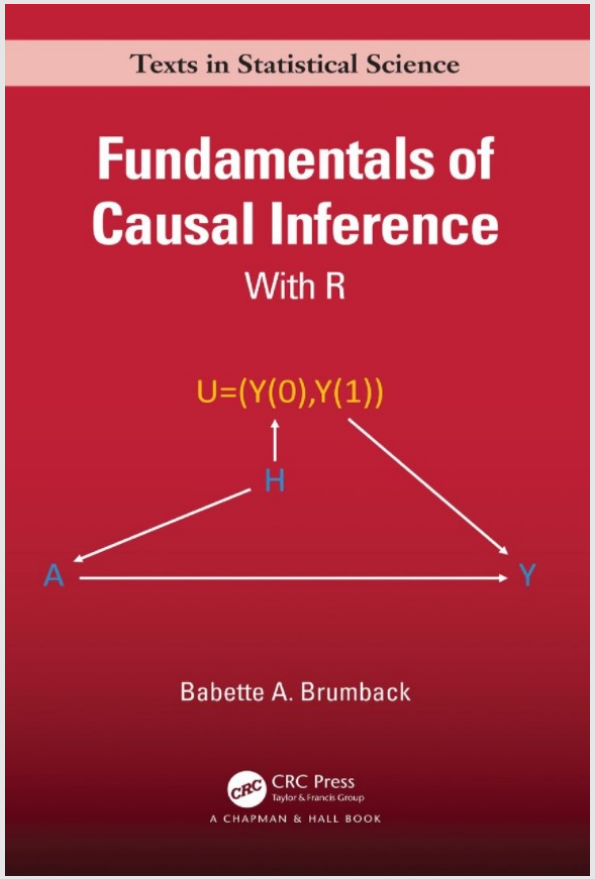
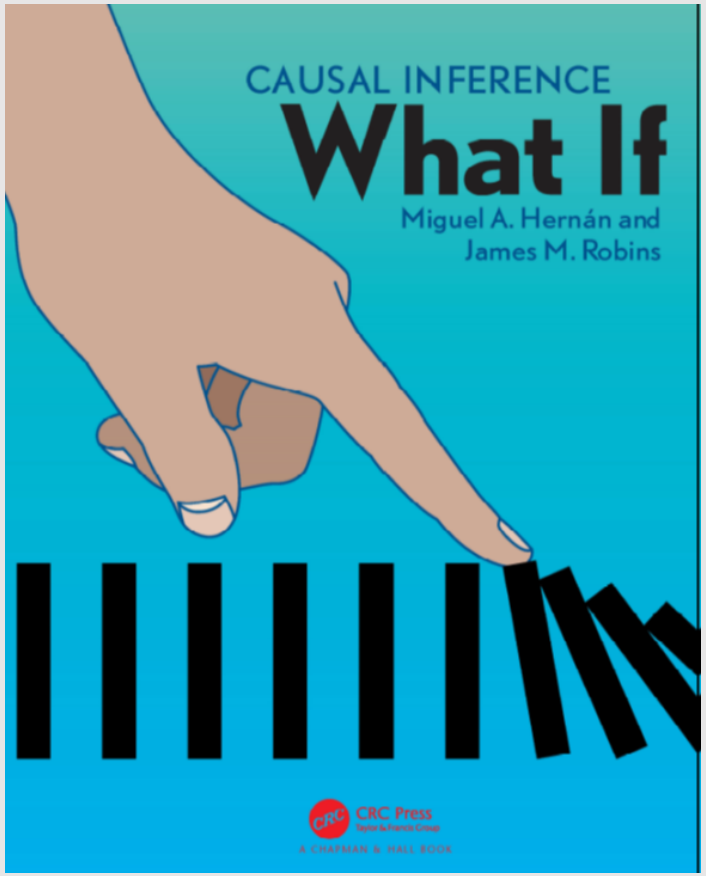
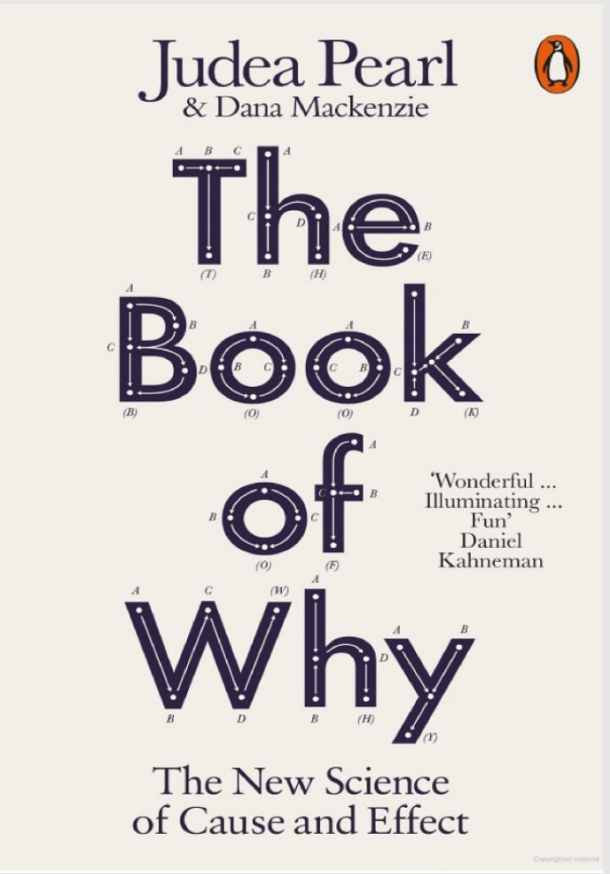
Causal Models in Epidemiological & Clinical Research (basic ideas…)







Explanatory/Causal Models (Observational Studies)

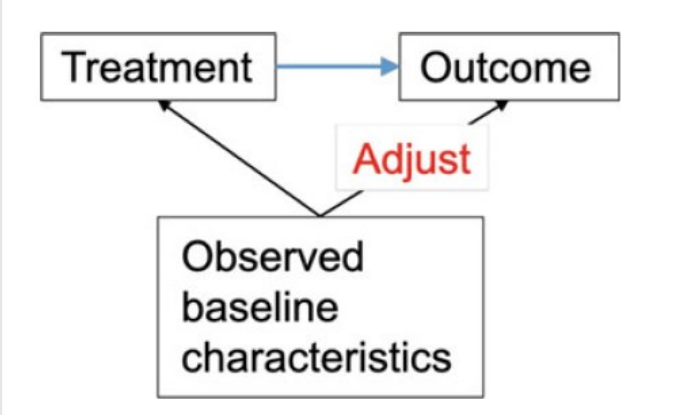
Confounding is one of the major concern in epidemiological analyses of observational studies, where we aim to estimate causal effects.

When treatments/exposures are compared, groups are often quite different **because of a lack** of randomization.

For example, subjects with specific characteristics ***are more likely*** to receive a certain treatment than other subjects (*confounding by indication*).

If these characteristics also affect the outcome, a direct comparison of treatments is **biased** and may merely reflect the lack of initial comparability.

Often, randomization is not possible, and **observational studies are the only possible design**. Dealing with confounding is an essential step in such analyses.



what is the treatment effect if baseline characteristics were *similar* between treatment groups?

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In this context, **causal inference** methods must bridge a gap between goals and means.

Researchers seek **causation**, but the data, on their own, only communicate **associations**.

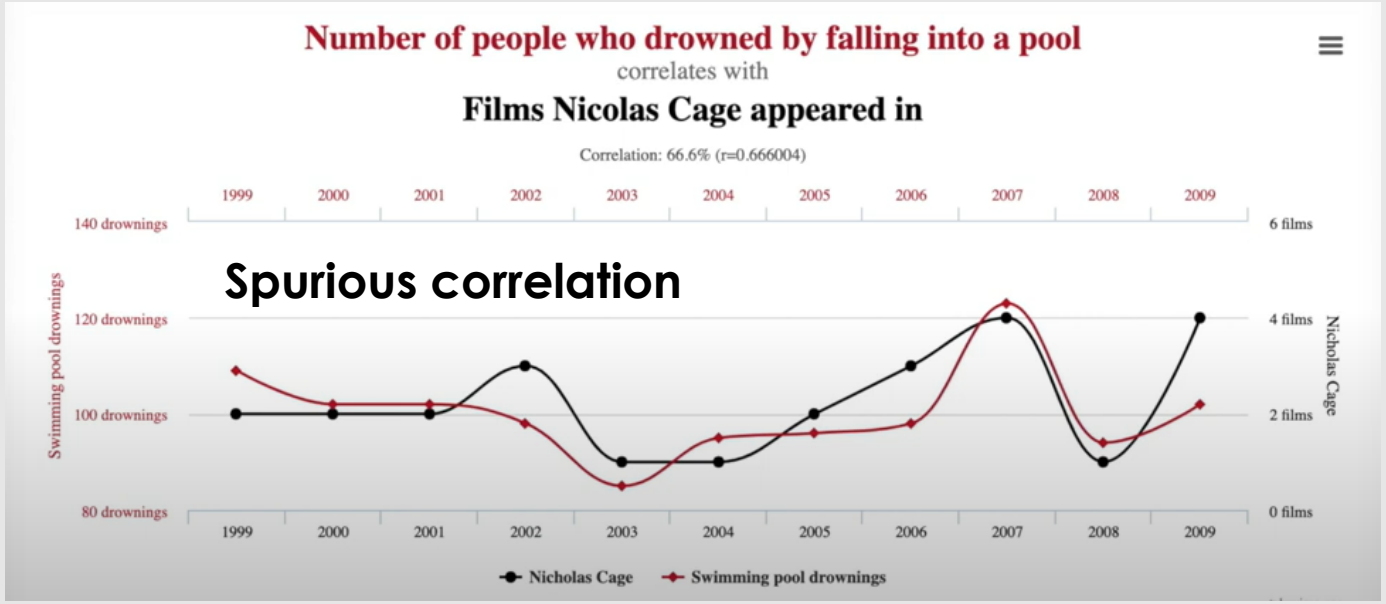
Associations usually consist of a **mixture** of causal and non-causal (spurious) components.

Therefore, a first step of ***identification analysis*** should determine whether, and under which conditions, it is possible to strip an observed association of all its spurious components.

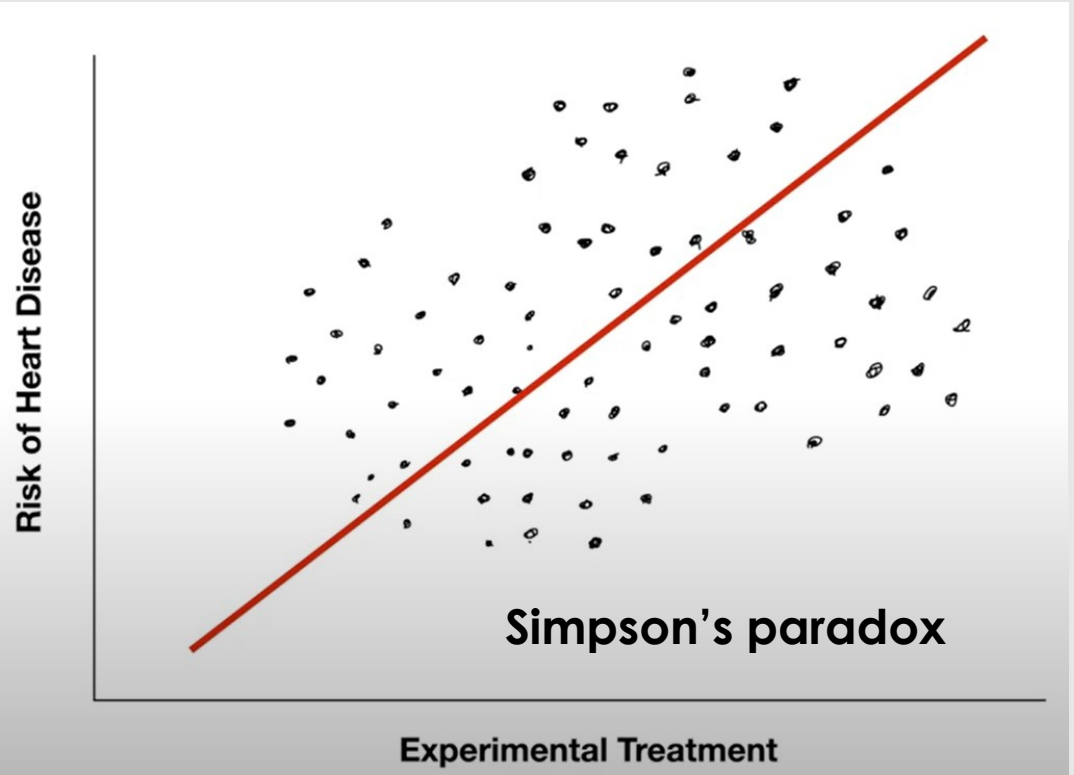
Identification analysis requires causal **assumptions** about how the data were generated.

The sum of these causal assumptions is called a **causal model**, which must describe both *how the world works* (how observed and unobserved variables take their values) and *how the data were collected* (**which** variables and variable values are recorded/which **study design**).

Block 3.2

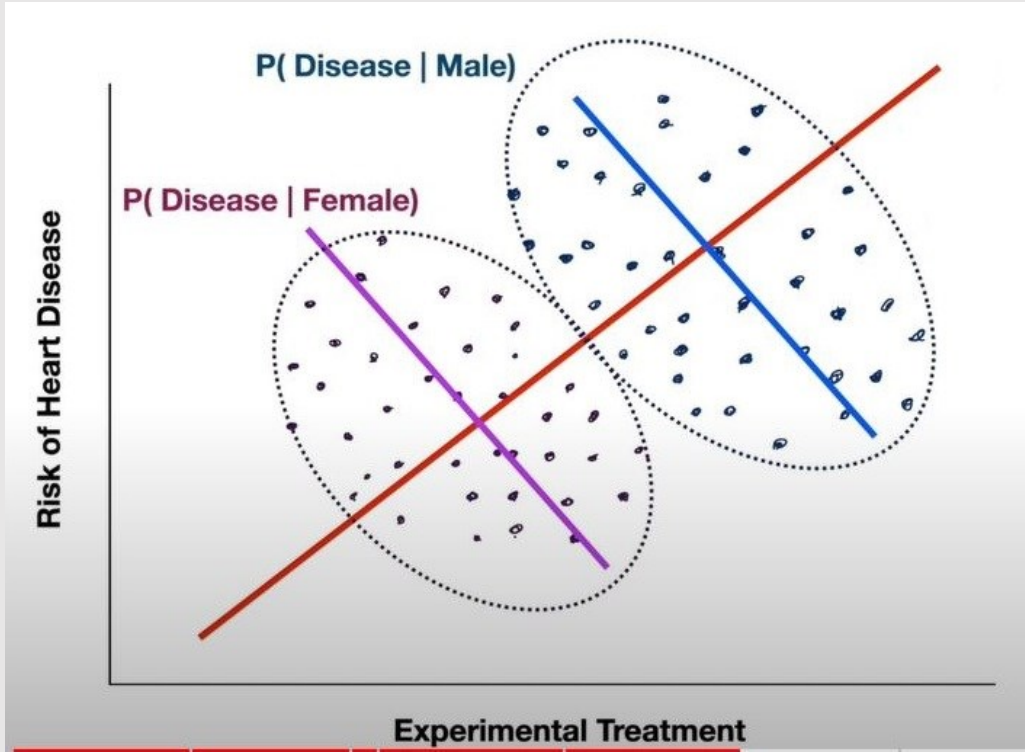


Spurious correlation



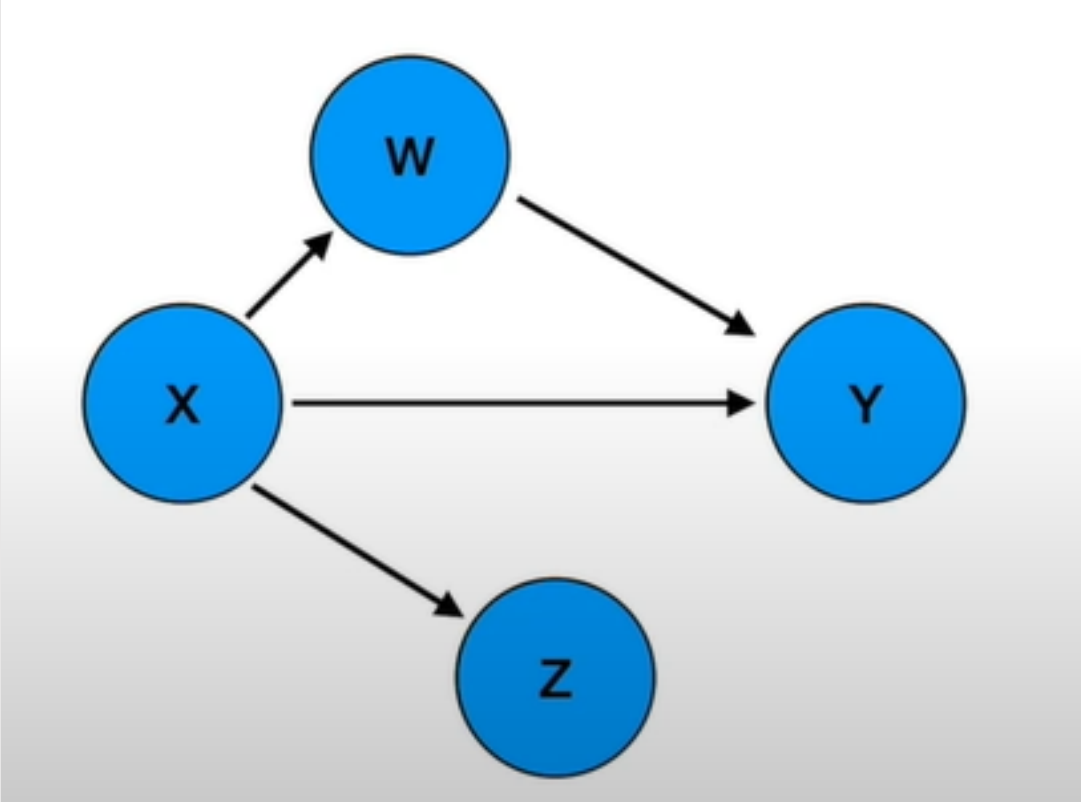
Simpson's paradox

Treatment is good for a man, good for a woman but bad for a person



Causality

X causes Y if *when all confounders are adjusted*, an *intervention* in X **results in a change** in Y, but intervention in Y **does not change** X



A causal model could be represented using a **DAG** (**D**irected **A**cyclic **G**raph)

Each arrow represents a causal influence

The graph is:

- **Directed** : each connection between two variables consists of an arrow
- **Acyclic** : no "reverse" cycles

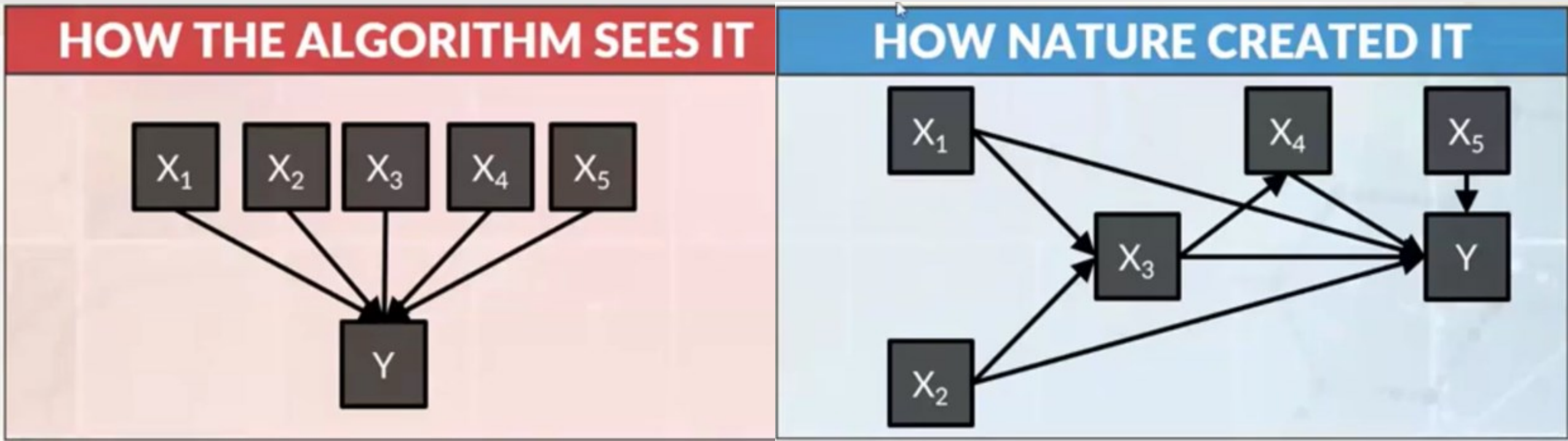
A variable can't cause itself; however time varying processes can be depicted adding one *realization* of each variable per time unit

Knowledge of the data-generating mechanism has to be provided by **external theory** and **understanding**

→ i.e. a **causal** model

No software/algorithm can (currently) ***understand*** this

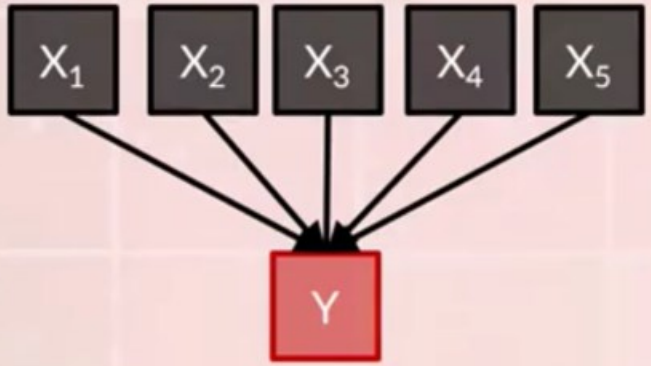
Prediction models can not be in general *causally interpreted* – however transparent they are …



Predictive vs causal modelling

PREDICTIVE MODEL

- **Outcome**-focused

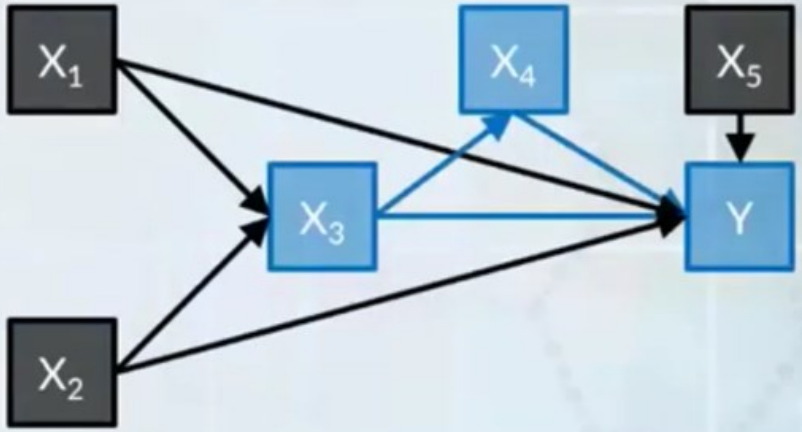


X_i is ____ Y

'correlated with'
'a predictor of'
'associated with'

CAUSAL MODEL

- **Effect**-focused



The ____ of X_2 on Y is...

'total causal effect'
'direct causal effect'

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Predictive vs causal modelling

Predictive Model

Aim: Predict values of outcome (p)

Maximise: performance measures (R^2, calibration, AUC…)

Covariates selection focused on:

- Balancing precision & parsimony
- Availability of variables
- Maximising joint information

Coefficients: *associations*

Automation: Favoured

Causal Model

Aim: Estimate a causal effect

Maximise: accuracy of the effect estimate

Covariates selection focused on:

- External knowledge & judgement
- Role of variables
- Minimizing confounding

Coefficients: *Interpretable in the causal sense*

Automation: Not possible

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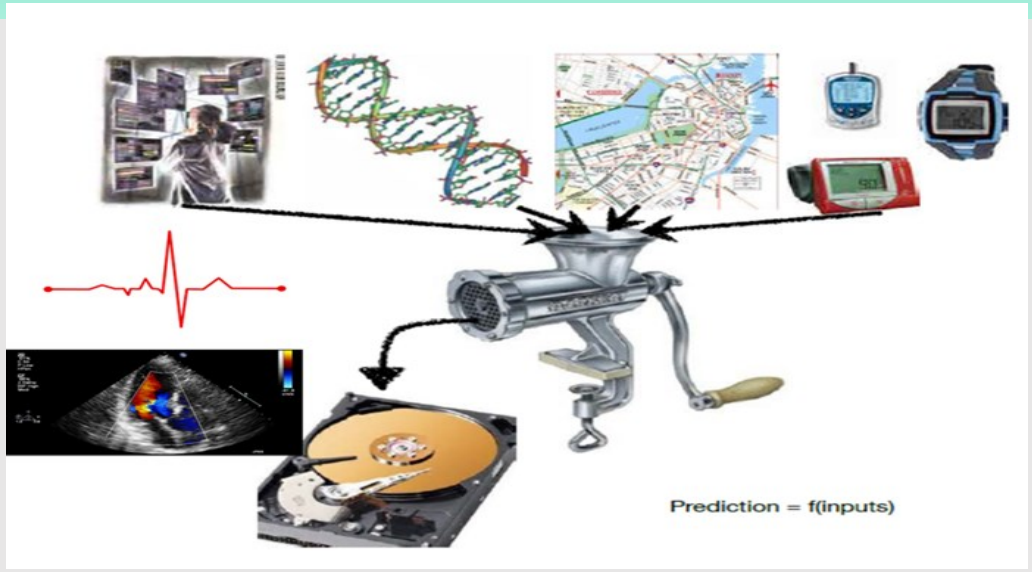
Two *extremes* in regression models

Prognostic/Predictive modelling

- We are trying to find **predictors** of some outcome
- It is their **joint value** as predictors that is important
- We simply want the **most predictive** model
- We compare entire models to judge which is best



Causal/explanatory analysis

- The putative causal factor **must be** in the model
- Other factors are in the model because **help us understand** the causal factor (they are of no interest in themselves)
- We focus on the **estimation** of the putative causal effect (at a population level)

Smoking & Lung Cancer
A Tale of Two Statisticians

Works in public health (**explanatory**):

- I wish to establish whether it is causal
- If so I can warn smokers to quit and this will benefit their health [**intervention**]
- It is important for me to rule out possible confounding factors

Works in life insurance (**predictive**):

- I don't care if it is causal or not
- The data show that smokers are much more likely to get lung cancer
- That's enough for me to take account of it in setting the premiums

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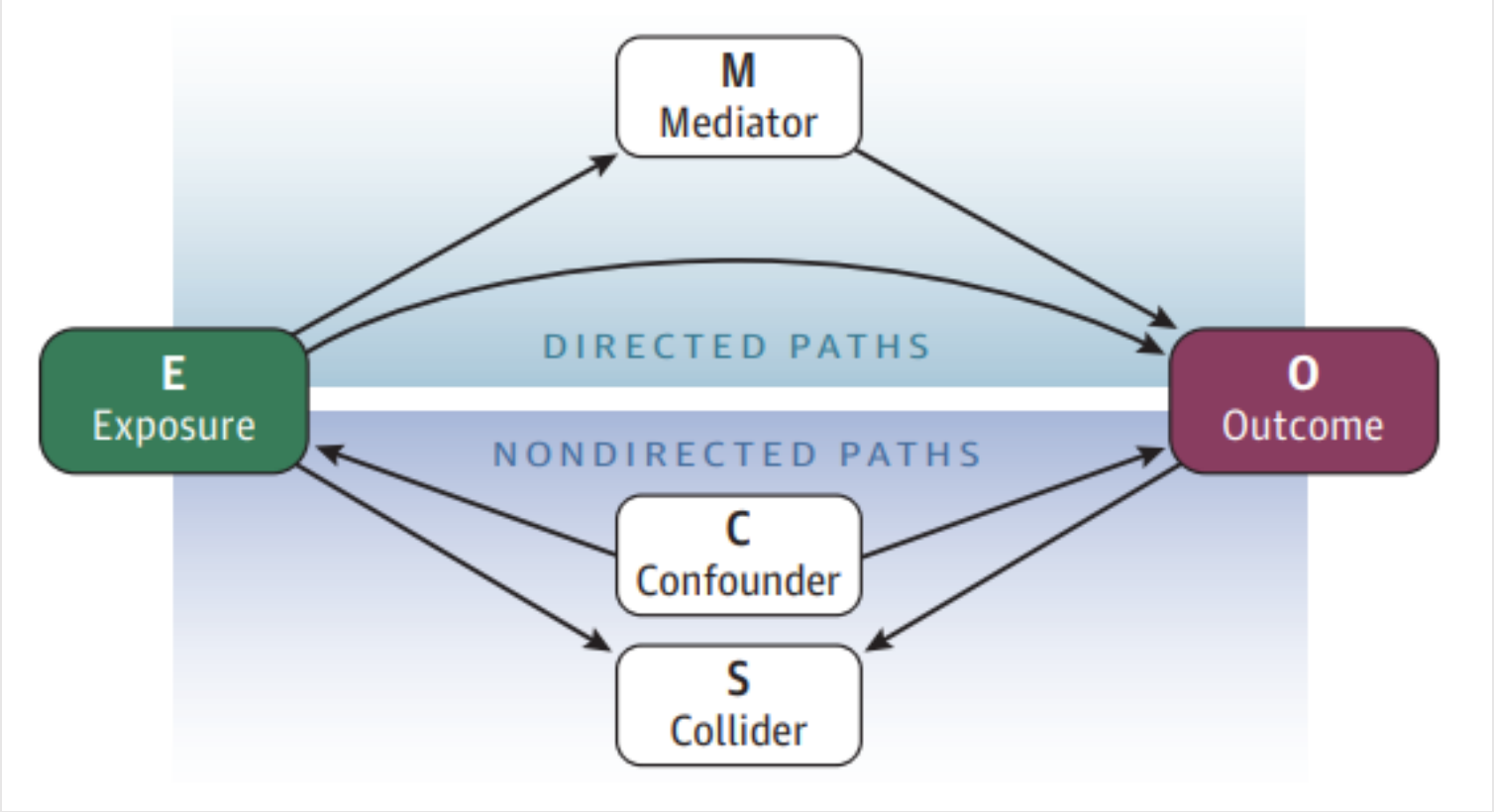
…so again: how to *represent* the role of covariates ?

DAGs are visual representations of qualitative causal assumptions

They encode researchers' expert knowledge and beliefs about *how the world works*



Do you remember? Chocolate Consumption, Cognitive Function, and Nobel Laureates….

N Engl J Med, 2012 Oct 18;367(16).

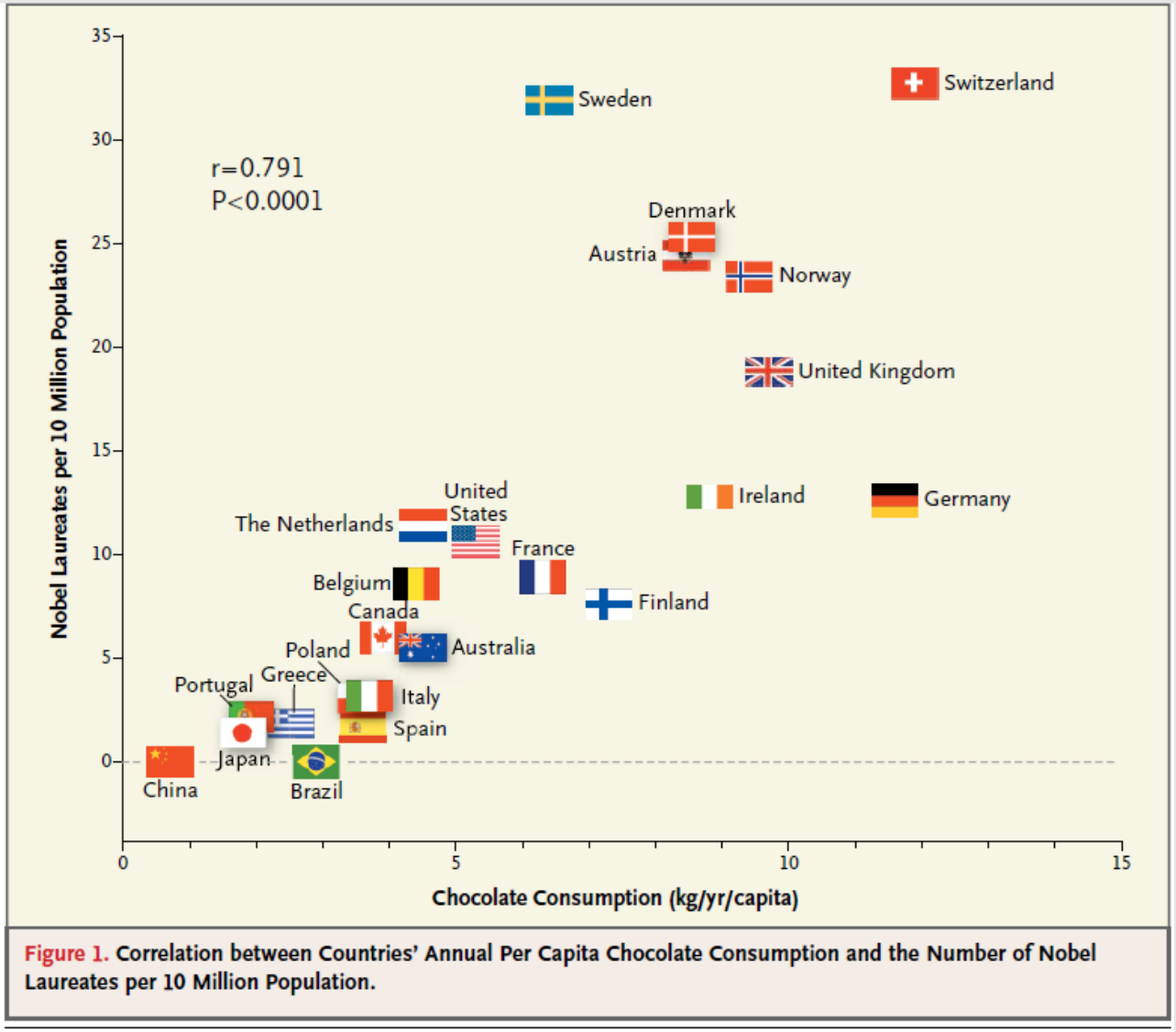
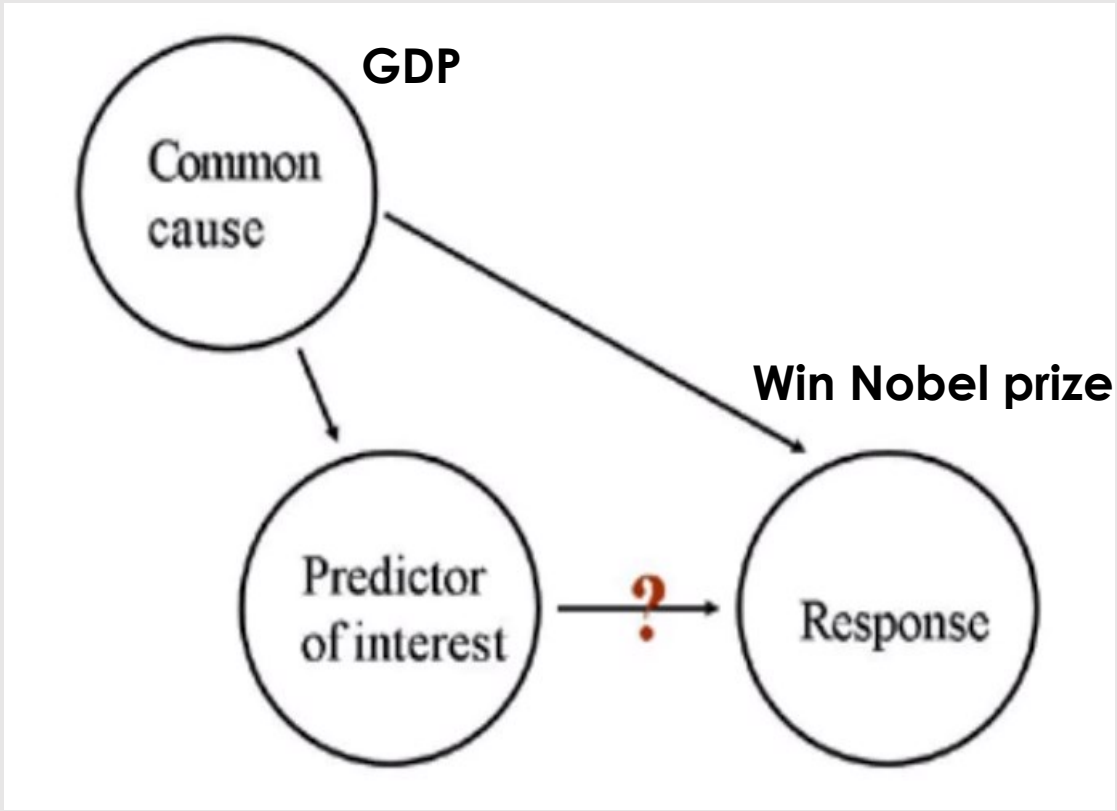
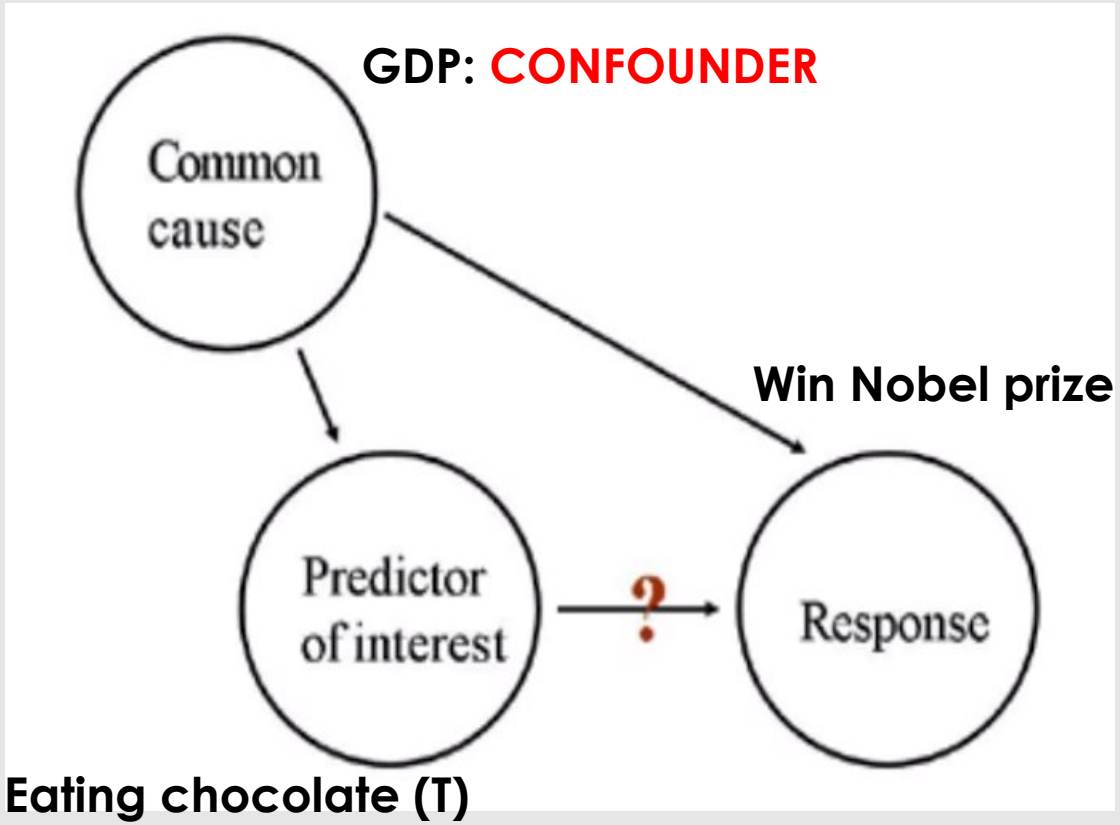


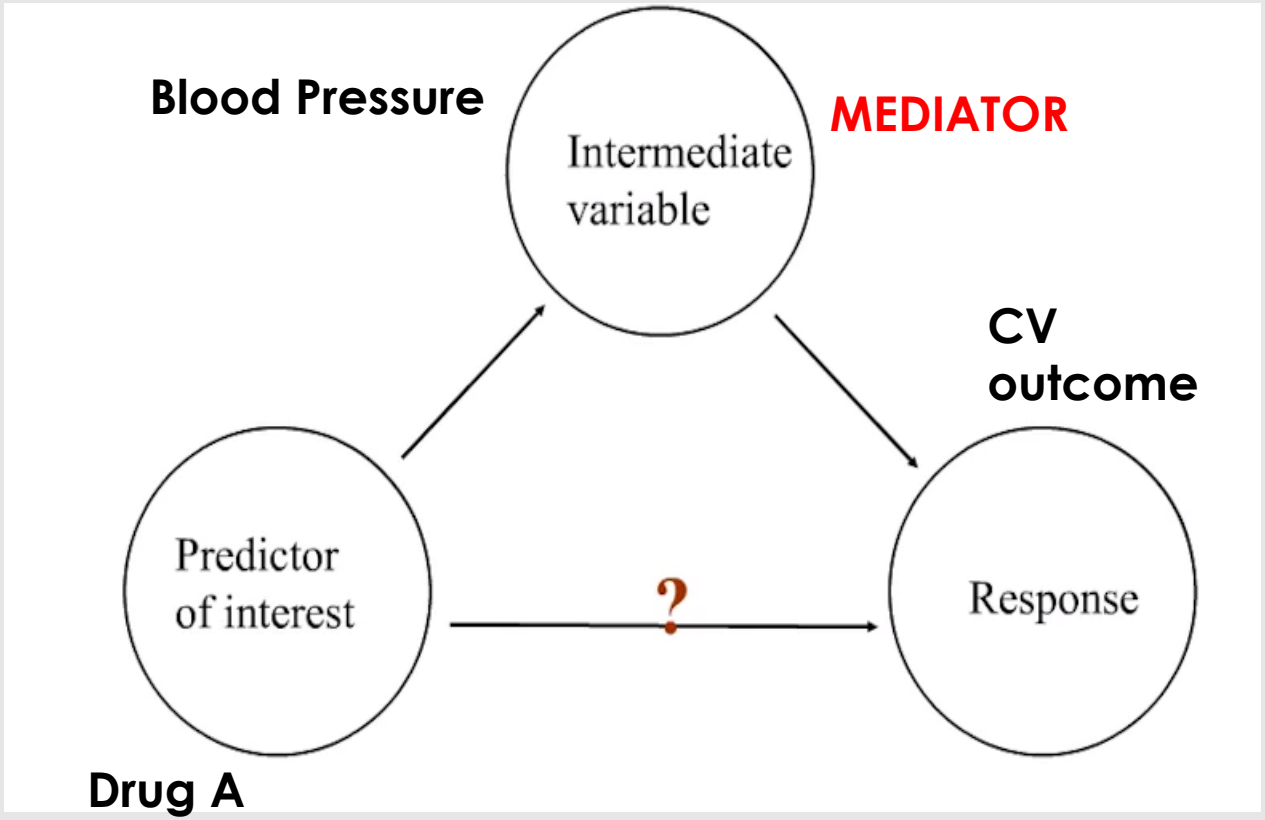
Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.



Eating chocolate (T)

Examples





First: **Define relationships** between variables […a priori knowledge]

***Intermediate/Mediator vs Confounder: confounder IS NOT on the *causal pathway* between predictor and outcome**

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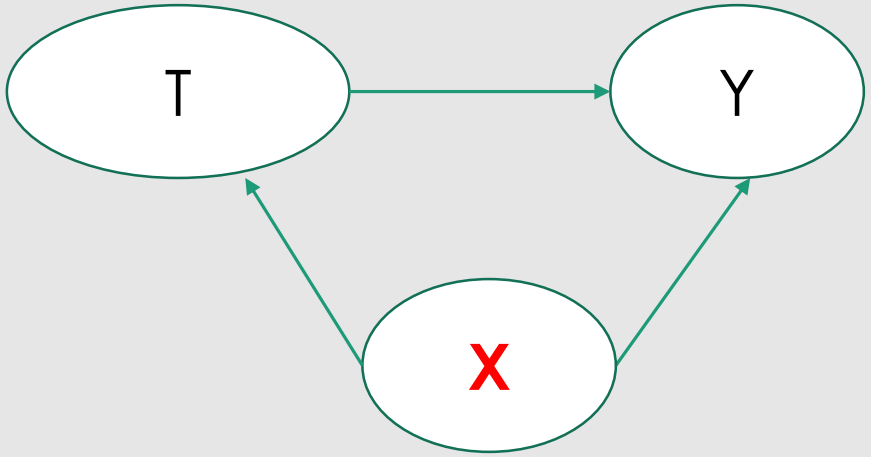
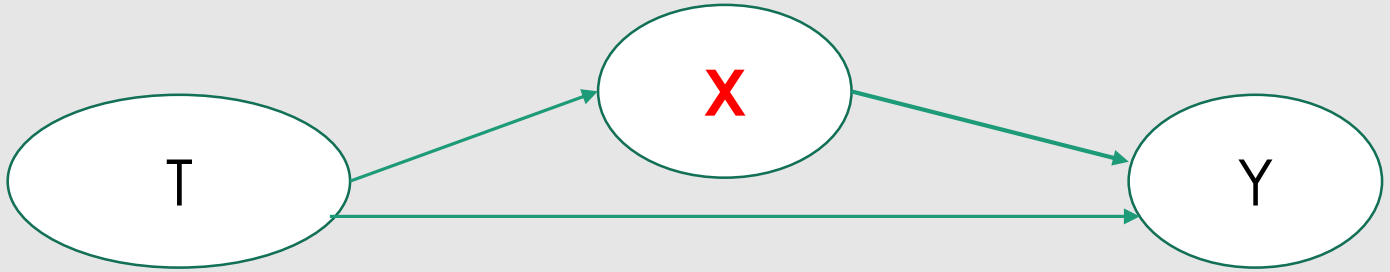
Examples of different DAGs

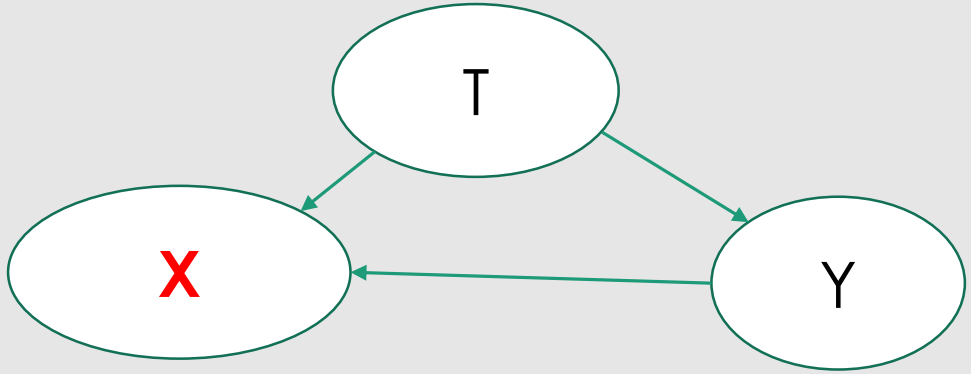
1. Confounder



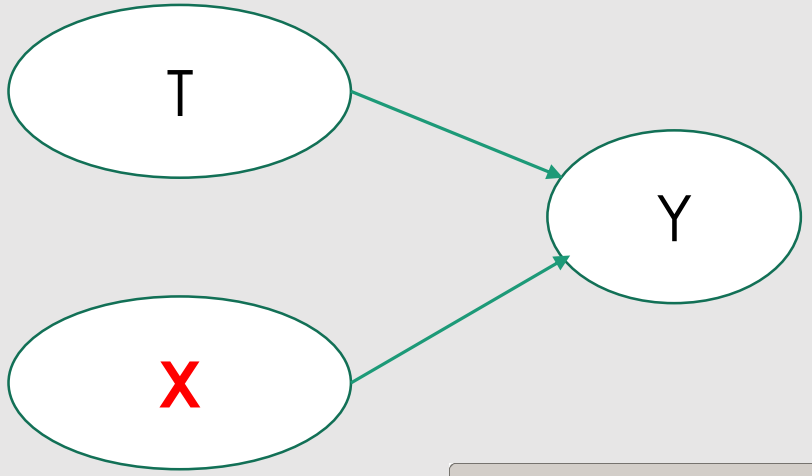
2. Mediator/Intermediate



3. Collider



4. Independent Predictor



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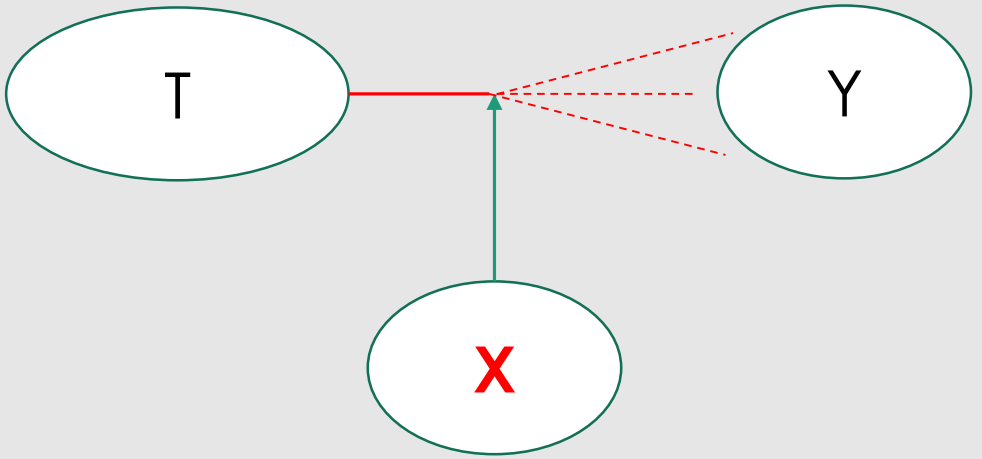
When a treatment has different effect among different subgroups defined by X, there is effect modification (moderators) :

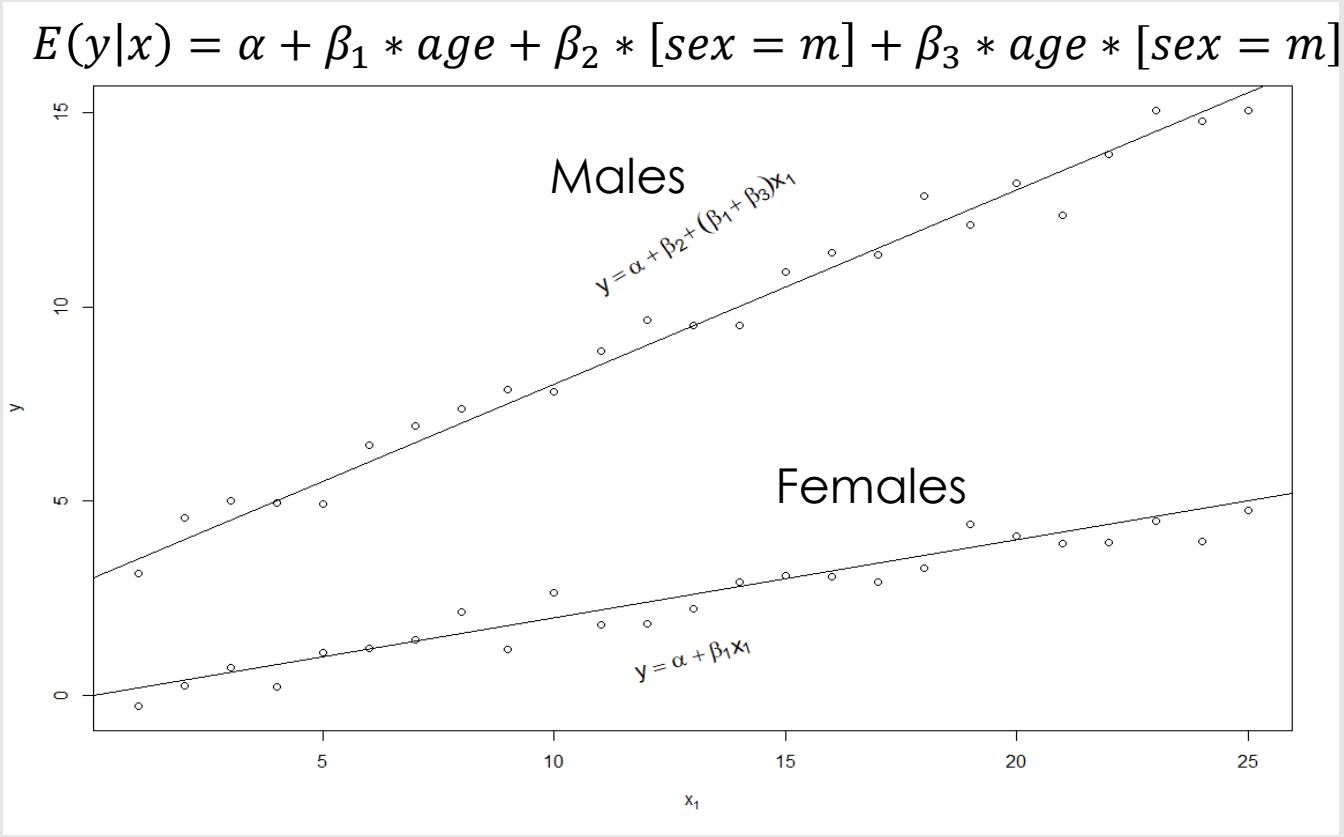
$$E(Y_1 - Y_0)|X = x_i) \neq E(Y_1 - Y_0|X = x_j)$$

! Could not be *represented* in a DAG !

5. Effect modifier



$$E(y|x) = \alpha + \beta_1 * age + \beta_2 * [sex = m] + \beta_3 * age * [sex = m]$$



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Building a DAG is a team-work…

Not this but….

This !

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Basically there are **two types of effects that are of interest** in causal inference:

Average Causal Effect of a treatment or intervention on an outcome *across the entire population (or on the treated)* ATE/ATT

MARGINAL EFFECT

- Standardization*
- IPTW (Inverse Probability of Treatment Weigths)

Causal effect of a treatment within specific subgroups or conditions defined by certain covariates (CATE)

CONDITIONAL EFFECT

- Stratification
- Regression modelling

* similar to the concept of std rates in block 1

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Regression model for the outcome (no interaction)

Suppose a "true" model has a treatment T and a confounder x for outcome y :

$$y_i = \beta_0 + \beta_1 T_i + \beta_2 x_i + e_i$$

β_1 : conditional and marginal treatment effect (ATE=CATE)

If we want here to calculate the marginal effect we can average (standardize) over values of X:

$$\widehat{ATE} = \beta_0 + \beta_1 + \beta_2 E(X) - \beta_0 - \beta_2 E(X) = \beta_1$$

The conditional effect is equal to the marginal effect when there is no interaction between the treatment variable and any other covariate included in the model.

Regression model if we *ignore* a confounder

Suppose a "true" model has a treatment T and a confounder x for outcome y :

$$y_i = \beta_0 + \beta_1 T_i + \beta_2 x_i + e_i$$

If x *is related* to the treatment, we could write:

$$x_i = \gamma_0 + \gamma_1 T_i + \nu_i$$

If we *ignore* the confounder x, we would fit the model:

$y_i = \beta_0^* + \beta_1^* T_i + e_i^*$ $\quad$ β_1^* : estimated effect if x is omitted

If we *come back* to the true model:

$$y_i = \beta_0 + \beta_1 T_i + \beta_2 x_i + e_i = \beta_0 + \beta_1 T_i + \beta_2(\gamma_0 + \gamma_1 T_i + \nu_i) + e_i$$

$$= \beta_0 + \beta_2\gamma_0 + (\beta_1 + \beta_2\gamma_1)T_i + \beta_2\nu_i + e_i$$

$$\beta_1^* = \beta_1 + \beta_2\gamma_1$$

Estimation *without* x is correct only if $\beta_2\gamma_1$=0

- β_2=0 x not associated with y
- γ_1=0 x not associated with T

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Regression model for the outcome (with interaction)

Suppose a "true" model has a binary treatment T and a confounder X for outcome y that has an interaction with the treatment (effect modifier):

$$y_i = \beta_0 + \beta_1 T_i + \beta_2 x_i + \beta_3 x_i * T_i + e_i$$

$$\widehat{ATE} = \frac{1}{N}\sum_{i=1}^{N}[\beta_0 + \beta_1 + \beta_2 x_i + \beta_3 x_i - \beta_0 - \beta_2 x_i]$$

$$= \frac{1}{N}\sum_{i=1}^{N}[\beta_1 + \beta_3 x_i] = \beta_1 + \beta_3 E(X)$$

Here the conditional effect is not equal to the marginal effect since there is an interaction between the treatment variable and a covariate included in the model.

General basic rules

1. **Confounder**: include (adjust/stratify)

2. **Mediator**: exclude

(for *total effect* estimation, then there are more advanced topic: disentagle direct and indirect effects…)

3. **Collider**: **to be discussed with experts, in general *exclude*** (but depend on the path…)

4. **Independent predictor**: include/exclude (in relation to sample size/precision)

5. **Effect modifier**: include (interaction)

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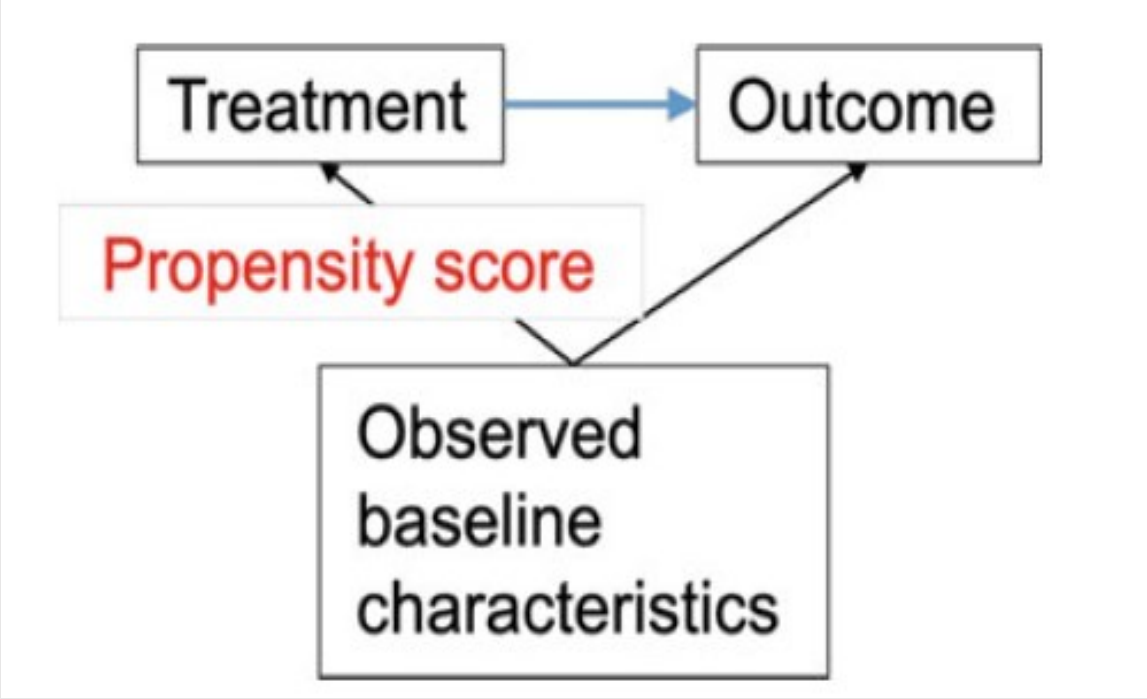
Assumptions behind causal approaches

- ***No interference***
  - *Stable Unit Treatment Value Assumption*
  - The treatment/exposure of one individual **does not affect** the potential outcome of another individual
- ***Positivity***
  - $0 < \Pr(T = 1|X) < 1$
  - $0 < \Pr(T = 1|PS) < 1$
  - each subject in the population could be potentially treated/exposed
- ***Consistency***
  - $Y_t = Y$ with $T = t$ There are no ***multiple version*** of treatment
- ***No unmeasured confounding***
  - $Y_t \perp T|X$
  - $Y_t \perp T|PS$
  - conditional exchangeability

Regression models for the outcome are used to **estimate treatment effects *trying to adjust* for (measured) confounders** between treatment groups.

This approach relies on the underlying assumption that the ***specified*** model is correct. Another issue is that there is *no warning* if there is no **overlap** (positivity violation) between the treated and controls.

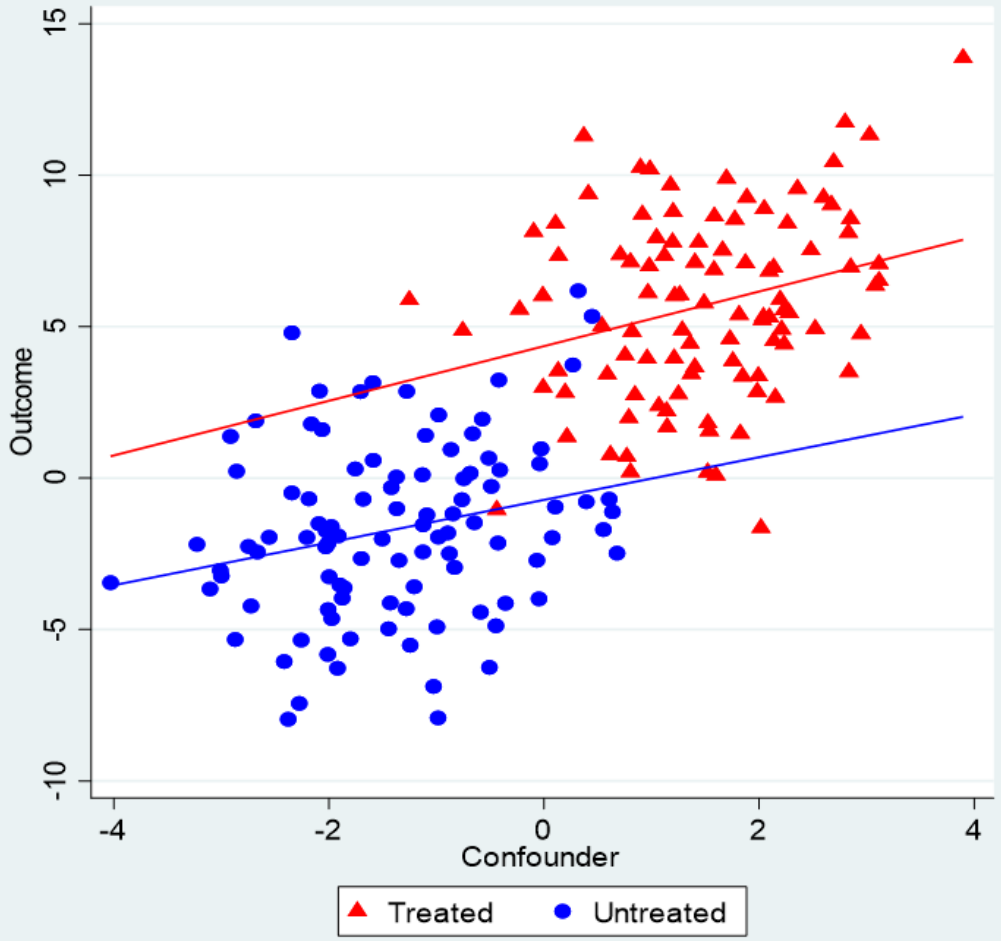
In other words, models could be estimated over regions with no or little data.

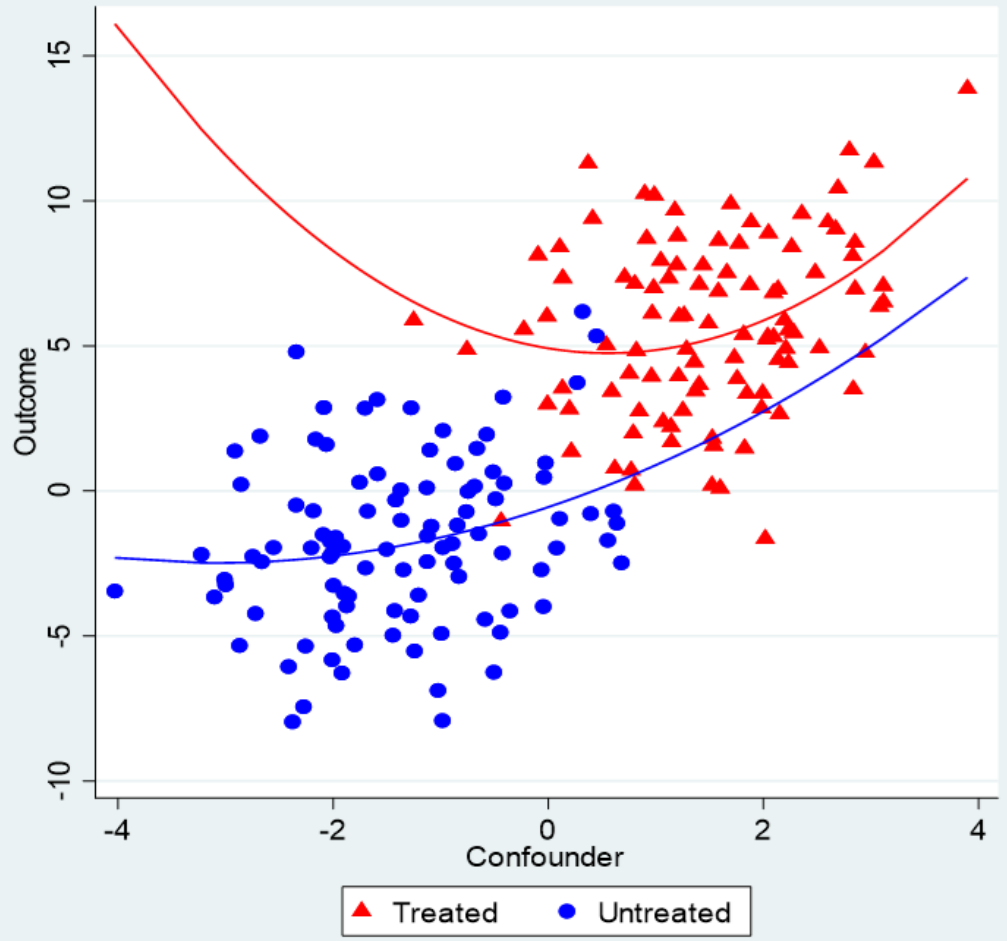


Adjustment with regression analysis is moreover **problematic** when the outcome is relatively **rare** or we have a **high-dimensional** confounders set.

An alternative is to use the **propensity score**, which could be especially attractive in the setting of rare outcomes.

No overlap on the confounder range : dangerous extrapolation !





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Propensity Score

The Propensity Score (**PS**) for each subject *i* (Rosembaum & Rubin, 1983) is defined as follows:

$$e_i = \Pr(T_i = 1 | \boldsymbol{X_i})$$

The **PS** is a **balancing score**, $e = b(X)$ such that:

$$X \perp T | \boldsymbol{b(X)}$$

Treated (T=1) and control (T=0) subjects with the same propensity score $e(x)$ have the same distribution of the observed covariates X

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Conditional Exchangeability

T=0 | (PS=p)

T=1 | (PS=p)

$$Y_t \perp T|X \Rightarrow Y_t \perp T|PS$$

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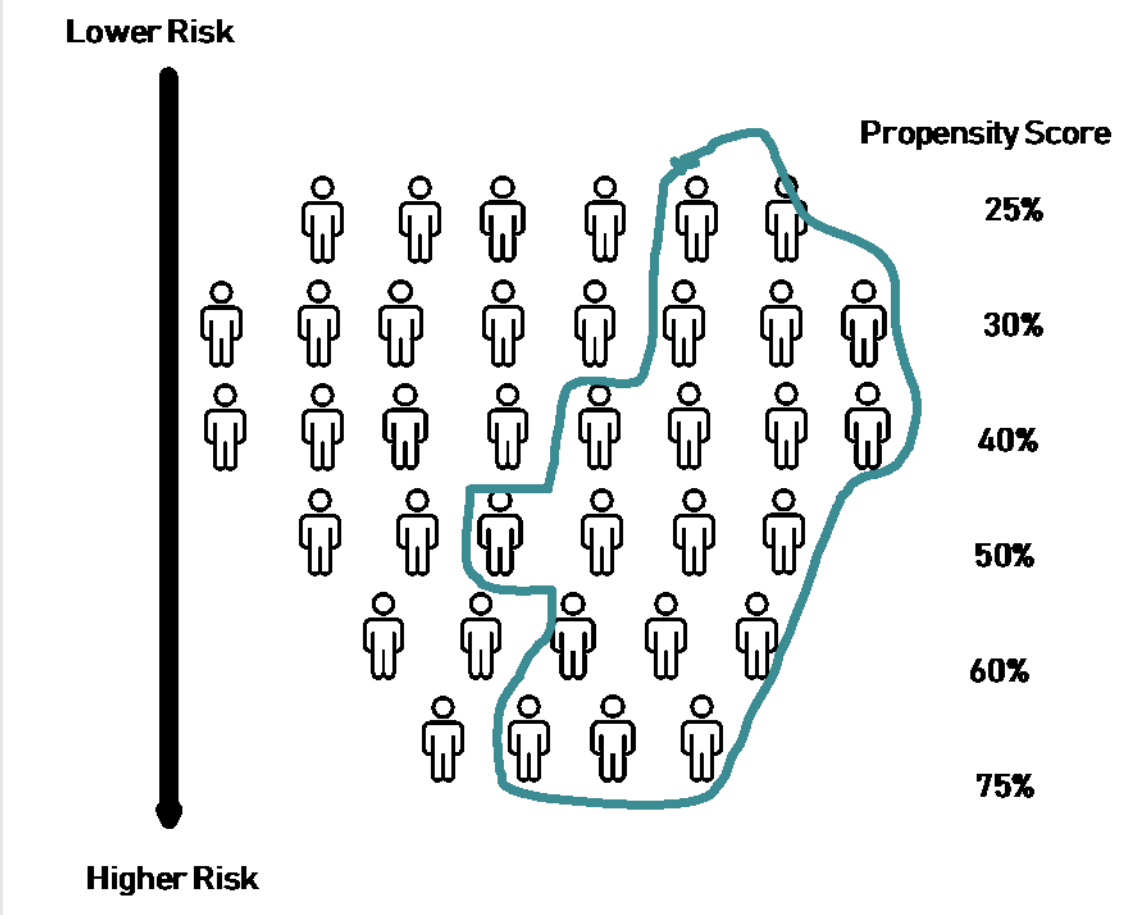
We **can estimate the propensity score** from the data:

e.g. using logistic regression:

$$\log\left(\frac{e_i}{1-e_i}\right) = X_i\alpha$$

$$e_i = \frac{\exp(X_i\alpha)}{1+\exp(X_i\alpha)}$$

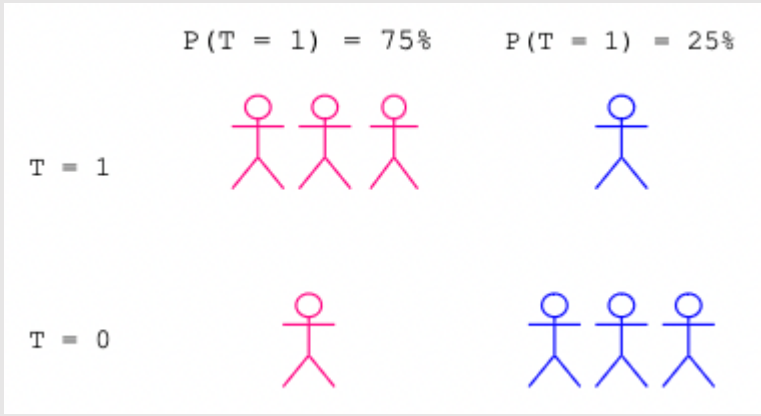


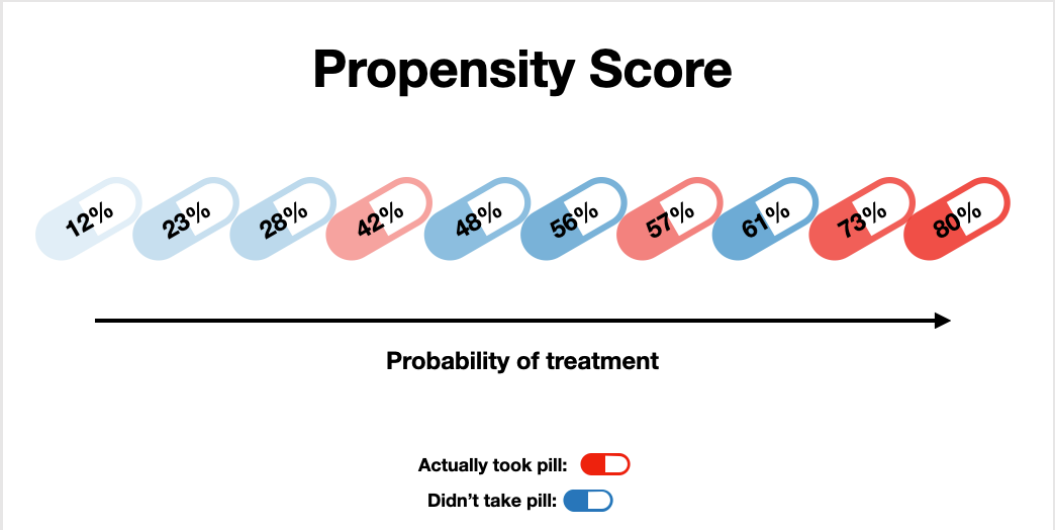
…Or using **machine learning** algorithms !
The important thing here is just to have a predicted probability to receive the treatment

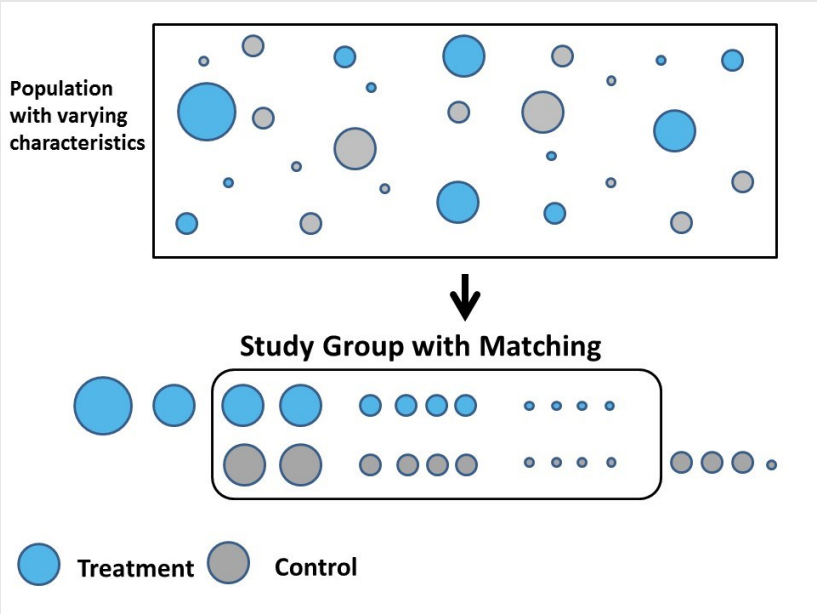
Construction of the *control* group:

Four *main* approaches:

1. Covariate Adjustment
2. Matching
3. Stratification
4. **I**nverse **P**robability of **T**reatment **W**eighting (IPTW)







Covariate Adjustment: use PS as a covariate !

Method

$$Y_i = T_i\beta + f(\widehat{e_i})$$

$\hat{\beta}$ is the average[conditional] treatment effect

Simple, efficient …

Diagnostic Tools

1. The distribution of the PS in the two groups **can help verifying the positivity assumption**

Assumption of *some* functional relationship between the outcome and the PS

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Matching

Method

We can form matched sets of **treated** and **untreated** subjects **who share a similar value of PS**

In the matched sample we can compare the outcome using **statistical methods** for **paired experiments**

Only the ATT effect could be estimated

Many variants for the matching procedure

It has been argued that appropriate SE are hard to obtain

It discards a lot of data in a non-deterministic manner

Diagnostic Tools

1. The distribution of the PS in the two groups **can help verifying the positivity assumption**
2. **Characteristics can be compared in the matched sample to assess achievement of balance**

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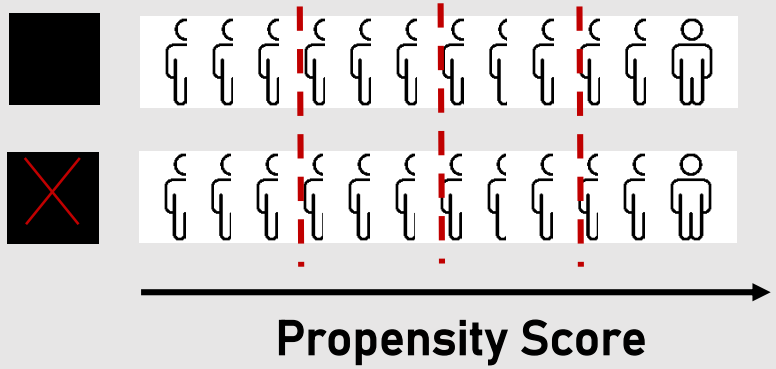
Stratification

Method

We obtain exclusive subsets according to values of the propensity scores

In **each stratum we can** compare the outcome between the two treatment groups (**CATE**) and then eventually use a **weighted mean** to obtain the marginal treatment effect (**ATE**)



Simple

It can leave residual confounding

We need to be careful to have a sufficient sample size per strata/outcomes

Diagnostic Tools

1. The distribution of the PS in the two groups **can help verifying the positivity assumption**
2. **Pre-treatment characteristics can be compared within strata**

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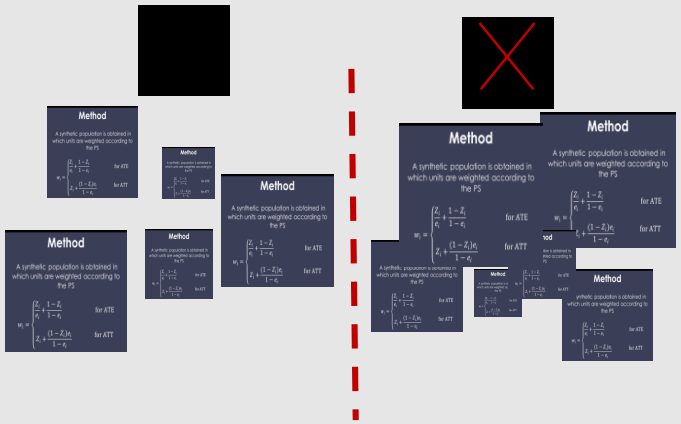
IPTW

Method

A **synthetic** population is obtained in which units are weighted according to the PS

$$w_i = \begin{cases} \frac{T_i}{e_i} + \frac{1 - T_i}{1 - e_i} & \text{for ATE} \\ T_i + \frac{(1 - T_i)e_i}{1 - e_i} & \text{for ATT} \end{cases}$$

Extremes weights → imprecise estimates



Mathematically appealing

Extends to complex scenarios

Diagnostic Tools

1. The distribution of the PS in the two groups **can help verifying the positivity assumption**
2. **Pre-treatment characteristics can be compared in the weighted dataset**

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