Causation

- The epidemiological approach to causation
- The causal inference approach (Intro)

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The epidemiological approach to causation

One of the main goal of epidemiology is to learn about what **causes** and **prevents** diseases.

How epidemiologists determine causative and preventive factors involves a process known as **causal inference**. This process is particularly complex in **observational** studies.

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The epidemiological approach to causation

Epidemiological principles stand on **two** basic assumptions:

- Human disease does not occur *(completely…)* at random
- The disease and its cause - as well as preventive factors - can be identified by a thorough **investigation** of population.

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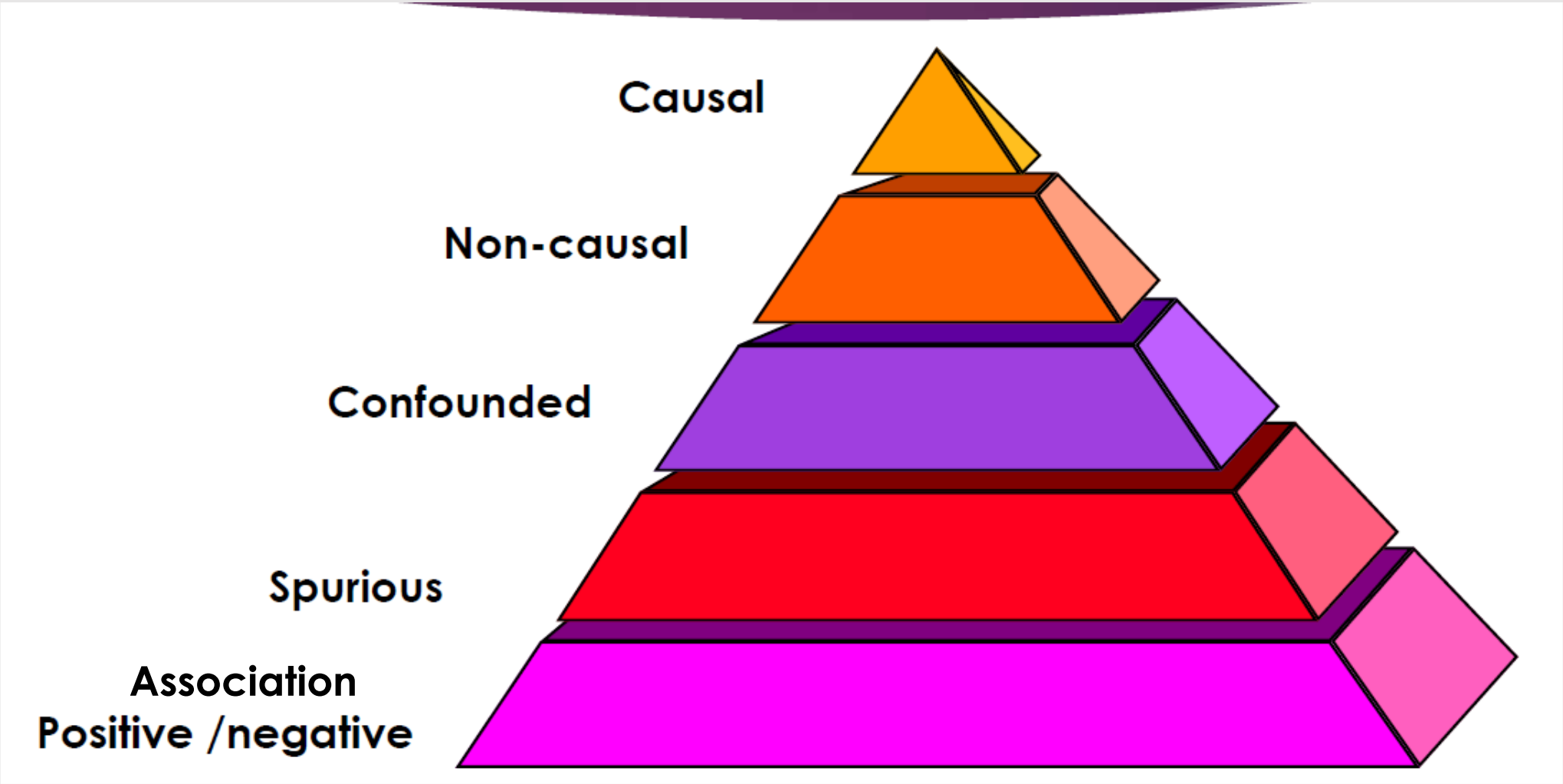
Pyramid of *Associations*



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The epidemiological approach to causation

What is Association?

Simultaneous *occurrence* of two variables *more often* than would be expected by chance.

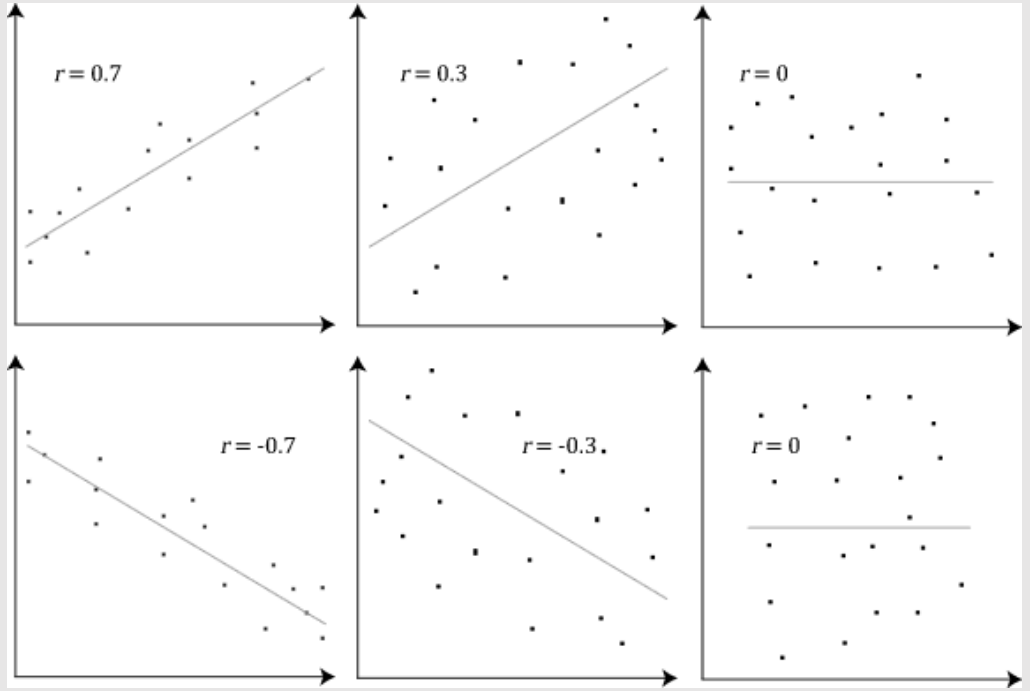
If two attributes, say A and B, are found to co-exist ***more often*** *than an ordinary chance*.

Useful to consider **as a first step** the concept of correlation

Correlation [statistics] : degree of [linear] association between two variables

Gender/ Education	Low Ed. level	High Ed. level	Tot
Male	80	20	100
Female	30	70	100
Tot	110	90	200

Categorical variables:
Chi-square/Fisher test…



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Chocolate Consumption, Cognitive Function, and Nobel Laureates

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

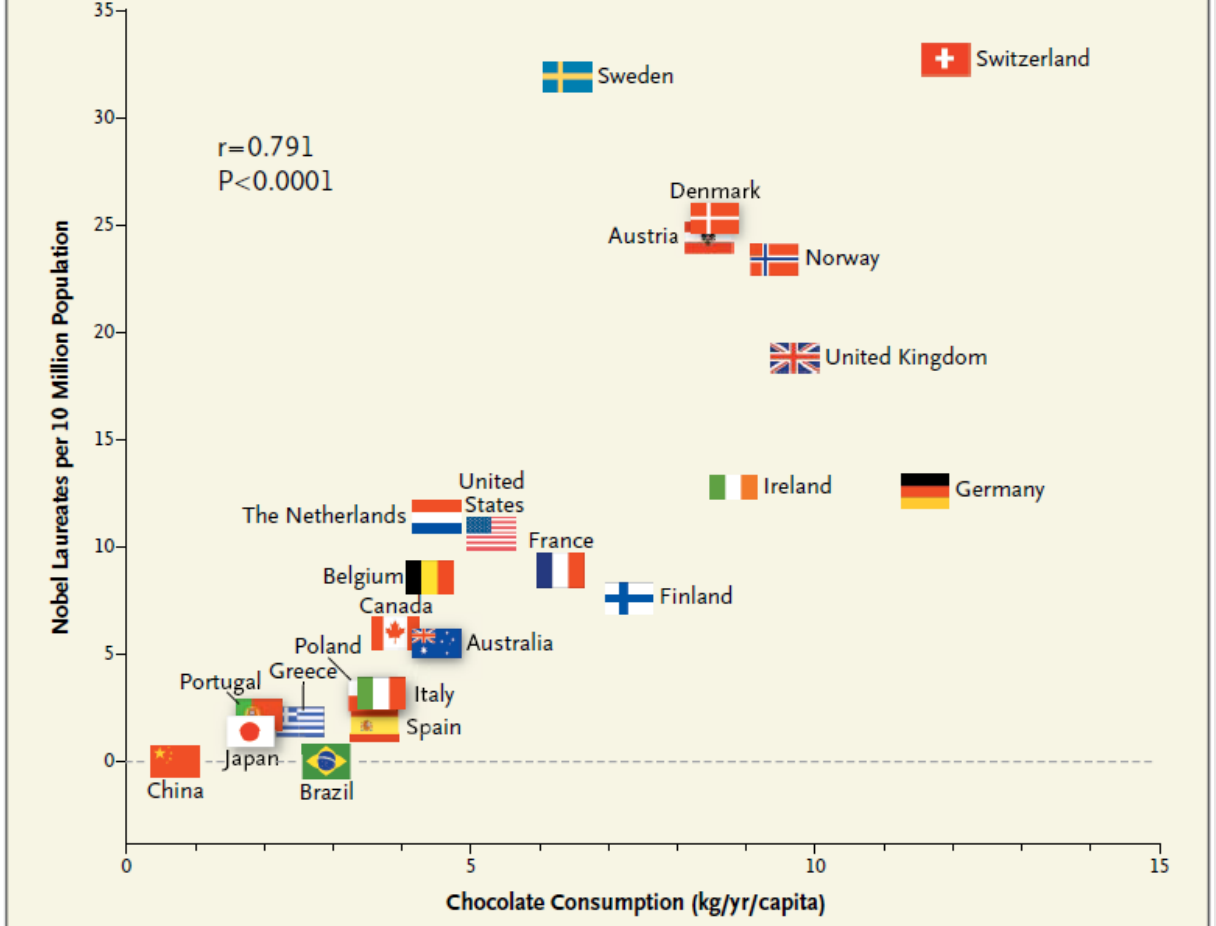

Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

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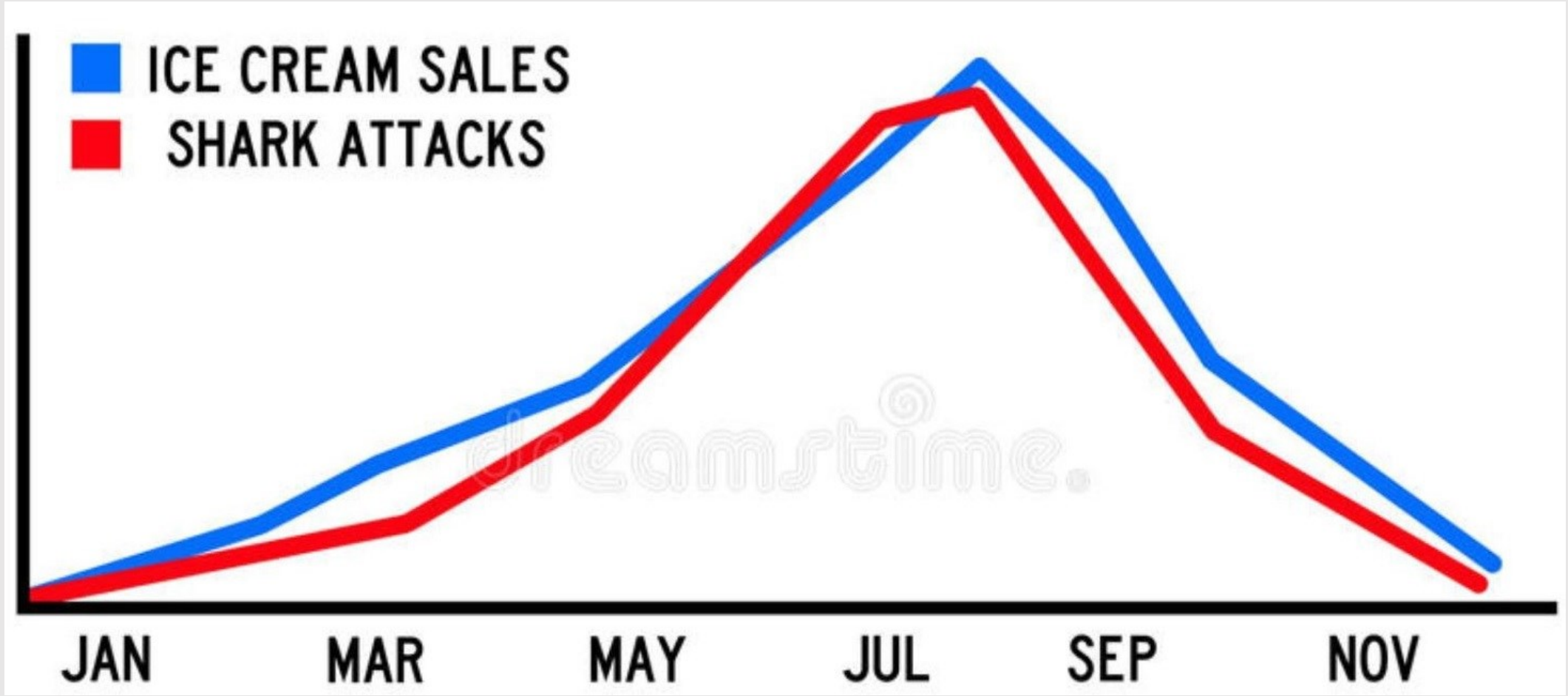

They both increase during summer months

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Association can be…

Spurious : not real, artificial, fortuitous, false, non-causal associations *due to chance*

An observed association between a disease and suspected factor *may not be real*

The ringing of alarm clocks **AND** the rising of the sun

Cock's crow causes the sun to rise (?!)

Neonatal mortality higher in those who were born in a hospital rather than at home.
Is home delivery ***better*** for newborn's health ?

high risk deliveries higher in the hospital than at home (***selection bias…***).

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Indirect/Confounded Association:

It is a statistical association between a characteristic of interest and a disease due to the presence of ***another factor*** i.e. a common factor (**confounding** variable).

So the association is due to the presence of another factor which is **common** to both.

- Altitude and endemic goiter [confounding factor is iodine deficiency]
- Glucose and CHD (*Coronary Heart Disease*) [confounding factor could be cigarette smoking]

(it increases the consumption of coffee/amount of sugar consumed **and** the risk of CHD!)

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Non-causal: *Non-directional* (true) association between two variables

Ex: alcohol use and smoking

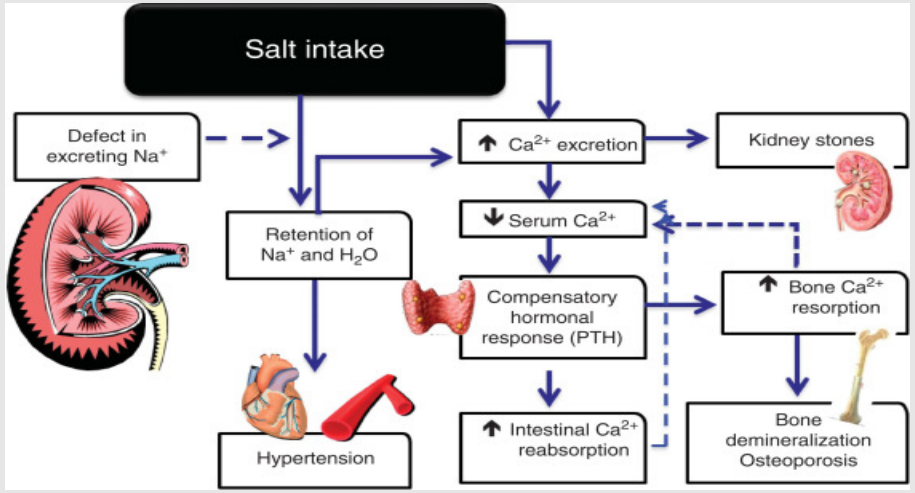
Finally…causal:

- a change in the **independent** variable must cause ***change*** in **dependent** variable

- **time** and **direction** (salt intake and hypertension)

- the association between the two attributes is not through a third attribute

- when the disease is present, the factor must also be present



The American Heart Association recommends <= 2.5 mg of salt a day [ideal limit <= 1.5 mg per day], especially for those with high blood pressure.

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So…how to establish a causal relationship in observational epidemiology?

Statistical methods help but **prior** knowledge is required …

We could use some criteria:

- Temporal association
- Strength of association [-> *effect size*]
- Dose-response relationship
- Biological plausibility
- Alternate Explanations
- Effect of cessation of exposure
- Consistency of association [reproducibility]
- Specificity of association

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1. Temporal association:

- The causal attribute must **precede** the disease or unfavorable outcome
- Exposure to the factor must have occurred **before** the disease developed
- **Length of interval** between exposure and disease is very important
- Its more obvious in *acute* disease than in *chronic* disease

Cause must precede the effect.

Drinking contaminated water → occurrence of diarrhea

[In many chronic cases, because of *insidious onset* and ignorance of precise ***induction period***, it gets hard to establish a temporal sequence as which comes first -the suspected agent or disease].

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2. Strength of the association [*effect size*]:

- Relationship between cause and outcome could be strong or weak.
- With the *increasing* level of exposure to the risk factor there should be an *increase in the incidence* of the disease.
- Strong associations are more likely to be causal than weak.
- Weaker associations are more likely to be explained by undetected **bias**.
- But weaker association does not rule out causation.

Strength of association can be **quantified** by (statistical) estimate of **risk**

[odds ratios, relative risk, attributable risk… etc…]

(Relative risks/Odds ratio **greater than 2** can be considered strong, more on this later in this block !)

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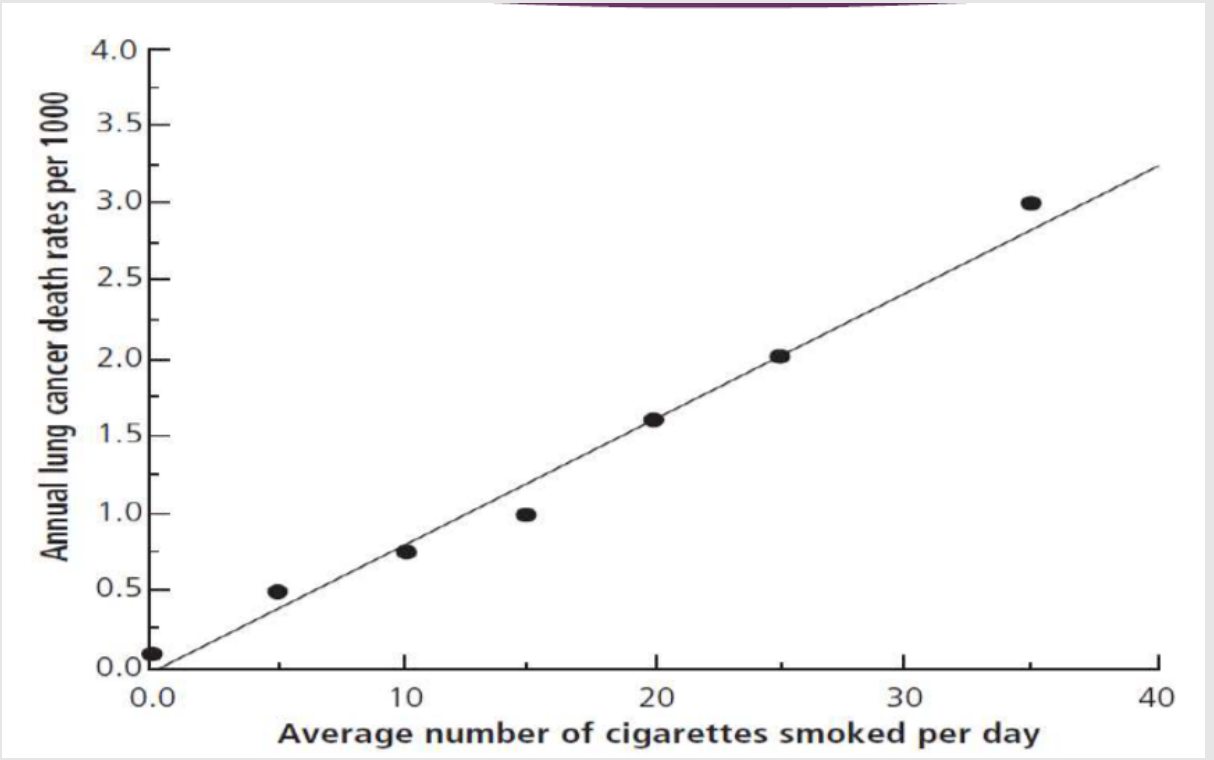
3. Dose-Response Relationship
(*The Biological Gradient*)

- As the dose of exposure increases, so does the risk of disease
- If a dose-response relationship is present, there is strong evidence for a causal relationship.
- However: the absence of a dose-response relationship does not necessarily rule out a causal relationship [think to *binary* exposures].
- In some cases in which a ***threshold*** may exist, no disease may develop *up to a certain level* of exposure; above this level, disease may develop [non-linearity…]

Death rates from lung cancer (per 1000) by number of cigarettes smoked, British male doctors, 1951 –1961



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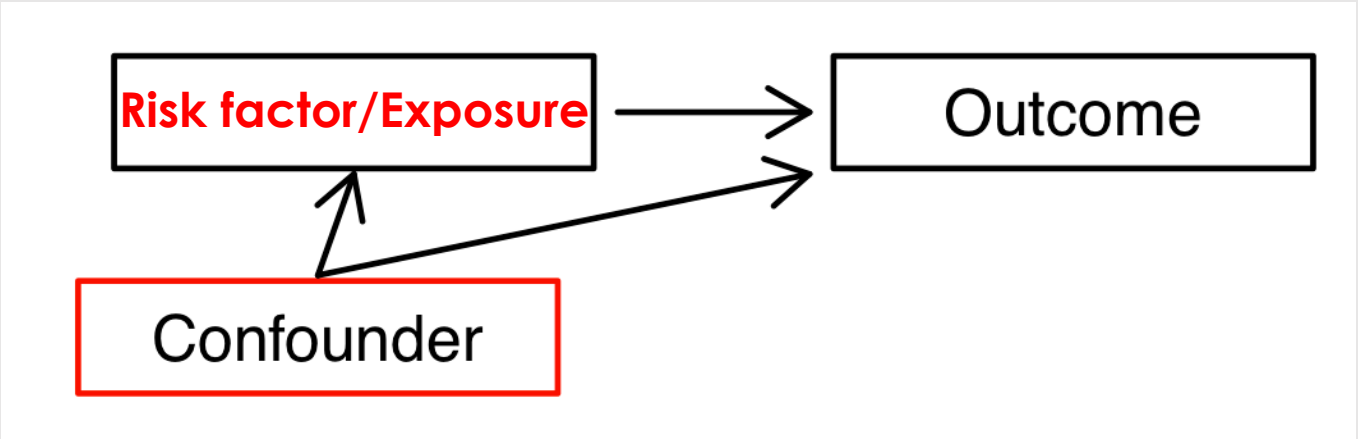
4. Biologic Plausibility

The association must be **consistent** with the other knowledge (mechanism of action, evidence from animal experiments …etc…).

Sometimes the lack of plausibility may simply be due to the **lack of sufficient knowledge** regarding the pathogenesis of a disease.

It is not so often based on logic or data but only on prior beliefs.

It is difficult to demonstrate where a **confounder** exhibits a biological gradient in relation to the outcome.



Risk Factor: Body Mass Index

Outcome: Heart Disease

Confounder: amount of fatty foods in the diet

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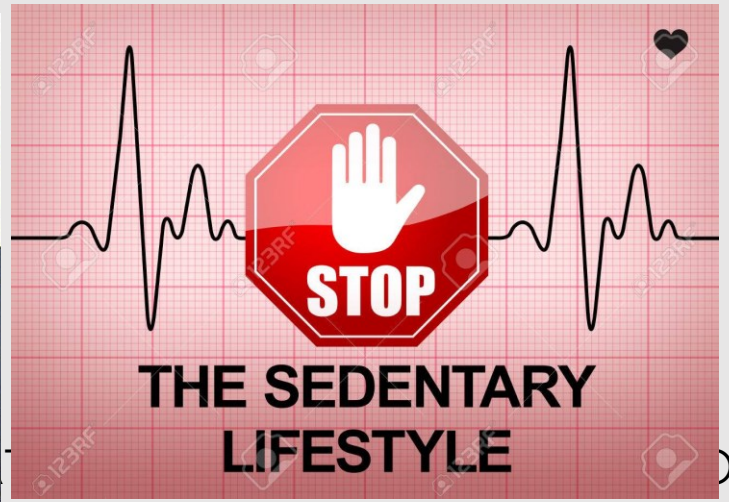
5. Consideration of alternate explanations:

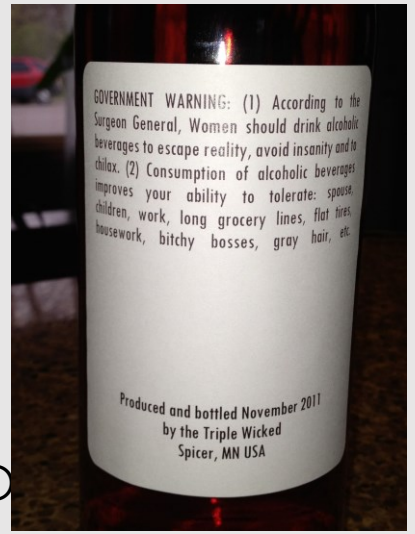
Interprets an observed association in regard to whether a relationship is causal or is the result of confounding.

In judging whether a reported association is causal, the extent to which the investigators have taken **other possible explanations** into account and the extent to which they have ruled out such explanations are important considerations.

6. Cessation of exposure:

If a factor is a cause of a disease, we would expect the risk of the disease to **decline** when exposure to the factor is reduced or eliminated…(basis of **public health policy actions**)





7. *Consistency* of the association:

Consistency is the occurrence of the association **at some other time and place repeatedly** unless there is a clear reason to expect different results.

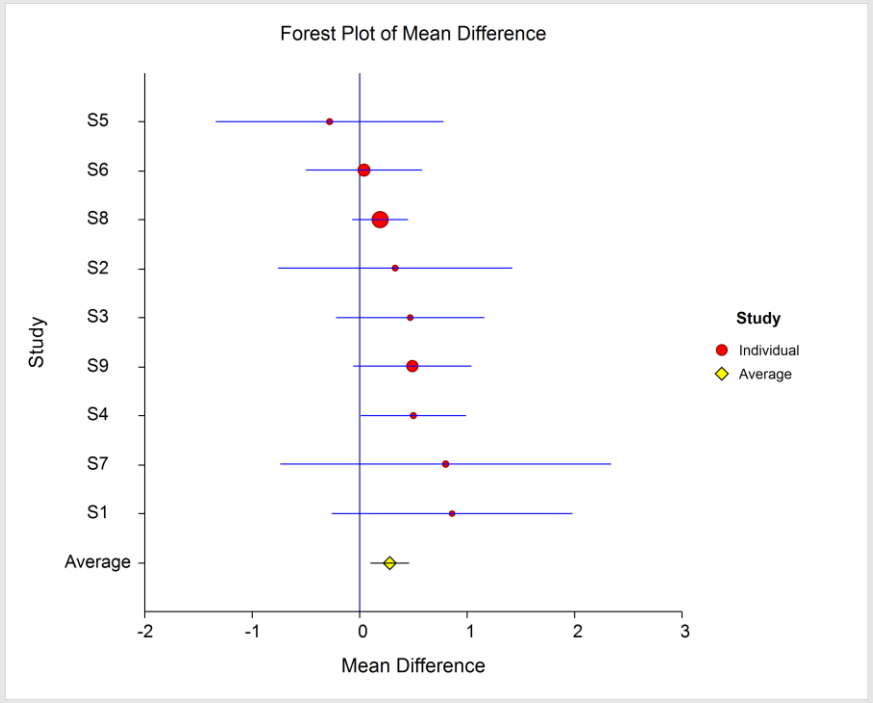
If a relationship is causal, the findings should be **consistent** with other data*. Lack of consistency however does not rule out a causal association**.

*Repeated observation of an association in ***different*** populations under ***different*** circumstances.

***Statistical tool: metanalysis**

https://youtu.be/SDSYB3nuYTE

https://youtu.be/4zZDa4IDsLc



** **different** populations? different methods ? …careful evaluation of all aspects of **study design** !

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8. Specificity of the association:
(the **weakest** of the criteria, should probably be eliminated…)

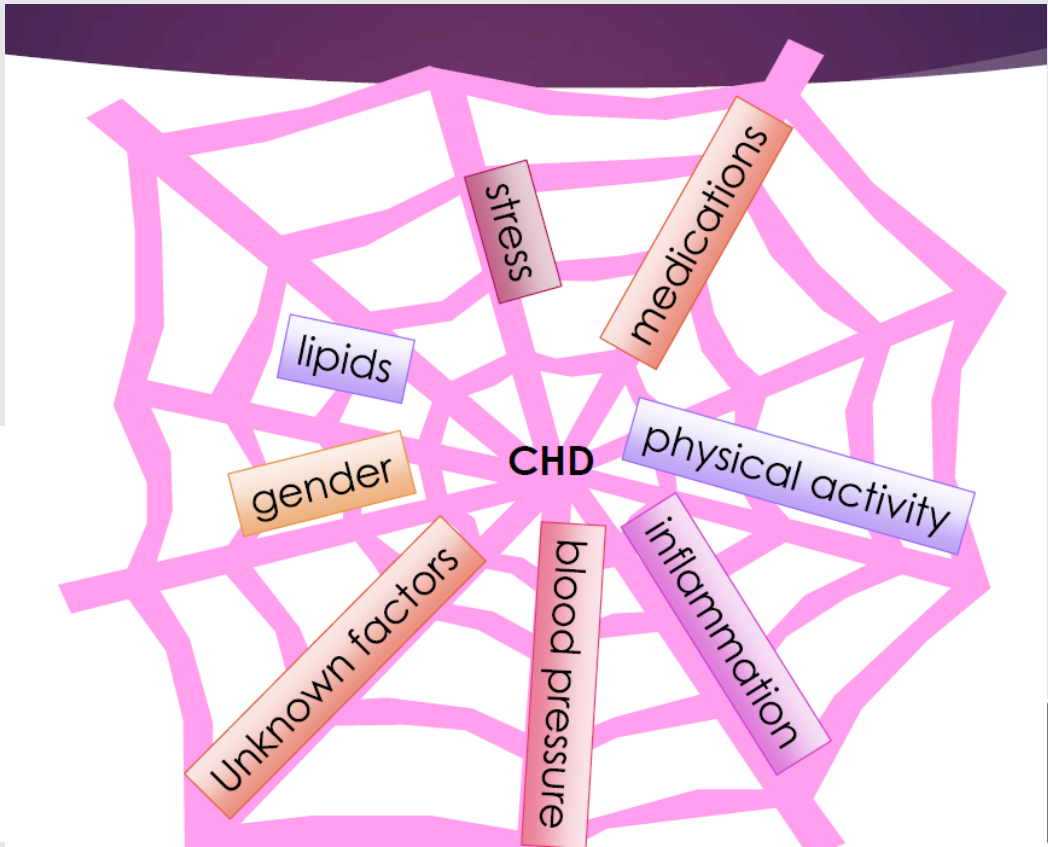
Specificity implies a **one to one** relationship between the cause and effect.

It's the most difficult to occur for 2 reasons:

- Single cause or factor can give rise to more than 1 disease

- Most diseases are due to multiple factors.

Ex: Smoking is associated with many diseases.
- Not everyone who smokes develops cancer
- Not everyone who develops cancer has smoked



The Statistical point of view on causality…(Intro!)

Causal inference is a complex scientific task that relies on triangulating evidence from multiple sources and on the application of a variety of methodological approaches.

We (as statisticians) remain *agnostic* about metaphysical concepts like causality and cause.

We rather focus on the identification and **estimation** of causal effects in populations, that is, **numerical quantities** that measure **changes in the distribution** of an outcome under **different interventions/exposures**.

[***EXPLANATORY*** models framework]

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A Classification of Data Science Tasks…

Descriptive summary

Prediction map some features (*inputs*) to other features (*outputs*)

Counterfactual **prediction** : predict something **as if the world had been different**, which is required in **causal inference** applications.

	Description	Prediction	Causal inference
Example of scientific question	How can women aged 60–80 years with stroke history be partitioned in classes defined by their characteristics?	What is the probability of having a stroke next year for women with certain characteristics?	Will starting a statin reduce, on average, the risk of stroke in women with certain characteristics?
Data	• Eligibility criteria • Features (symptoms, clinical parameters …)	• Eligibility criteria • Output (diagnosis of stroke over the next year) • Inputs (age, blood pressure, history of stroke, diabetes at baseline)	• Eligibility criteria • Outcome (diagnosis of stroke over the next year) • Treatment (initiation of statins at baseline) • Confounders • Effect modifiers (optional)
Examples of analytics	Cluster analysis …	Regression Decision trees Random forests Support vector machines Neural networks	Regression Matching Inverse probability weighting

https://www.hsph.harvard.edu/wp-content/uploads/sites/1268/2019/04/hernan_chance19.pdf

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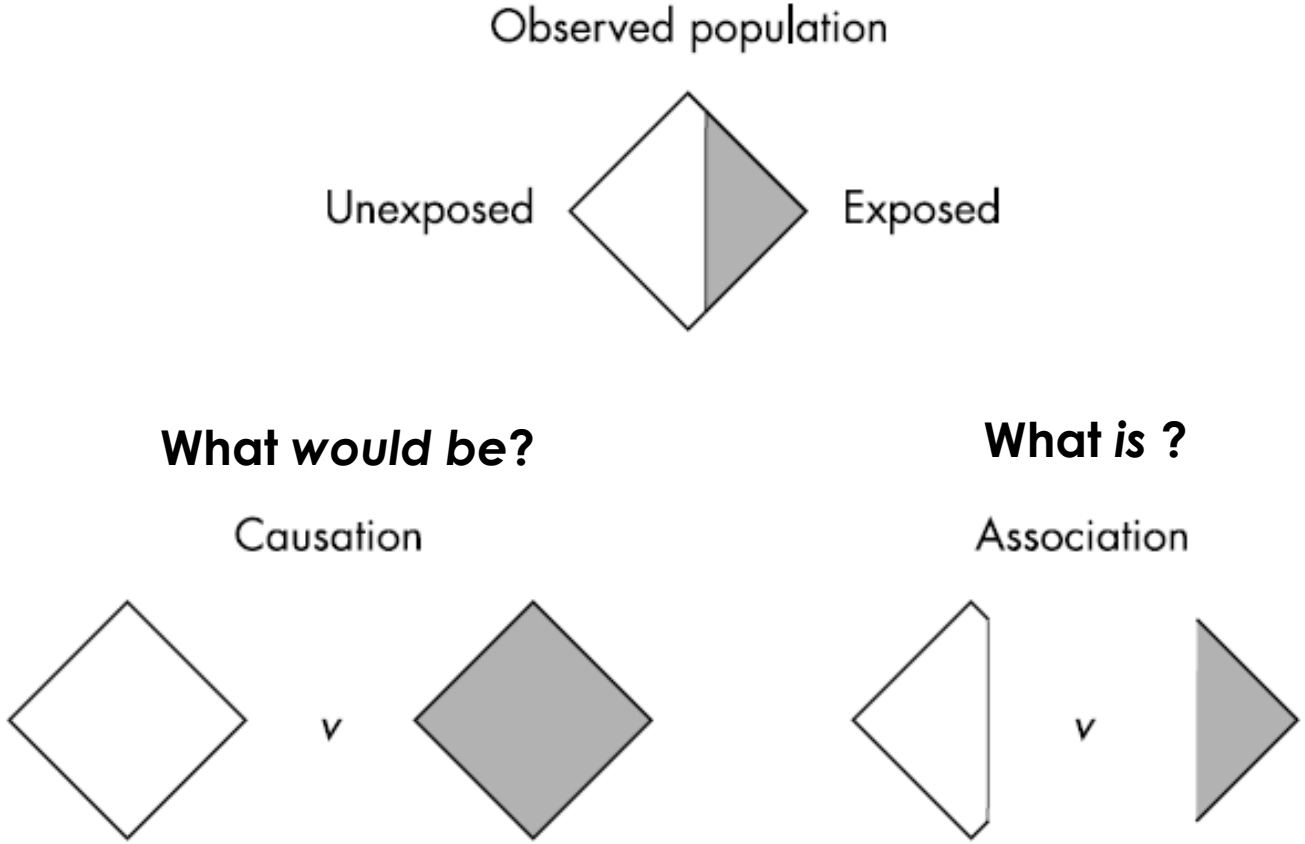
What is a **causal** effect?



Comparison of **potential outcomes** for **THE SAME** well defined population:

Y_1 Potential outcome if treated/exposed

Y_0 Potential outcome if control (**not** treated/exposed)

An **association** compares some outcome in two ***DIFFERENT*** groups …

Figure from Hernan: https://pubmed.ncbi.nlm.nih.gov/15026432/

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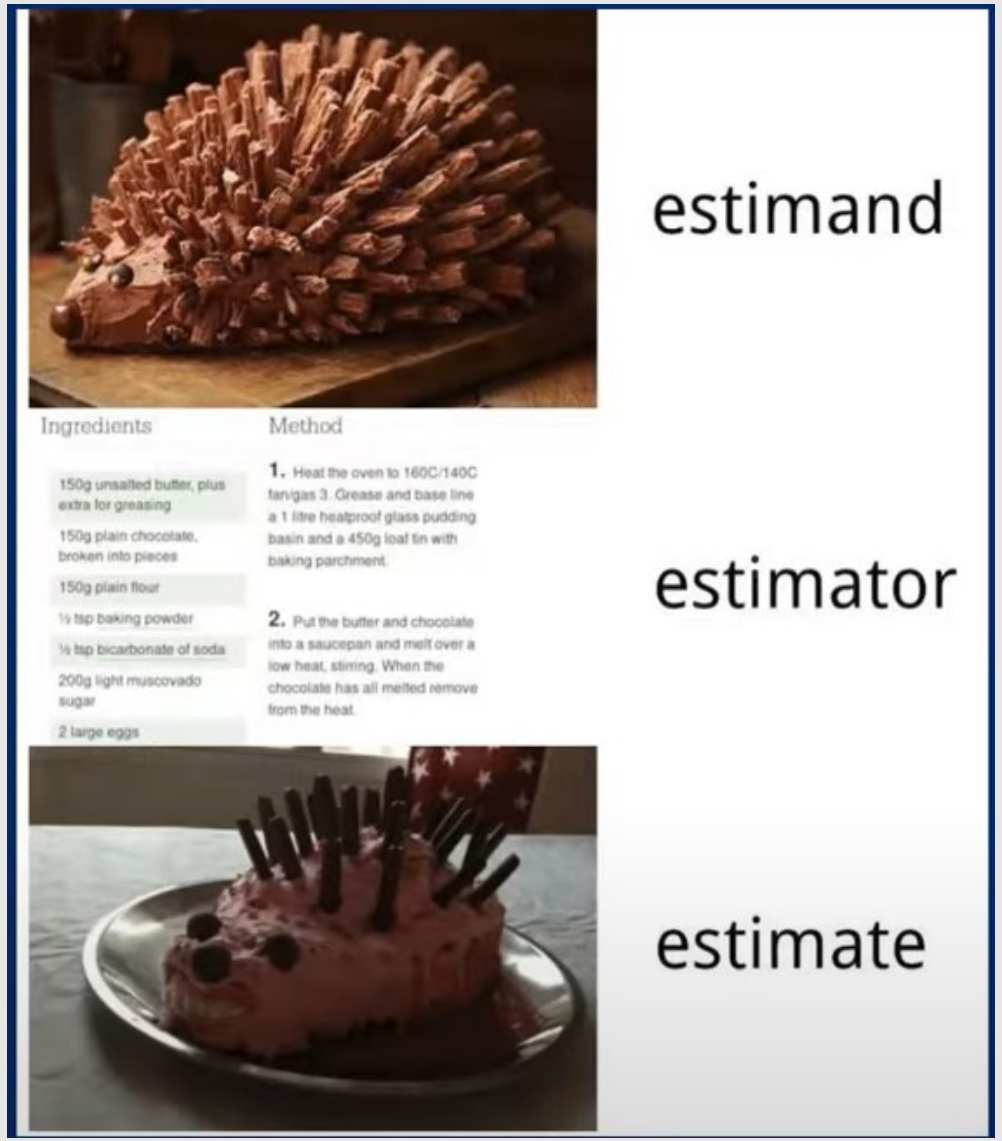

The estimand vs the *estimator*

It is confusing…in practice we often use observed data from two **different** groups to **estimate** a *causal* effect*…

But it is important to distinguish the ***estimand*** – the thing we want to learn about – from the ***estimator*** – how we learn about it …

* particularly easy in **randomized** studies…

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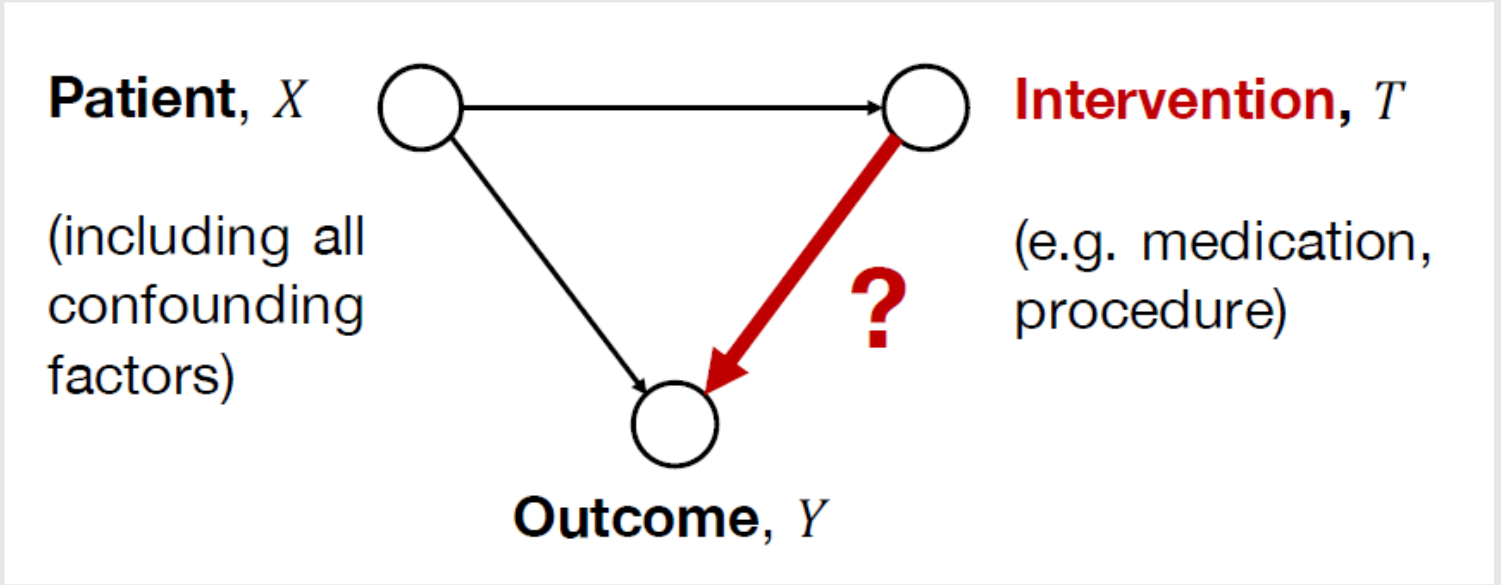
Typical context in observational studies



(High dimensional…)

In health research we often want to answer the questions that are causal ***by nature***

Ti is a binary exposure*:

$$T_i = \begin{cases} 0 & \text{Untreated} \\ 1 & \text{Treated} \end{cases}$$

*generalizable to categorical/continuous…

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Potential Outcomes Framework

(Rubin-Neyman Causal Model)

Each unit (individual) has **two** potential outcomes:

$Y_0(i)$ is the potential outcome had the unit *i* **not** been treated: **control** outcome

$Y_1(i)$ is the potential outcome had the unit *i* been treated: **treated** outcome

Individual treatment effect for subject *i*:

$$ITE_i = Y_1(i) - Y_0(i)$$

Average Treatment Effect**:

$$ATE = E[Y_1 - Y_0] = E[ITE_i]$$

****simple to estimate*** in RCT (**randomized** control trials)

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Potential Outcomes Framework

(Rubin-Neyman Causal Model)

Each unit (individual) has **two** potential outcomes:

$Y_0(i)$ is the potential outcome had the unit **not** been treated/exposed: **control (unexposed)** outcome

$Y_1(i)$ is the potential outcome had the unit been treated/exposed: **treated (exposed)** outcome

$$T_i = \begin{cases} 0 & \text{Untreated} \\ 1 & \text{Treated} \end{cases}$$

Observed **factual** outcome:

$$y_i = t_i Y_1(i) + (1 - t_i) Y_0(i)$$

Unobserved **counterfactual** outcome:

$$y_i^{CF} = (1 - t_i) Y_1(i) + t_i Y_0(i)$$

The so-called **fundamental problem of causal inference** is that one can never **directly** observe causal effects, because we can never observe **both** potential outcomes for any individual (***at the same time***).

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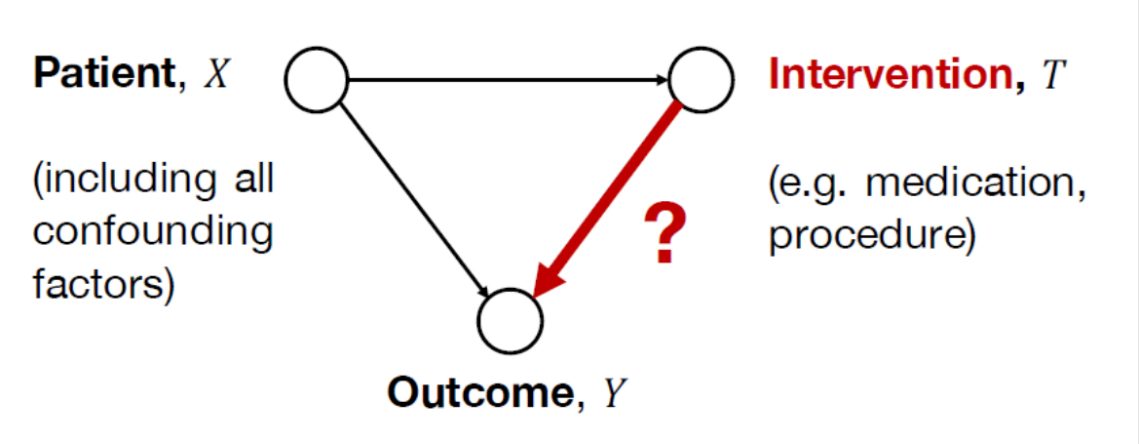
Potential Outcomes Framework

(Rubin-Neyman Causal Model)



If we *take into account* some characteristics of subjects [indicated by X]:

$$CATE_x = E[Y_1 - Y_0 | X = x]$$

Conditional Average Treatment Effect

among individuals with the same *covariates* X

$$ATE = E_x[E[Y_1 - Y_0 | X = x]]$$

Average Treatment Effect

over a population represented by the distribution of X

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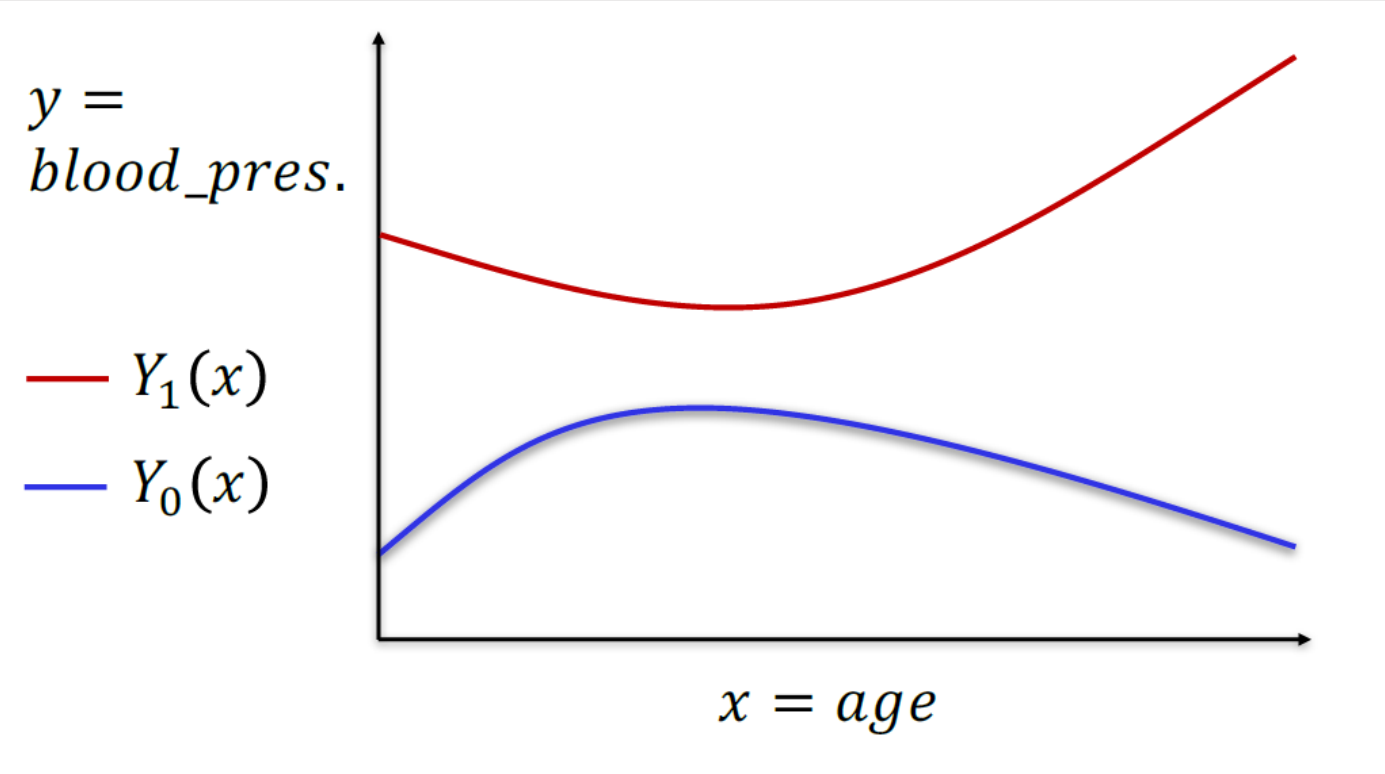
The fundamental problem of causal inference

We only ever observe **one** of the [*two*] potential outcomes

Example – Blood pressure and age:



Suppose individuals are characterized by just one feature X: age.

The two curves are the ***potential*** outcomes of what would happen to blood pressure (BP) under treatment zero, (**blue** curve), or treatment one, (**red** curve).

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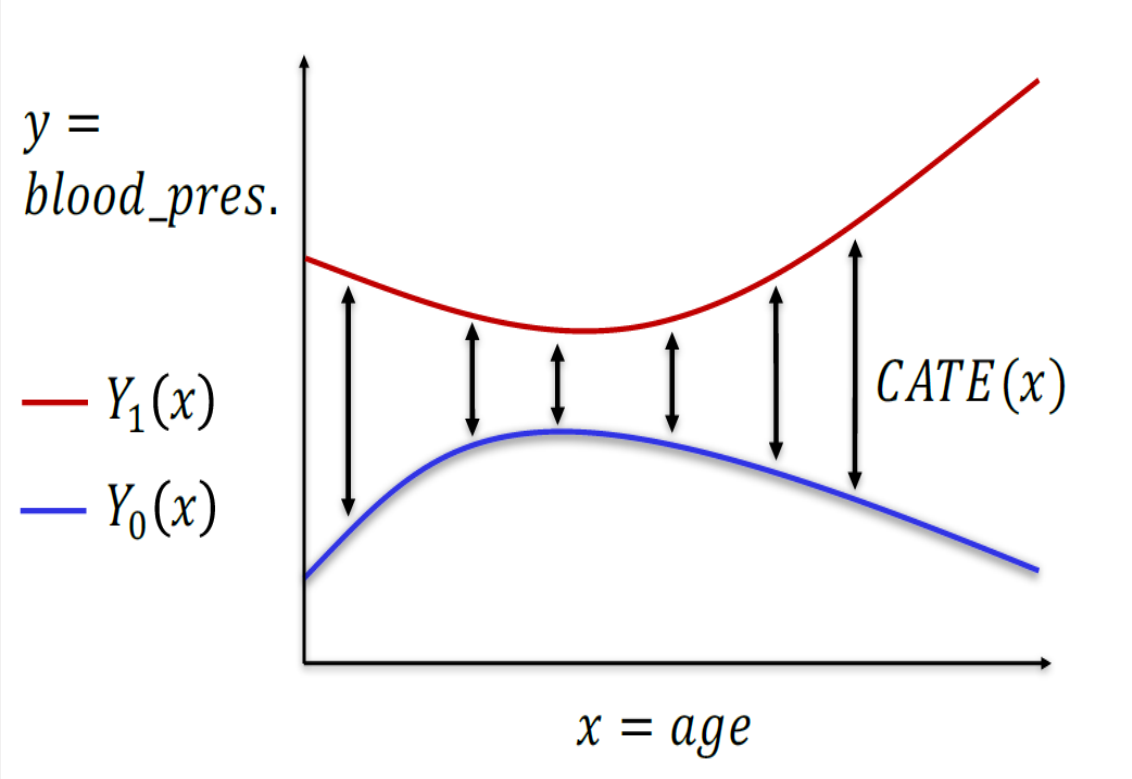
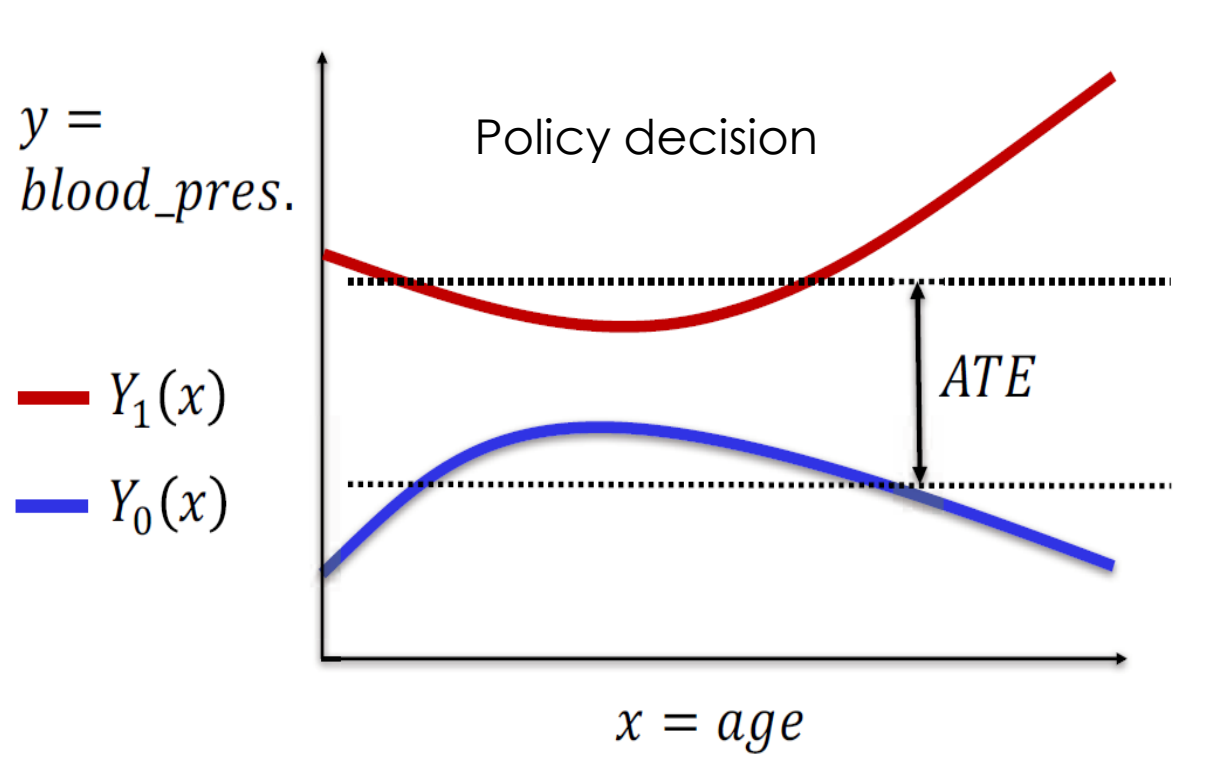




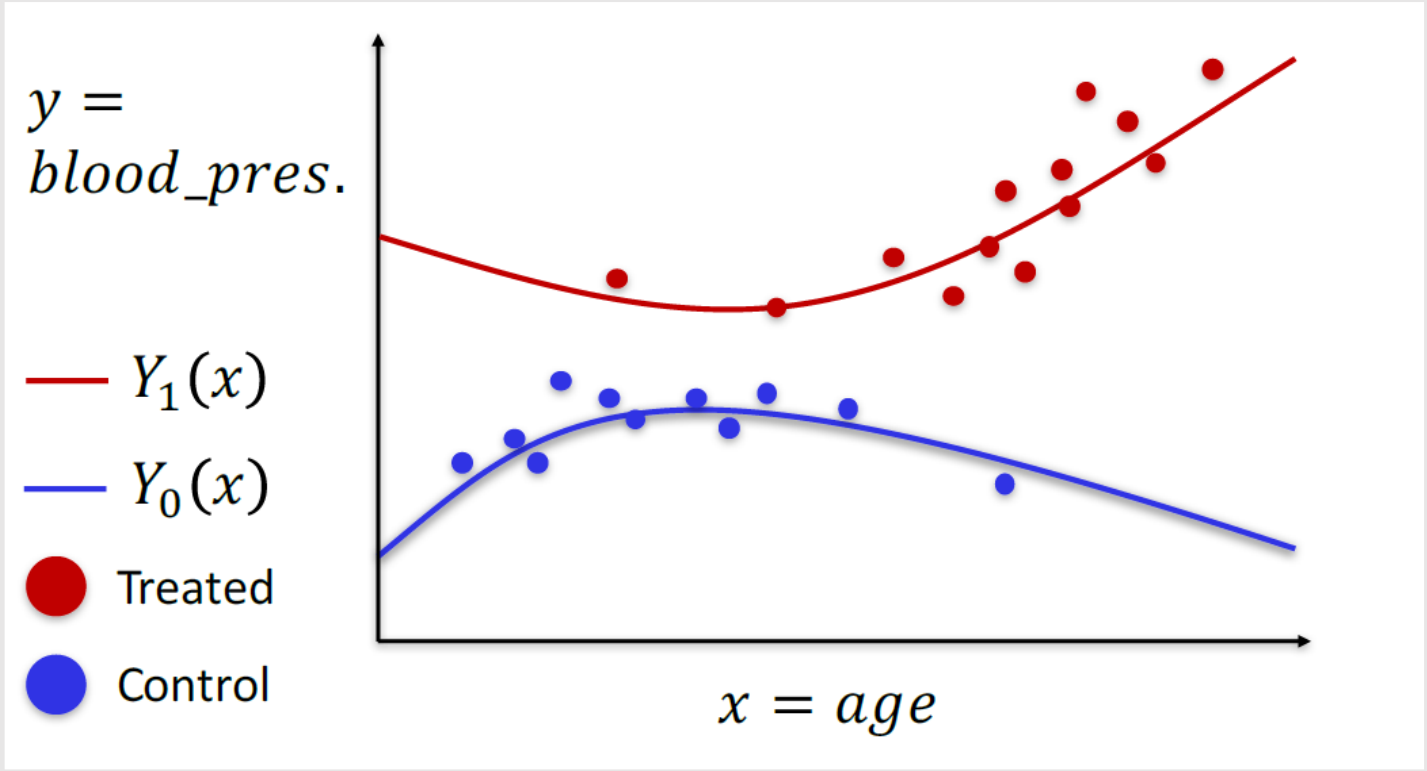
Blue: BP is low for the young and for the elderly. For middle age, BP is in the higher range.

Red: young people have much higher BP, and so do older people.

What about the ***difference*** for each subject at certain age ? That is the CATE effect

And what about ***observed*** data ??

STATISTICAL LEARNING IN EPIDEMIOLOGY



We **observe** data points that might be **unevenly** distributed [esp. in observational studies].

Blue treatment happens to be given more to young, and **red** more to older people.

Variety of reasons: access to medication, socioeconomic reasons, existing treatment guidelines…..

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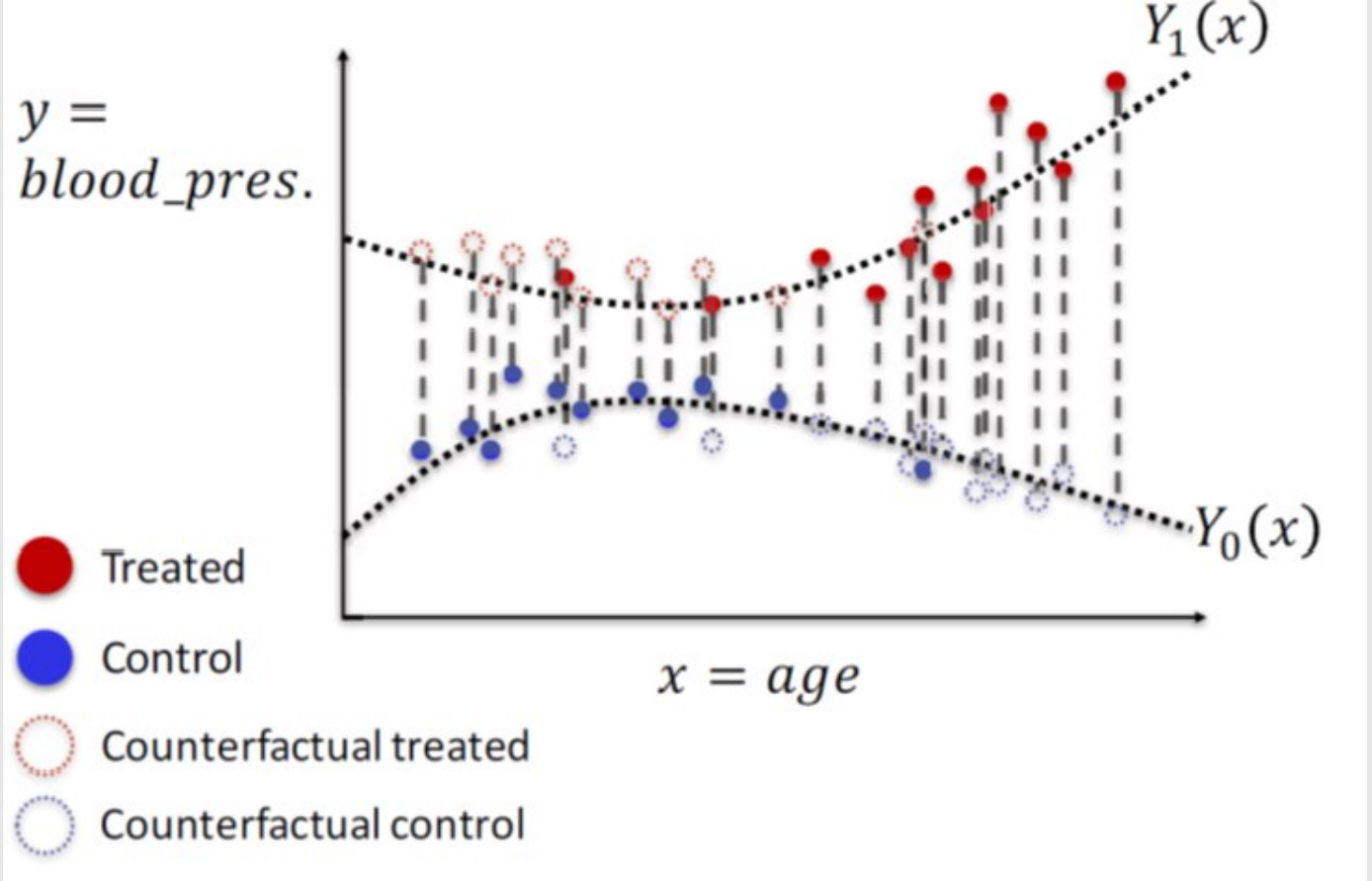

For each subject, **what would have happened** if he/she had gotten ***the other*** treatment?
→ counterfactuals/potential outcomes.

[dots are not exactly ***on*** the curves, because there could be some *stochasticity* in the outcome…]

Dotted lines are the ***expected*** potential outcomes and the circles are the ***realizations*** of them.

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(age, gender, exercise,treatment)			Observed sugar levels
(45, F, 0, A)			6
(45, F, 1, B)			6.5
(55, M, 0, A)			7
(55, M, 1, B)			8
(65, F, 0, B)			8
(65,F, 1, A)			7.5
(75,M, 0, B)			9
(75,M, 1, A)			8

mean(sugar | medication B)-mean(sugar | medication A) = ?

7.875 -7.125 = 0.75

To solve the problem, we have to **make some assumptions**…(in **observational** studies much more than in **randomized** studies!)

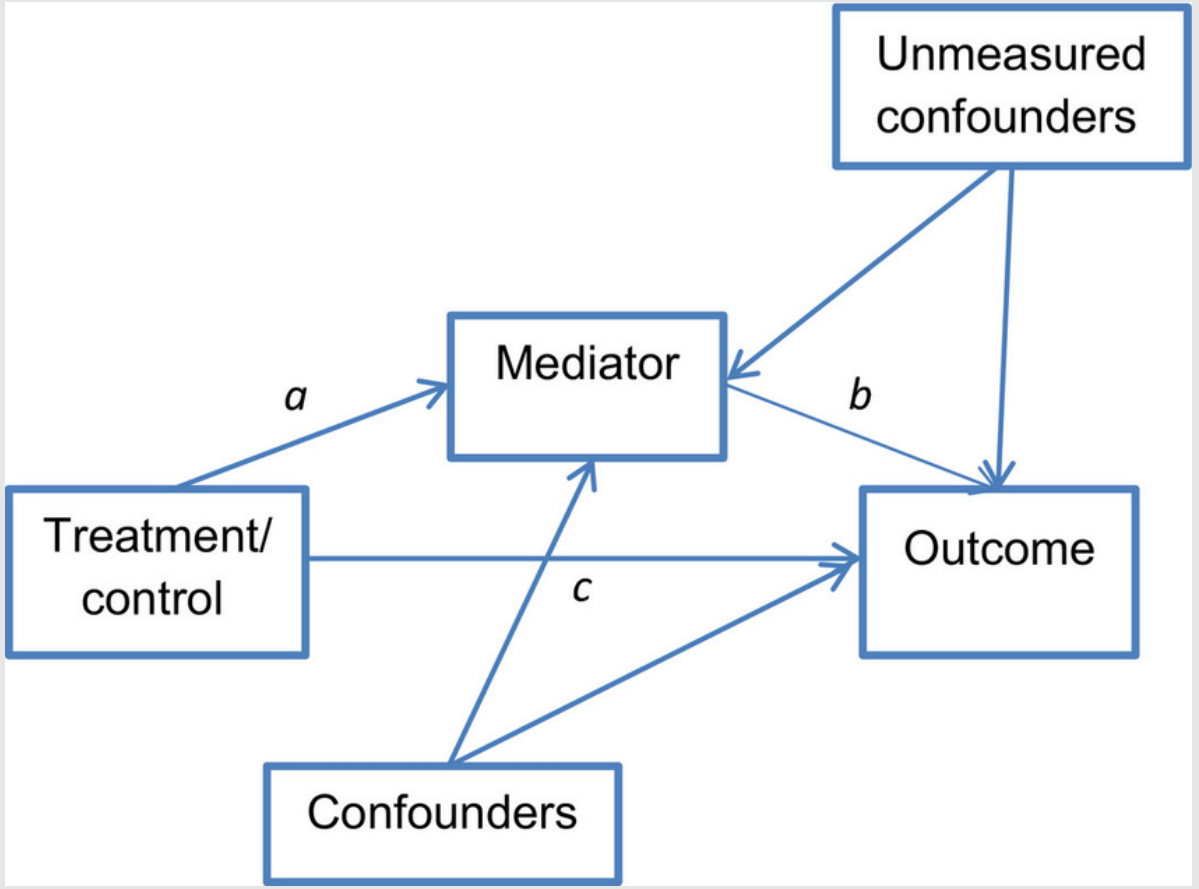
age, gender, whether they exercise regularly, what treatment they got, which is A or B.

Observed sugar glucose levels at the end of the treatment.

mean(sugar | *had they received B*) – mean(sugar | *had they received A*) = ?

7.125 -7.875 = -0.75

(age, gender, exercise)	Y_0: Sugar levels *had they received* medication A	Y_1: Sugar levels *had they received* medication B	Observed sugar levels
(45, F, 0)	6	5.5	6
(45, F, 1)	7	6.5	6.5
(55, M, 0)	7	6	7
(55, M, 1)	9	8	8
(65, F, 0)	8.5	8	8
(65,F, 1)	7.5	7	7.5
(75,M, 0)	10	9	9
(75,M, 1)	8	7	8



Stay tuned !!... Something more in block 3...

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