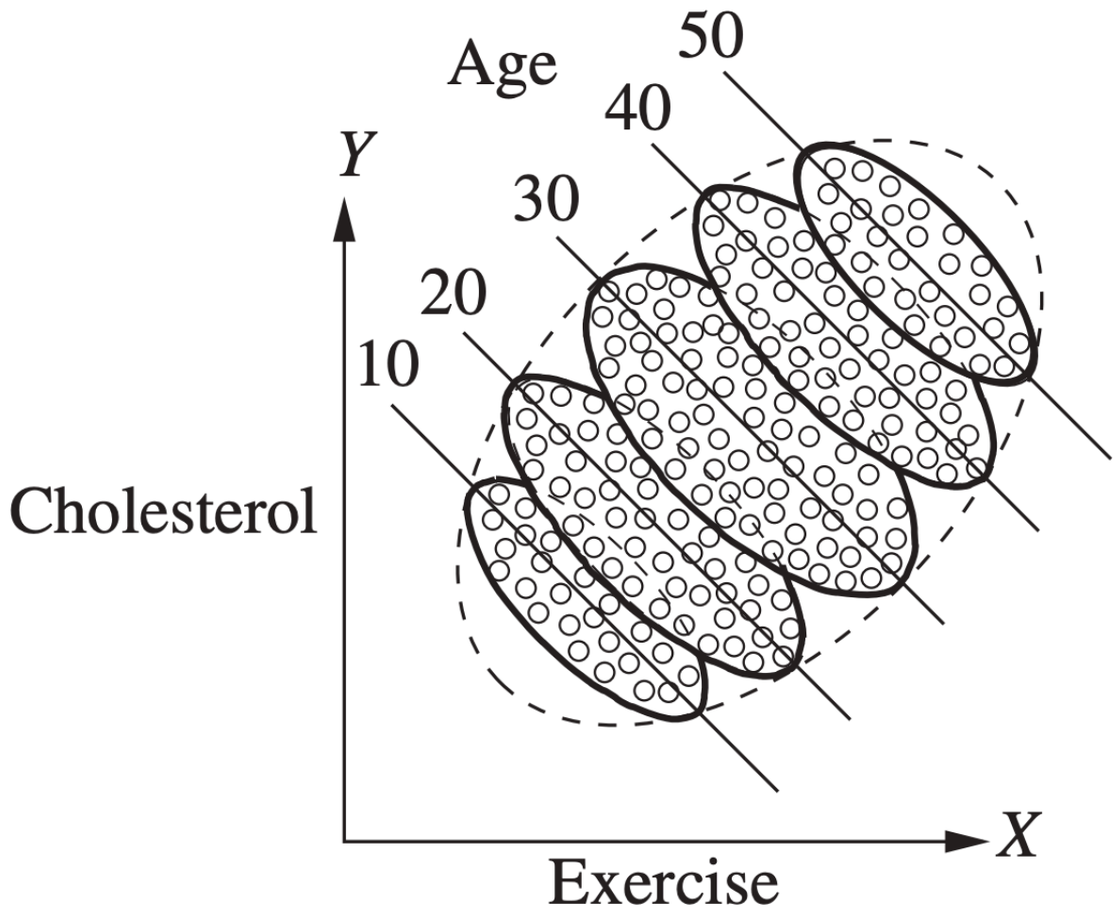




Language of causality and the roles of variables

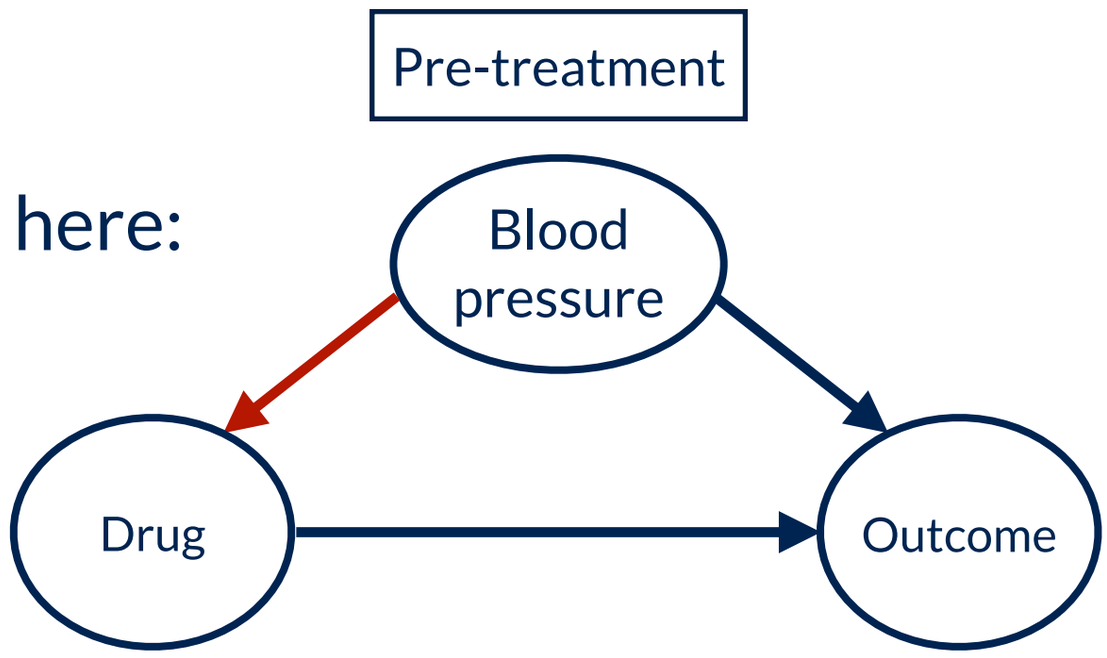
"What intervention", "how much", "when", "how often", "Control", "effect of", "why did", "what if", …

Causality language

Patient: Info on DNA variants and biomarkers, traits/disease, confounders
Clinician: Which medication, what dose, when, how often, …

Consider all variables affecting the system of interest and **the role each plays.**

Example, blood pressure is a **confounder** here:



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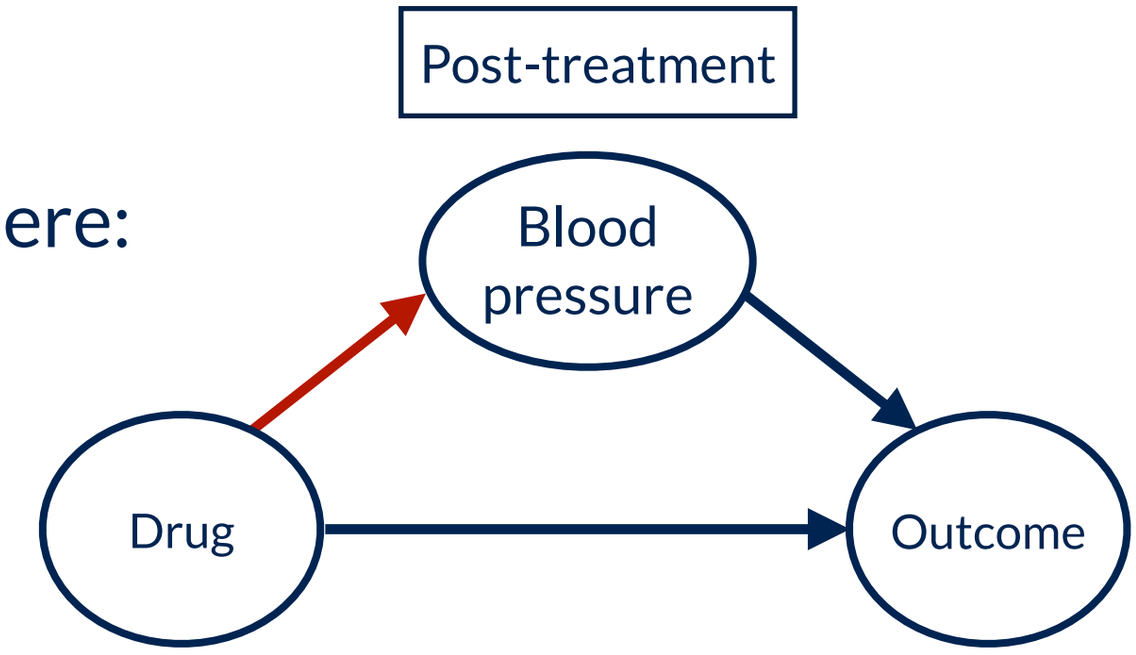

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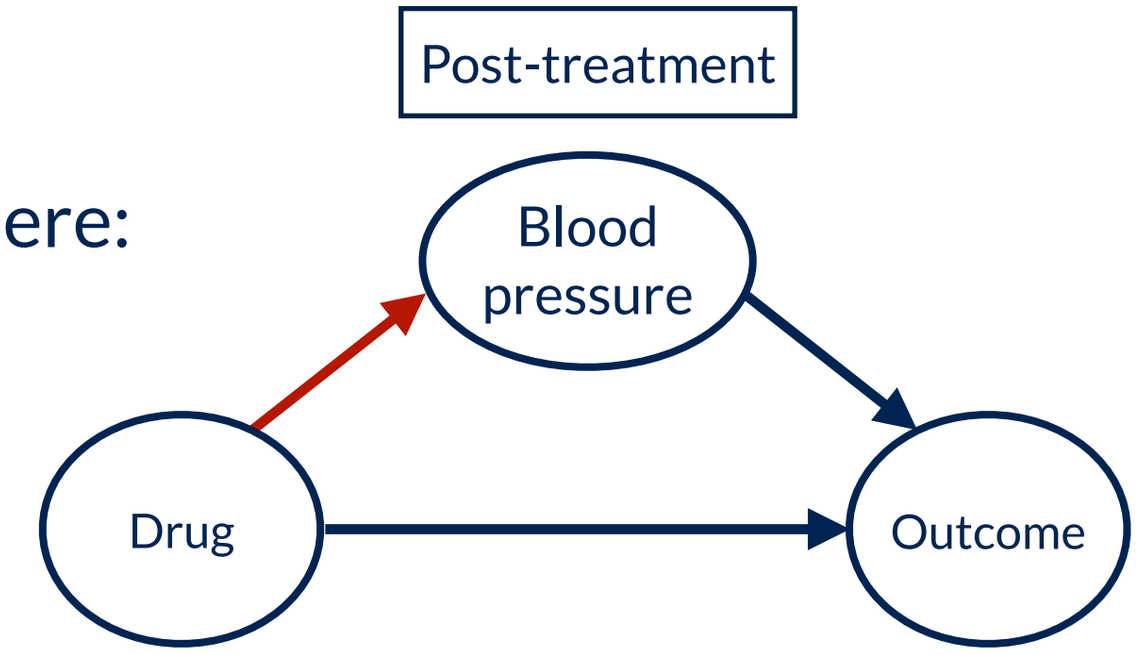
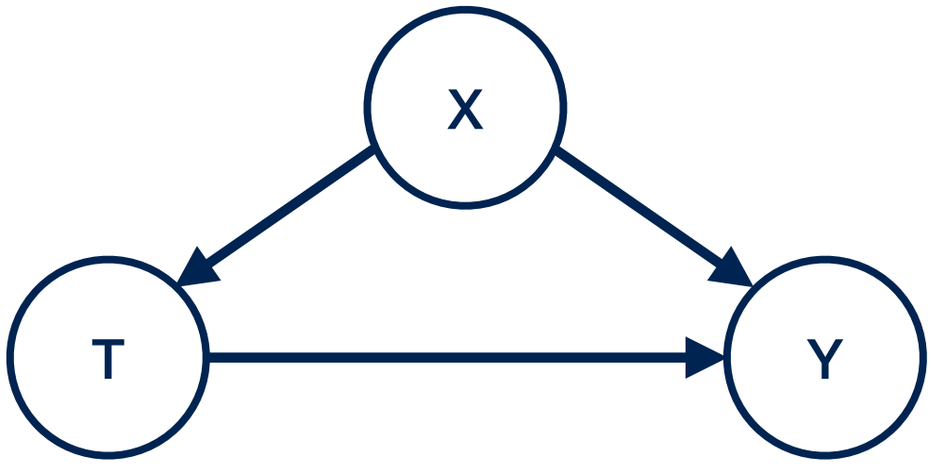
What happens when there are lots of variables?



Conventions

- Variable to be manipulated: **treatment (T)**, e.g. medication
- Variable we observe as response: **outcome (Y)**,
  e.g. success/failure of medication
- Other observable variables that can affect treatment and outcome causally and we wish to correct for: **confounders (X)**,
  e.g. age, sex, socio-economic status, …
- Unobservable confounder **(U)**



Causal effect estimation

Have a prior causal knowledge (may be incomplete) and know the treatment/outcome pair.
Counter example: weight gain, hours online

Interested in estimating the **effect size**:

$$\mathbb{E}\left[y_{t=1}(x) - y_{t=0}(x)\right] = \int \left(y_1(x) - y_0(x)\right) p(x) dx$$

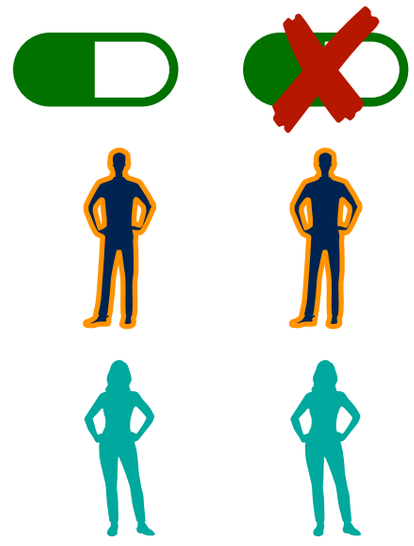
Note: The features/confounders x for both treatment and control groups are drawn from the **same** distribution $p(x)$

Goal: Find an **unbiased estimator**, e.g. signal/noise ratio

Randomised experiments: Already in causal framework

In a **randomised experiment**, the distribution of the confounders p(x) is designed to be the same for both treatment groups (t=0 or t=1)

Paired '**clones**' in treatment and outcome groups



Simply take the difference of the averages:

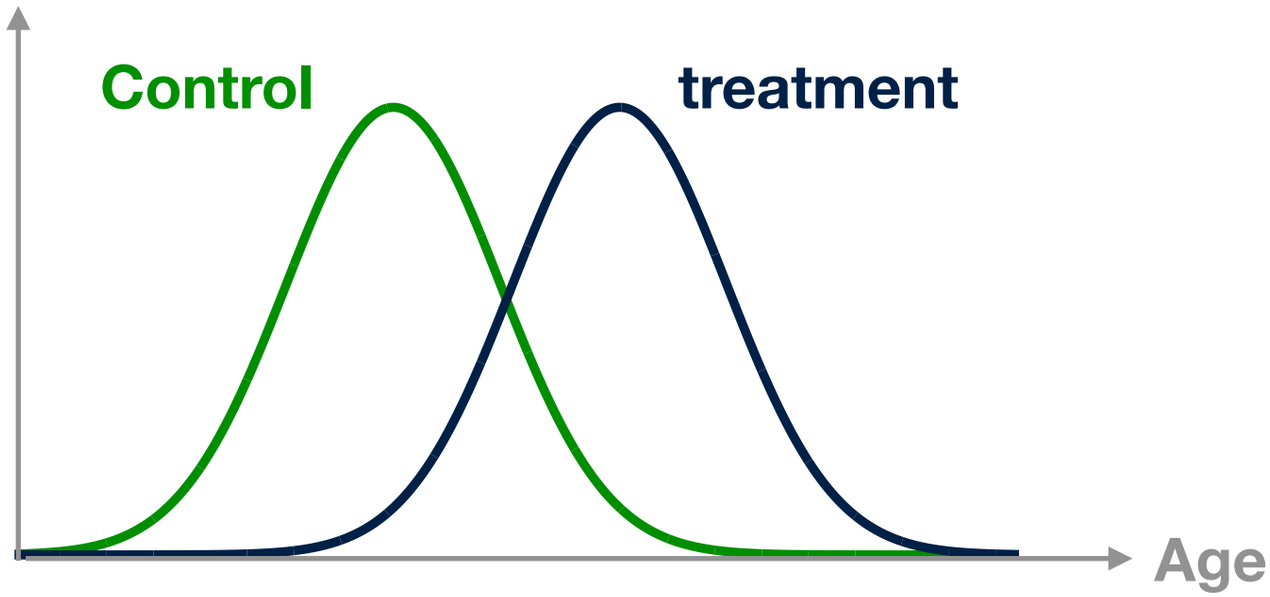
$$\Delta\hat{\mu} = \hat{\mathbb{E}}\left[y_{t=1}(x) - y_{t=0}(x)\right] = \frac{1}{N}\sum_{i=1}^{N}\left(y_1^{(i)}(x) - y_0^{(i)}(x)\right)$$

Perform statistical test: e.g. T-test and p-values …

$$\frac{\Delta\hat{\mu}}{\sqrt{\frac{(\hat{\sigma}_{\Delta\mu})^2}{N}}} > t^*$$

Observational data: What goes wrong?

$$p(x|t=1) \neq p(x|t=0)$$



$$\left(\int y_1(x)p(x|t=1)dx \; - \int y_0(x)p(x|t=0)dx\right) \neq \int \big(y_1(x) - y_0(x)\big)p(x)dx$$

Observational data: Stratification

- Measure outcome (success/failure), **within** each of the young/old groups **separately**
- Take weighted average by the probability of being young/old:

$$\mathbb{E}(\text{Healed}|t=1) = \mathbb{E}(\text{Healed}|t=1,\text{young})p(\text{young}) + \mathbb{E}(\text{Healed}|t=1,\text{old})p(\text{old})$$

vs

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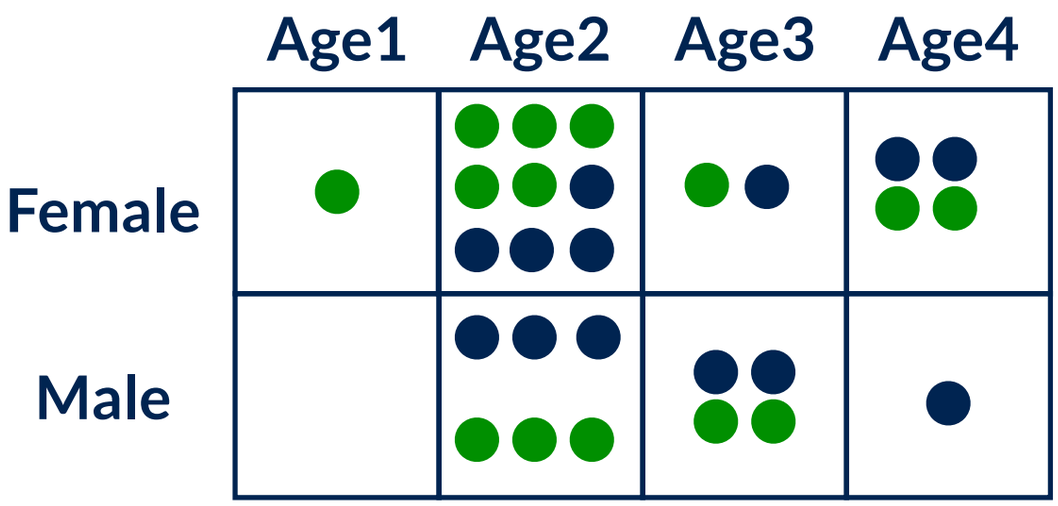
Issues: (i) All possible confounders need to be observed
(ii) Assume overlap between the two distributions (if there is no overlap, sample is not representative, e.g. performing the experiment only for old people),
(iii) Poor estimates as confounder dimensionality increases



Need specific causal effect estimation techniques

Real-world data (RWD)

Definition. "Real-world data (RWD) is data relating to patient health or experience or care delivery collected outside the context of a highly controlled clinical trial." NICE RWE framework: corporate document (23 June 2022)

Examples:
Primary care: **CPRD**, anonymised patient data from GP practices, millions of patients.
DataLoch (NHS Lothian, South-East Scotland), health & social care routinely collected data.
Prospective: **UK Biobank**, an observational cohort of ~0.5 million individuals with de-identified genetic, lifestyle and health information (also collects primary care data).
All-of-US in the US, **Our Future Health**, …

Strength/weaknesses: # individuals, # features, missingness, ..

Most RWD sources are *observational*, i.e., any interventions or exposures are not determined by a study protocol but by patients and healthcare professional

—> Need generally applicable methodologies

Real-world evidence (RWE)

Definition. "Real-world evidence (RWE) is evidence generated from the analysis of real-world data."

RCT may not be possible/applicable due to:

- ethical/feasibility considerations, cost, small number of eligible patients
- Comparators not applicable to standard of care in the NHS
- Limited follow up
- Difference in population
- Difference in clinical support …

Examples of scenarios where RWD is used (given appropriate data quality):

- Clinical trials where real-world data is used as external control
- Pragmatic trial embedded in routine practice using EHR

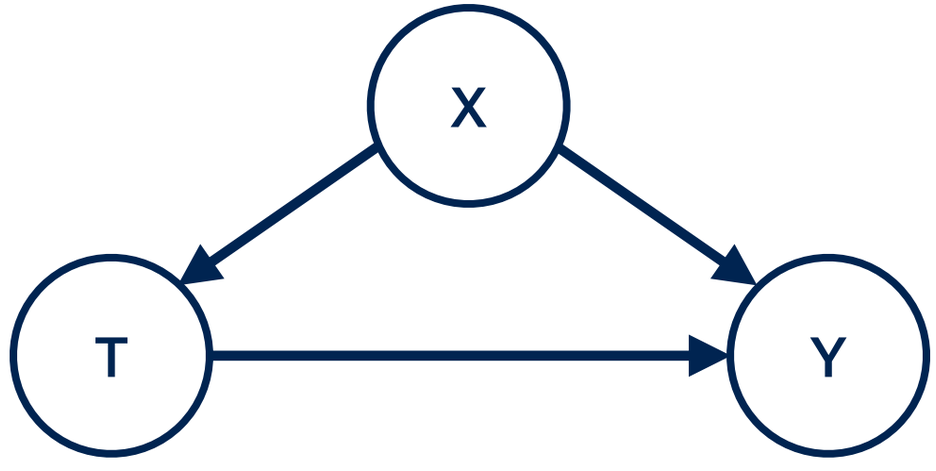
NICE RWE framework: corporate document (23 June 2022)
MHRA guidelines on RCTs using RWD (16 December 2021)

Two main Frameworks for causal identifiablity

- Potential outcomes framework (Neyman-Rubin):

- Requires a given treatment-outcome pair (known directionality)
- For causal estimation
- More familiar to biomedical researchers (this is changing …)

- Structural causal models (Pearl):



- Causal graphs
- Structural equations $x = f_x(\epsilon_x),\ t = f_t(x, \epsilon_t),\ y = f_y(x, t, \epsilon_y)$
- Algorithmic
- For causal estimation and discovery

Assumption: Independent noise terms: $\epsilon_x \perp\!\!\!\perp \epsilon_t \perp\!\!\!\perp \epsilon_y$

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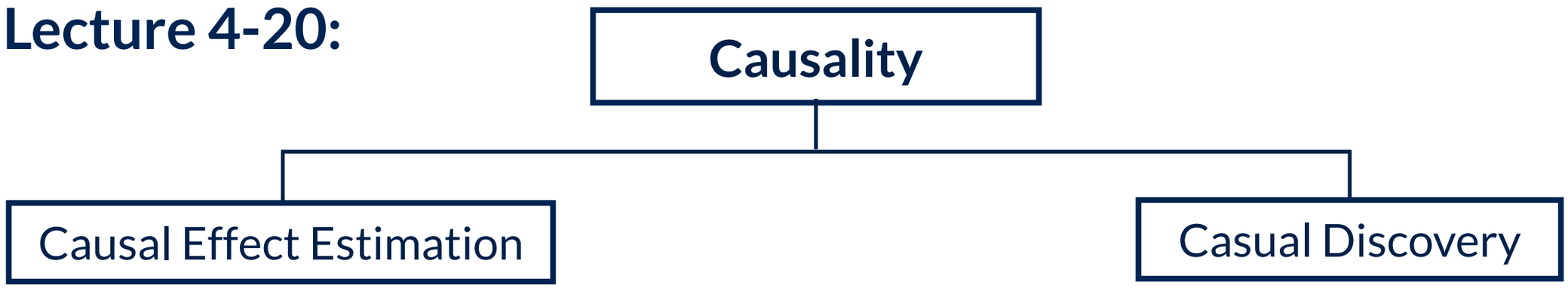

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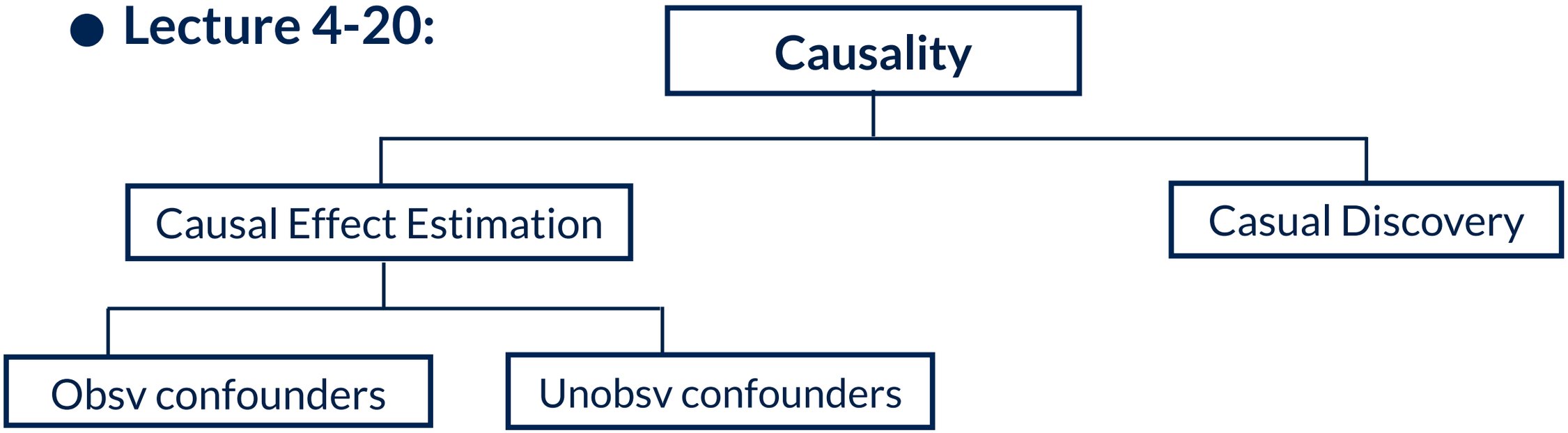

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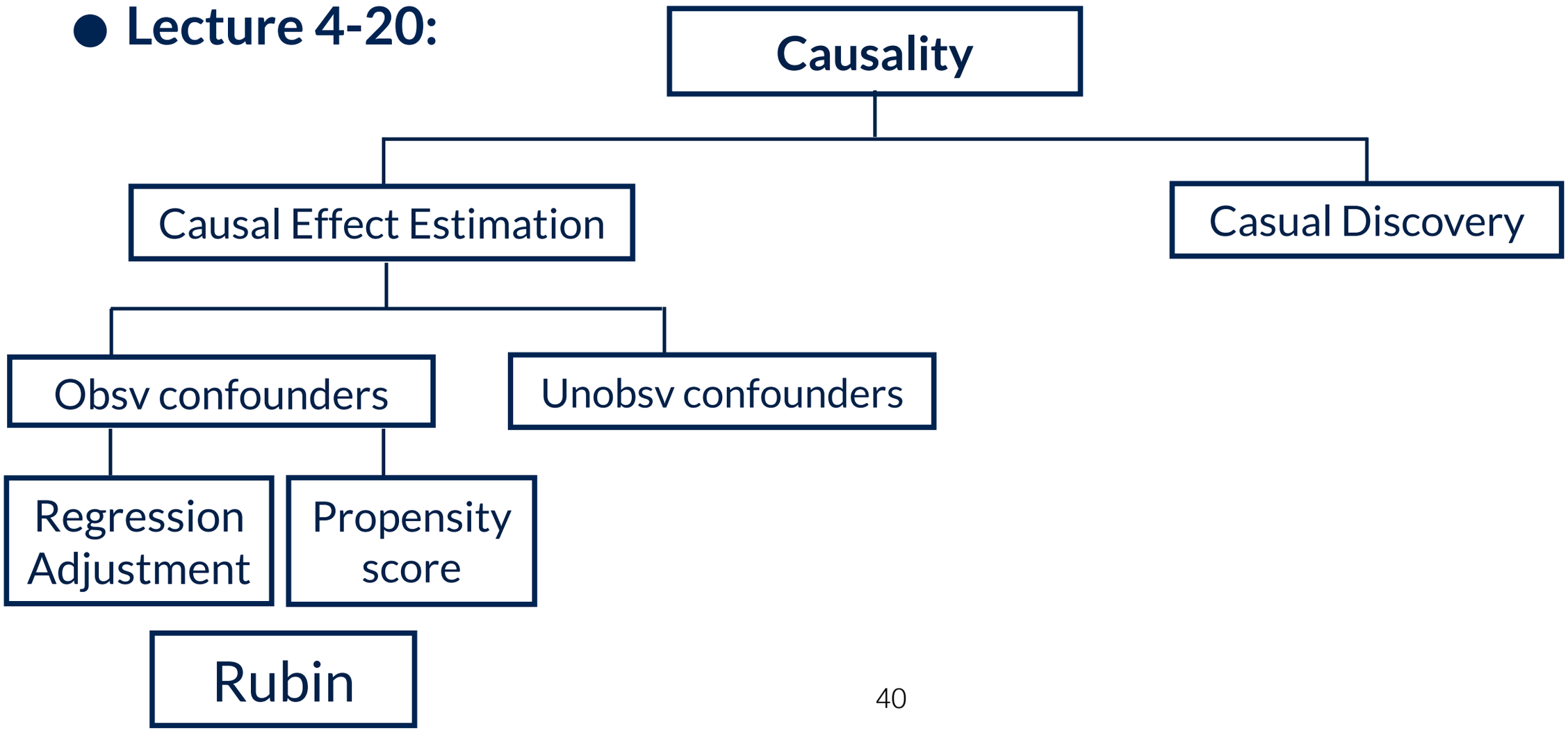

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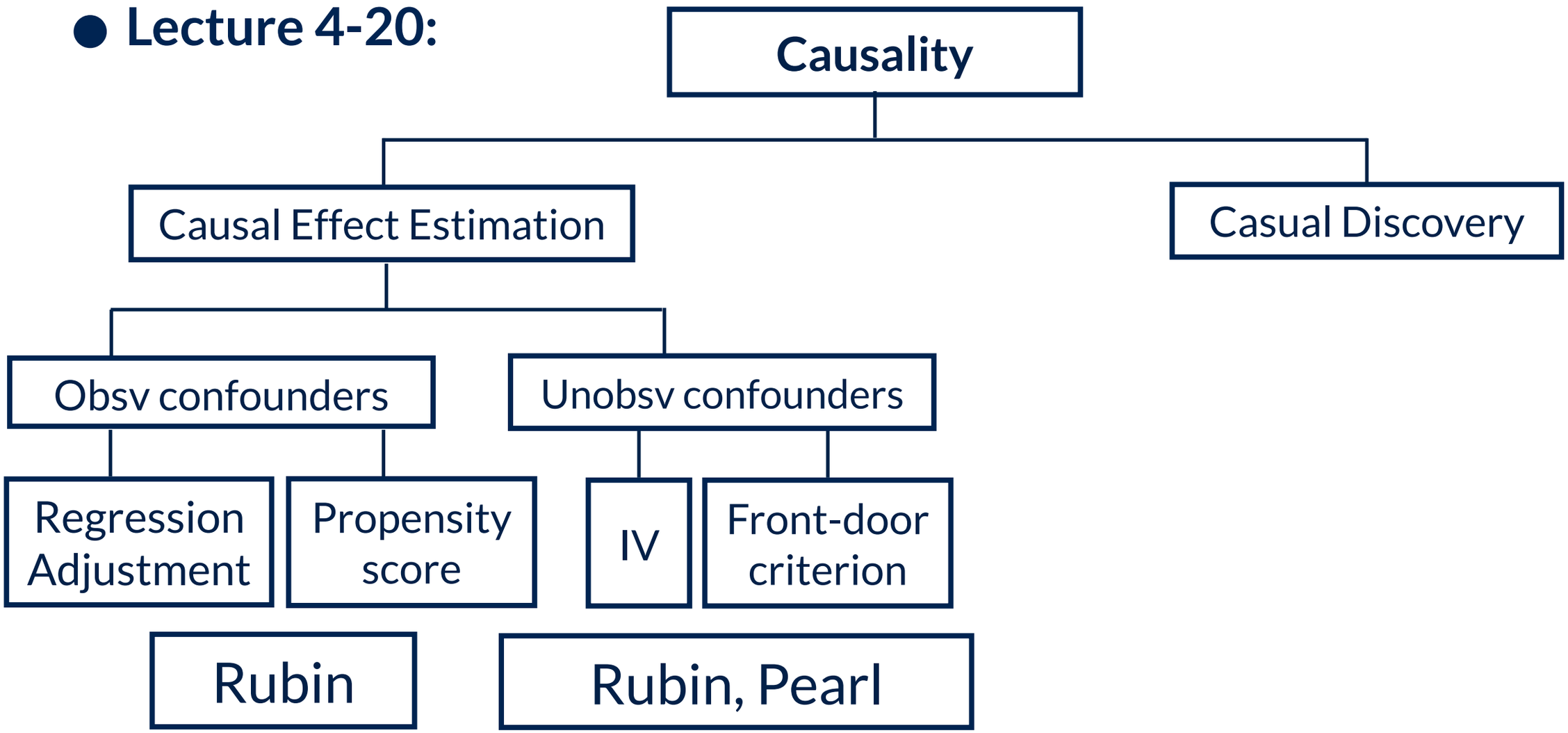

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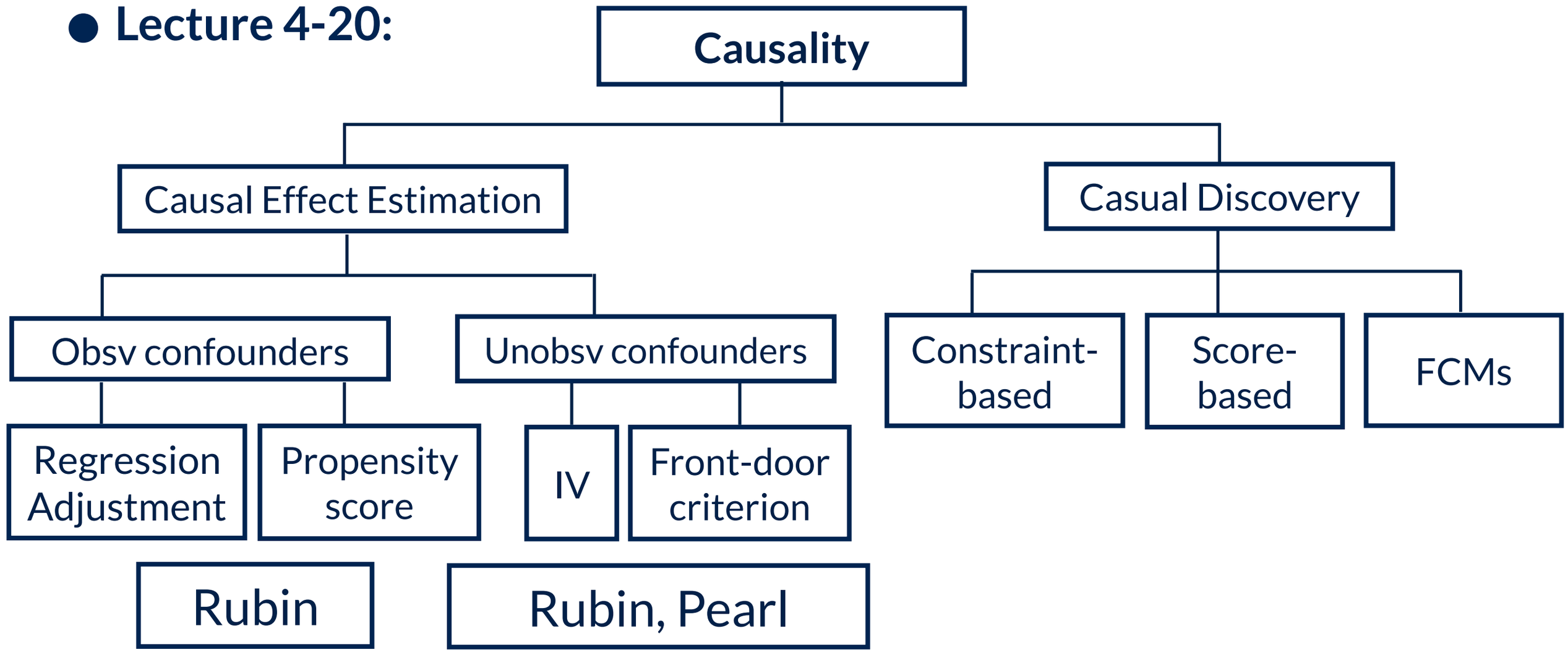

Causal Effect Estimation vs Causal Discovery

- **How much would some variables change if we manipulate the value of another variable?**
- Have a prior causal knowledge (may be incomplete)
- Wish to estimate degrees of causal dependencies

- **By modifying the value of which variables could we change the value of another variable?**
- Wish to discover the causal graph itself
- Many assumptions … difficult to get robust results that one can trust without perturbation data (even difficult with perturbation data!)