STATISTICS & ML WITH R

Mapping causal & predictive approaches

2024

M. Chiara Mimmi & Luisa M. Mimmi

WORKSHOP SCHEDULE

- Modules
  - 1. Intro to R and data analysis
  - 2. Statistical inference & hypothesis testing
  - 3. Modeling correlation and regression
  - 4 Mapping causal & predictive approaches
  - 5. Machine Learning
  - 6. Extra topics:
    - MetaboAnalyst;
    - Power Analysis

- Each day will include:
    - Frontal class (MORNING)
    - Practical training with R about the topics discussed in the morning. (AFTERNOON)

MODULE 4 – LECTURE OUTLINE

Mapping causal approaches

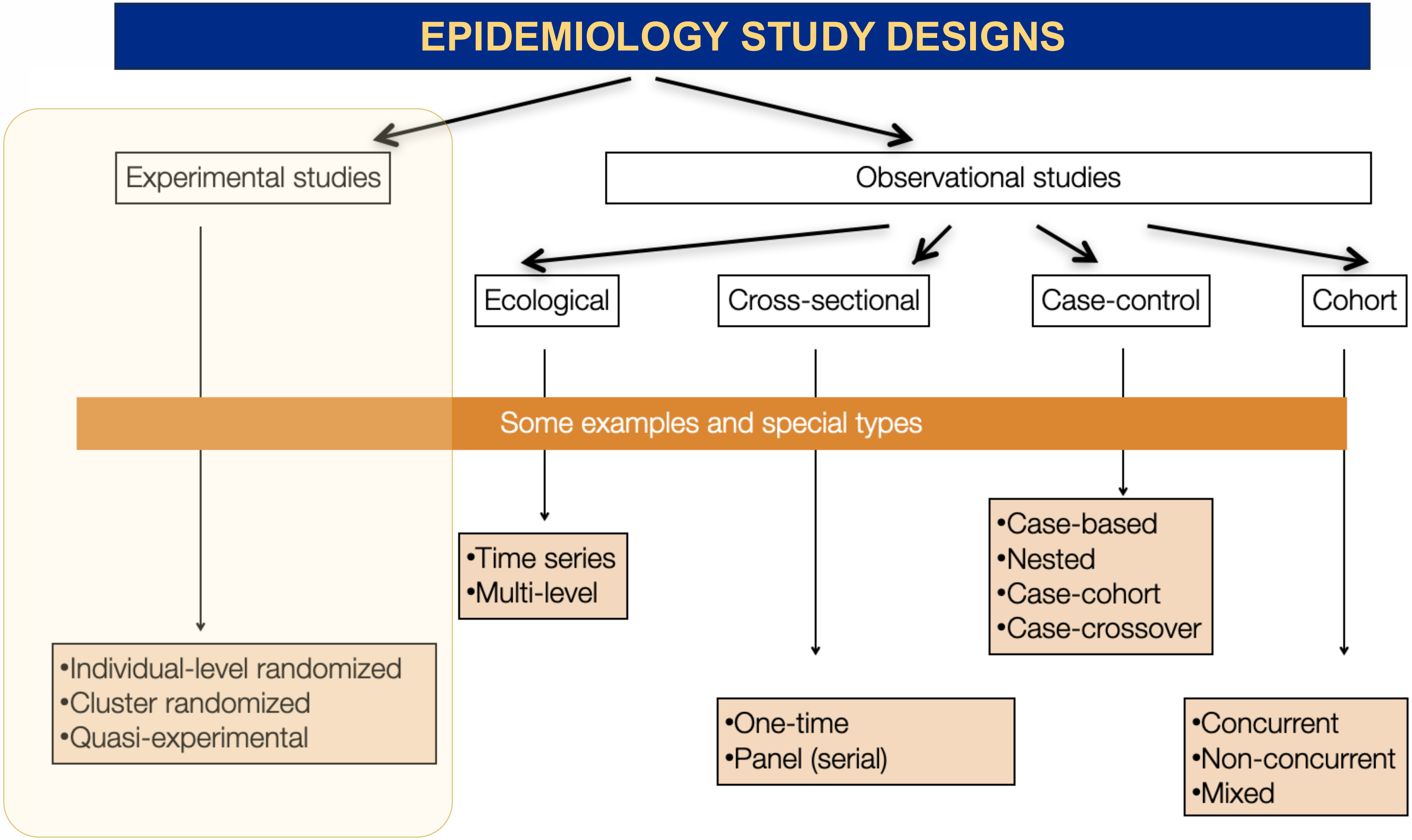
- Recall the essential features of experimental study designs
    - Learning the vocabulary of causal analysis
- Get a visual intuition of causal pathways, including challenging elements:
    - **Collider** variables
    - **Confounder** variables
    - **Mediator** variables
- Discuss the correct causal model to capture the association among exposure, outcome and other covariates, (including *challenging ones*)
- Define causal outcomes and choosing the appropriate “estimands”:
    - ATE, ATT, or ATU?
- Devise statistical methods to estimate ATE, ATT, and ATU based on research question and (sub)population of interest

From *observational* to *experimental* studies

- "**OBSERVATIONAL STUDIES**" on variables of interest and their relationships have *no controlled assignment of the treatment*
  - We may find CORRELATION / ASSOCIATION, but it DOES NOT IMPLY CAUSATION! Why?
  - … hidden variables may affect the relationship between the explanatory variable and the response variable
  - *…but often used (implicitly or not) to estimate causal effect of an exposure!*

- **"EXPERIMENTAL STUDIES"** seek to uncover CAUSATION, so they are *designed to provoke a response*
  - Researchers assign the treatment to an experimental unit (or subject) and observing its effect
  - These studies use some *ad hoc* design principles and controlled independent variables

Experimental and non-experimental study designs…



EPIDEMIOLOGY STUDY DESIGNS

Experimental studies

Observational studies

Ecological

Cross-sectional

Case-control

Cohort

Some examples and special types

- Individual-level randomized
- Cluster randomized
- Quasi-experimental

- Time series
- Multi-level

- One-time
- Panel (serial)

- Case-based
- Nested
- Case-cohort
- Case-crossover

- Concurrent
- Non-concurrent
- Mixed

Source: https://bookdown.org/jbrophy115/bookdown-clinepi/design.html

Different goals of statistical modeling (part 1/2)

1. **ASSOCIATION/CORRELATION** → observational studies
   - aimed at **summarizing or representing the data structure**, *without* an underlying causal theory
   - may help **form hypotheses** for explanatory and predictive modeling

2. **CAUSAL EXPLANATION** → experimental studies
   - aimed at **testing "explanatory connection"** between treatment and outcome variables
   - prevalent in "**causal theory-heavy**" fields (economics, psychology, environmental science, etc.)

- **Note**:
  - ✓ The **same modeling approach** (e.g., fitting a regression model) can be used for **different goals**
  - ✓ While they shouldn't be confused, **explanatory power** and **predictive accuracy** are complementary goals: e.g., in bioinformatics (which has little theory and abundance of data), predictive models are pivotal in generating avenues for causal theory.

3. **EMPIRICAL PREDICTION** → algorithmic machine learning and data-mining modeling

A framework for CAUSAL ANALYSIS

Key terminology

The conceptual framework for causal analysis (1/3)

- **Fundamental vocabulary**:
  - **Intervention** decisions and actions that change the behaviors or situation of people/firms/other subjects (drug, vaccine, program participation)
    - TREATMENT = commonly used in experimental studies when researchers directly "assigns" the **causal variable**
    - EXPOSURE = commonly used observational studies when participants "naturally" experience the the **causal variable**
  - **Subjects** = those that may be affected (at least in principle), in fact are
    - TREATED subjects
    - UNTREATED subjects
  - **Outcome** = variable(s) that may be affected by the intervention
    - can be caused by exposure either directly or through an intermediate process
  - **Causation** = causal processes that lead to the development of outcomes

The conceptual framework for causal analysis (2/3)

- **Fundamental vocabulary** (“*tricky ones*” 😉):
  - **Bias** = systematic error that can occur at different stages of the study: *data collection*, *analysis* or *interpretation* of the causal relationship exposure-outcome.
    - **Selection bias** = both the exposure and the outcome affect whether an individual is included in the sampled population
      - **Sampling bias** = some members of the intended population are less likely to be included than others
      - **Attrition bias** = participants who drop out of a study systematically differ from those who remain
      - **Non-response bias** = participants who refuse to participate in the study systematically differ from those who take part
    - **Recall bias** = a systematic difference in the ability of participant groups to accurately recall information
    - **Information bias** = there is misclassification or inaccurate measurement (e.g., patients underreporting smoking habits)
    - …

Check out this cool list of all types of bias:
https://quantifyinghealth.com/list-of-biases/

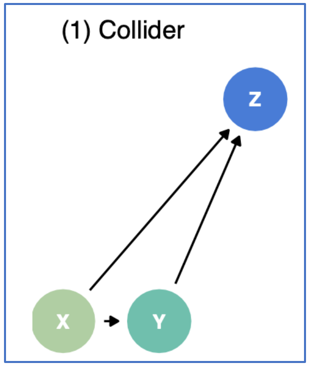
The conceptual framework for causal analysis (3/3)

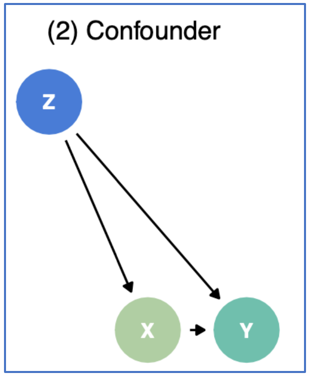
- **Fundamental vocabulary** (“*tricky ones*” 😉):

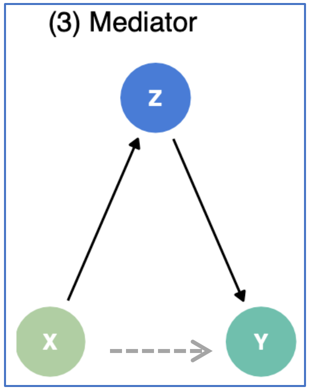
  - **Collider** = variable that is **influenced by treatment and outcome** (like a “common effect”)
    - **EXAMPLE**: sleepiness (Z), with shift work (X) and apnea (Y)
    - Conditioning on or controlling for a collider in the causal model can create a distortion *(“collider bias”)*

  - **Confounder** = variable that **affect both treatment and outcome** (“apparent” cause), but it is **not in the causal pathway**
    - **EXAMPLE**: smoking (Z), with exercise (X) and lung cancer (Y)
    - Most confounder variables involve some kind of *selection* (e.g., self-selection) that can be addressed stratifying subjects by it

  - **Mediator** = is a variable that is **in the causal pathway** and “explains” why **treatment** affects **outcome** (like a “mechanisms”)
    - **EXAMPLE**: immune function (Z), with exercise (X) and lung cancer (Y)
    - Conditioning on or controlling for a mediator can be done to assess what *part of the effect* they play


(1) Collider


(2) Confounder


(3) Mediator

Estimands, Estimators, Estimates

- The **estimand** is the *target outcome of interest* about the causal effect of a treatment in a population
  - EXAMPLEs: **ATE** (Average Treatment Effect), **ATT** (Average Treatment Effect on the Treated), or **ATU** (Average Treatment Effect on the Untreated)

- The **estimator** is the statistical method ("recipe") by which we approximate this *estimand* using data
  - EXAMPLEs: **difference-in-means** for ATE in a randomized controlled trial (RCT), or **propensity scores matching** (PSM) for ATT within observational data.

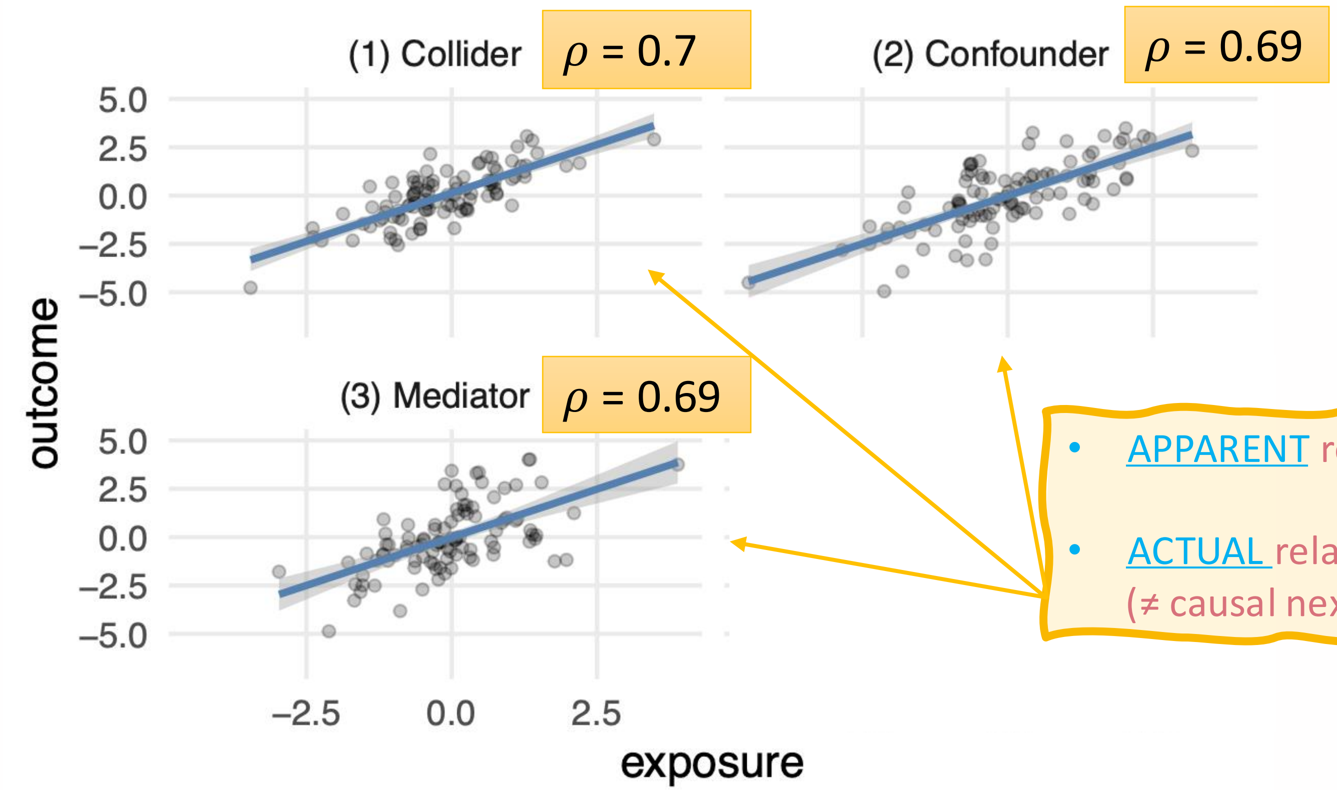
- The **estimate** is the numerical value we get when we plug our data into the estimator
  - EXAMPLE: we calculate an **ATE = 3.5 units** (e.g., a treatment improves test scores by 3.5 points on average in the entire population)

Visualizing causal maps

Using “DAGs” in guiding statistical modeling

Typical challenges in estimating causal effects: a.k.a. *“correlation does not imply causation”*

- Consider 3 distinct datasets: while their statistical summaries and visualizations are very similar, the **true causal nexus differs!**
- **Deciding the** correct model requires knowledge of the data-generating mechanism (i.e. the random assignment to exposure/not exposure in experiments)



- APPARENT relationship **similar**
- ACTUAL relationship **different** (≠ causal nexus)

Source: Barrett, M., McGowan, L. D., & Gerke, T. (2024). *Causal Inference in R*. Retrieved from https://www.r-causal.org/

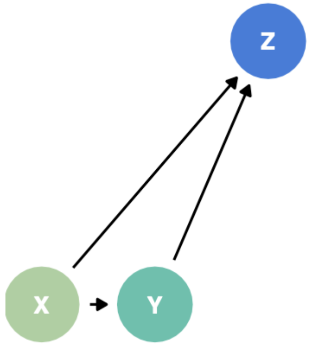
Typical challenges in estimating causal effects: visual intuition

- Directed Acyclic Graphs (DAGs) can offer visual intuition of the causal nexus at play in the 3 datasets. Failure to adjust models to these situation leads to BIAS
  - X is some exposure of interest, Y an outcome, and Z a known, measured factor

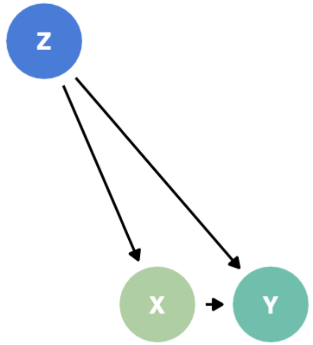
(1) a "**COLLIDER**", common effect (that invertedly connects). E.g.:

- X = sodium intake
- Y = systolic blood pressure
- Z = urinary protein excretion

(1) Collider



(2) Confounder



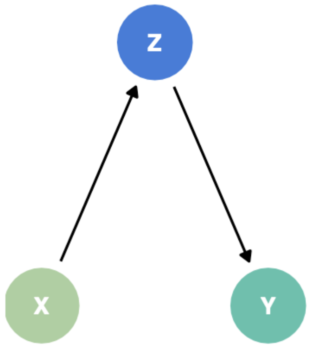
(2) a "**CONFOUNDER**", common cause. E.g.:

- X = smoking
- Y = lung cancer
- Z = alcohol (consumers also tend to be smokers)

(3) a "**MEDIATOR**" is caused by X and then it causes Y. E.g.:

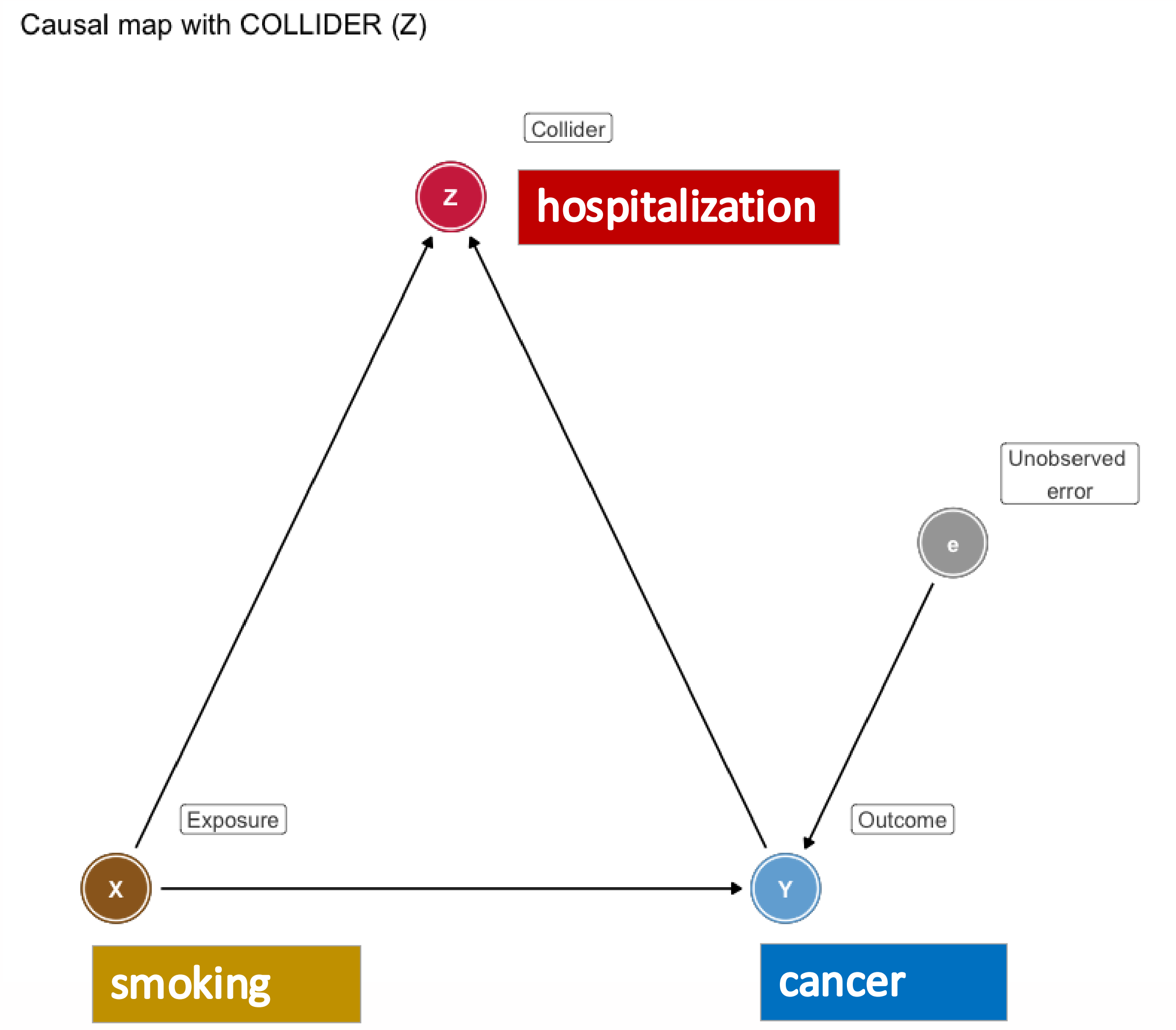
- X = screen time
- Y = obesity
- Z = physical exercise

(3) Mediator



Source: Barrett, M., McGowan, L. D., & Gerke, T. (2024). *Causal Inference in R*. Retrieved from https://www.r-causal.org/

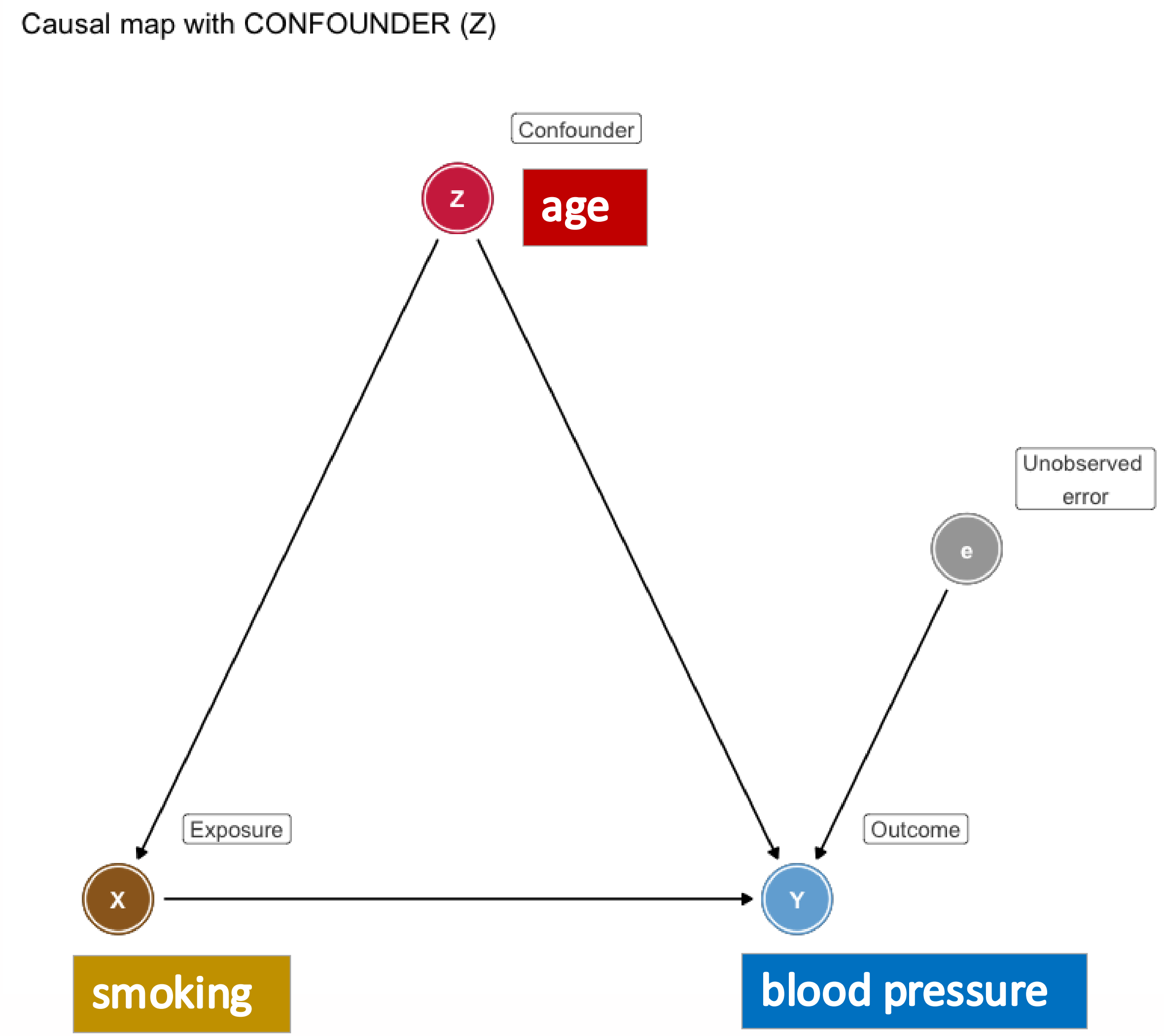
How to deal with collider *(common effect)* when modeling?



- We must **NOT** control for collider.
- **Colliders CAN HIDE REAL CAUSE EFFECTS**
  - i.e., it would distort the true relationship between the exposure and the outcome

(more in Lab. 4)

How to deal with confounder *(common cause)* when modeling?

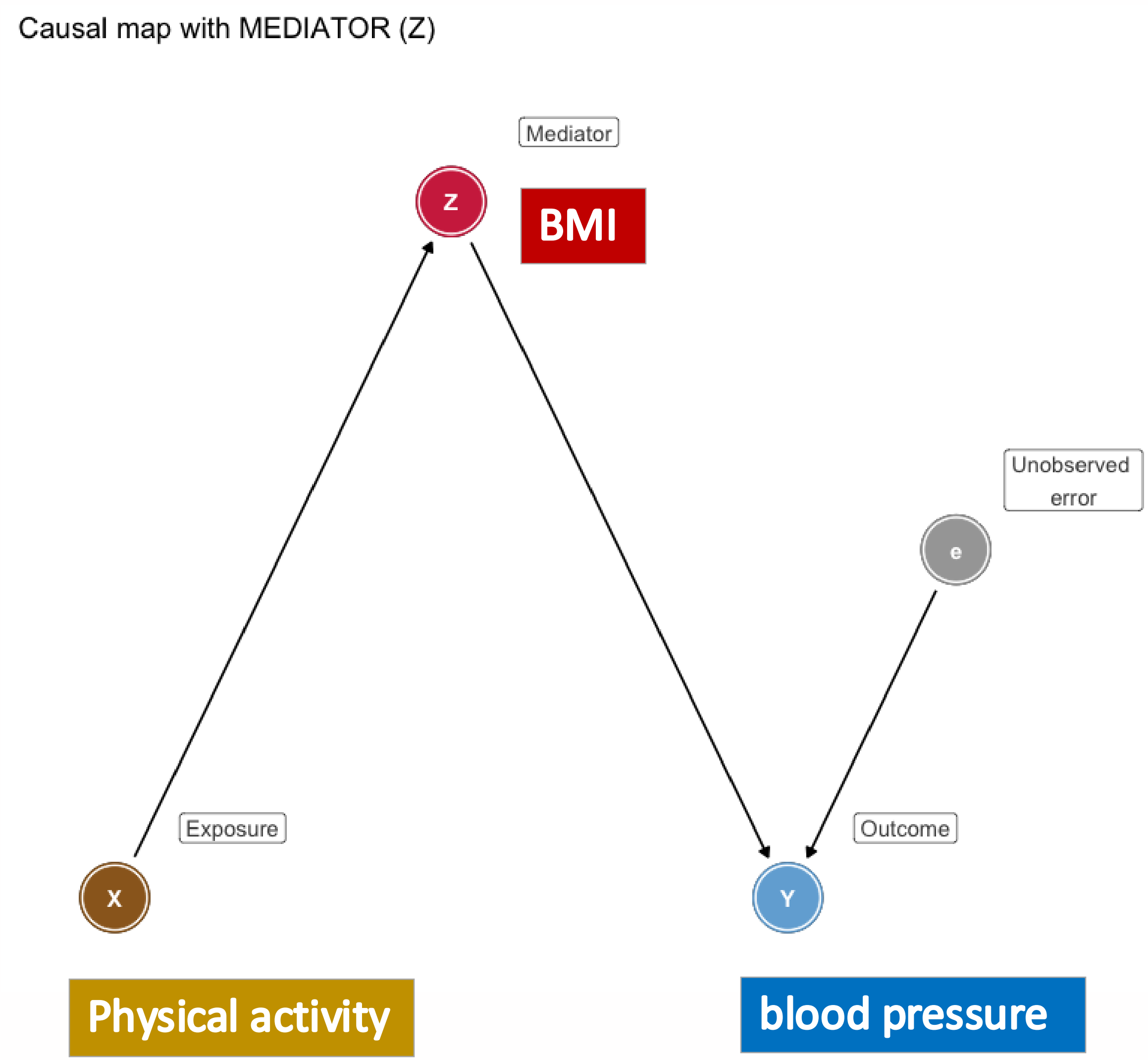


Source: Excellent reading https://quantifyinghealth.com/control-confounding/

- We must *control for* a confounder, so we reduce bias. HOW?
- 1) At **design** stage:
    - **Random assignment**
    - **Restriction** (*only participants of a certain confounder category*)
    - **Matching observations** *(confounder distributed evenly by exposure)*
- 2) In **analysis** stage:
    - **Stratifying sample in subgroups** *(by confounding)*
    - **Including term in regression**
    - **Inverse probability weighting** *(equalizing frequency of counfounder by exposure)*
    - **Instrumental variable estimation**

(more in Lab. 4)

How to deal with mediator *(mechanism)* when modeling?



- We *could* control for the mediator, depending on which effect we focus on:
  - with UNADJUSTED MODEL we get only the total effect (direct + indirect) of X on Y
  - with ADJUSTED MODEL we separate the direct effect of X on Y (not mediated), and the indirect effect of M on Y (mediated)
- *Normally both models are shown*
- *The Adjusted model enables to see the PROPORTION of the MEDIATOR mechanism in the causal path*

(more in Lab. 4)

Measuring causal outcomes of interest

Commonly used “estimands” (ATE, ATT, ATU) and how to select and interpret them correctly for making valid inferences

The explanation and examples below follow very closely these two sources:

1. **Noah Greifer, Elizabeth A. Stuart**, *Choosing the Causal Estimand for Propensity Score Analysis of Observational Studies*
2. **Andrew Heiss**, Demystifying causal inference estimands: ATE, ATT, and ATU

Defining estimands at the *subject level*

- **NOTATION:**
  - Y^0 and Y^1 are the potential outcomes in the *absence* and *presence* of treatment for patient i in a study on a new drug on blood pressure,
    - Y_i^0 = patient's blood pressure with receives standard of care
    - Y_i^1 = patient's blood pressure with takes new drug

- **ITE = Individual Treatment Effect** (*) = difference, for subject i , between potential outcome y if treated and if untreated

$$te_i = \delta_i = y_i^1 - y_i^0 \text{ where treatment is } T_i = \{0,1\}$$

  - (*) ITE is *never* observable!!
  - Hence, we will look at averages…

- **ATE = Average Treatment Effect** = average of ITE differences across subjects

$$E[te_i] = E[Y_i^1 - Y_i^0] = E[Y_i^1 | T_i = 1] - E[Y_i^0 | T_i = 0]$$

  - (*) The Avg of the differences = the difference of Averages!
  - ATE can hide different distributions of ITEs (e.g., positives and negatives that cancel each outer out)
  - Important to have a well-defined group or population

Defining estimands at the *subject level*

- **ATT (or ATET) = Average Treatment effect on the Treated =** average treatment effect across all subjects that end up TREATED

$$E[\delta_i \mid T_i = 1] = E[Y_i^1 - Y_i^0 \mid T_i = 1] = E[Y_i^1 \mid T_i = 1] - E\left[Y_i^0 \middle| T_i = 1\right]$$

  - This refers to the avg of the differences conditionally on the fact that both groups "received" the treatment ("$|T_i = 1$")
  - $[Y_i^0 | T_i = 1]$ is essentially the counterfactual for Y_i^1 in a 'parallel universe' where **exactly the same people** who were treated in this universe would not get the treatment

- **ATU = Average Treatment effect on the Untreated =** average treatment effect across all subjects who were NOT TREATED

$$E[\delta_i \mid T_i = 0] = E[Y_i^1 - Y_i^0 \mid T_i = 0] = E[Y_i^1 \mid T_i = 0] - E\left[Y_i^0 \middle| T_i = 0\right]$$

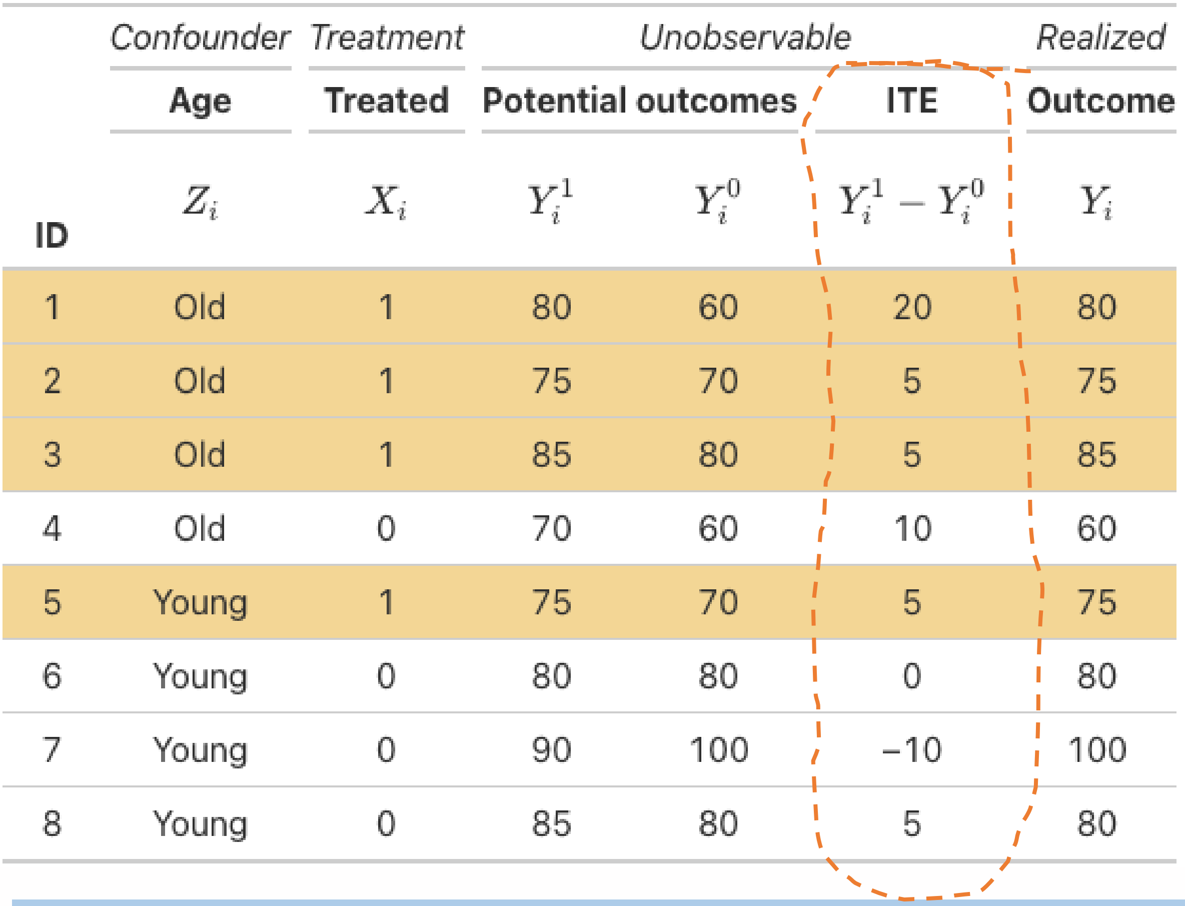
  - This time we seek the Avg of the differences ("$|T_i = 1$") conditionally on the fact that both groups were "assigned" to the treatment
  - $[Y_i^1 \mid T_i = 0]$ is essentially the counterfactual for Y_i^0 in a 'parallel universe' where **exactly the same people** who were NOT treated in this universe would get the treatment

By the way !

- **Treatment** is a binary random variable $T_i = \{0,1\}$
- **Outcome** of interest is $Y_i = \begin{cases} Y_i^0 & (if\ T_i = 0) \\ Y_i^1 & (if\ T_i = 1) \end{cases}$
- **ATE = Average Treatment Effect** = average of ITE differences across subjects
- **ATT/ATET = Average Treatment effect on the Treated =** average treatment effect across all subjects that end up TREATED

	EXAMPLE: Does hospitalization (T) increase health (Y) ?	
ATE =	$\mathrm{E}[\mathrm{Y}_i^1 \mid \mathrm{T}_i = 1] - \mathrm{E}[\mathrm{Y}_i^0 \mid \mathrm{T}_i = 0]$	Avg health of hospitalized group – avg health of NOT hospitalized group
ATT +	$\mathrm{E}[\mathrm{Y}_i^1 \mid \mathrm{T}_i = 1] - \mathrm{E}[\mathrm{Y}_i^0 \mid \mathrm{T}_i = 1]$	Avg health of treated group – [counterfactual] avg health $\mathrm{E}[\mathrm{Y}_i^0]$ of treated group IF NOT hospitalized
+ Selection bias	$\mathrm{E}[\mathrm{Y}_i^0 \mid \mathrm{T}_i = 1] - \mathrm{E}[\mathrm{Y}_i^0 \mid \mathrm{T}_i = 0]$ *(hospitalized have worse* Y_i^0 *than non hospitalized)*	Difference in [counterfactual] avg health $\mathrm{E}[\mathrm{Y}_i^0]$ of treated group IF NOT hospitalized - those who were NOT hospitalized

EXE. potential causal outcomes, ITE (δ_i), depends on patients' characteristics)



	Confounder	Treatment	Unobservable			Realized
	Age	Treated	Potential outcomes		ITE	Outcome
ID	Z_i	X_i	Y_i^1	Y_i^0	$Y_i^1 - Y_i^0$	Y_i
1	Old	1	80	60	20	80
2	Old	1	75	70	5	75
3	Old	1	85	80	5	85
4	Old	0	70	60	10	60
5	Young	1	75	70	5	75
6	Young	0	80	80	0	80
7	Young	0	90	100	−10	100
8	Young	0	85	80	5	80

$$\text{ATT} = \frac{20+5+5+5}{4} = \mathbf{8.75}$$

$$\text{ATU} = \frac{10+0-10+5}{4} = \mathbf{1.25}$$

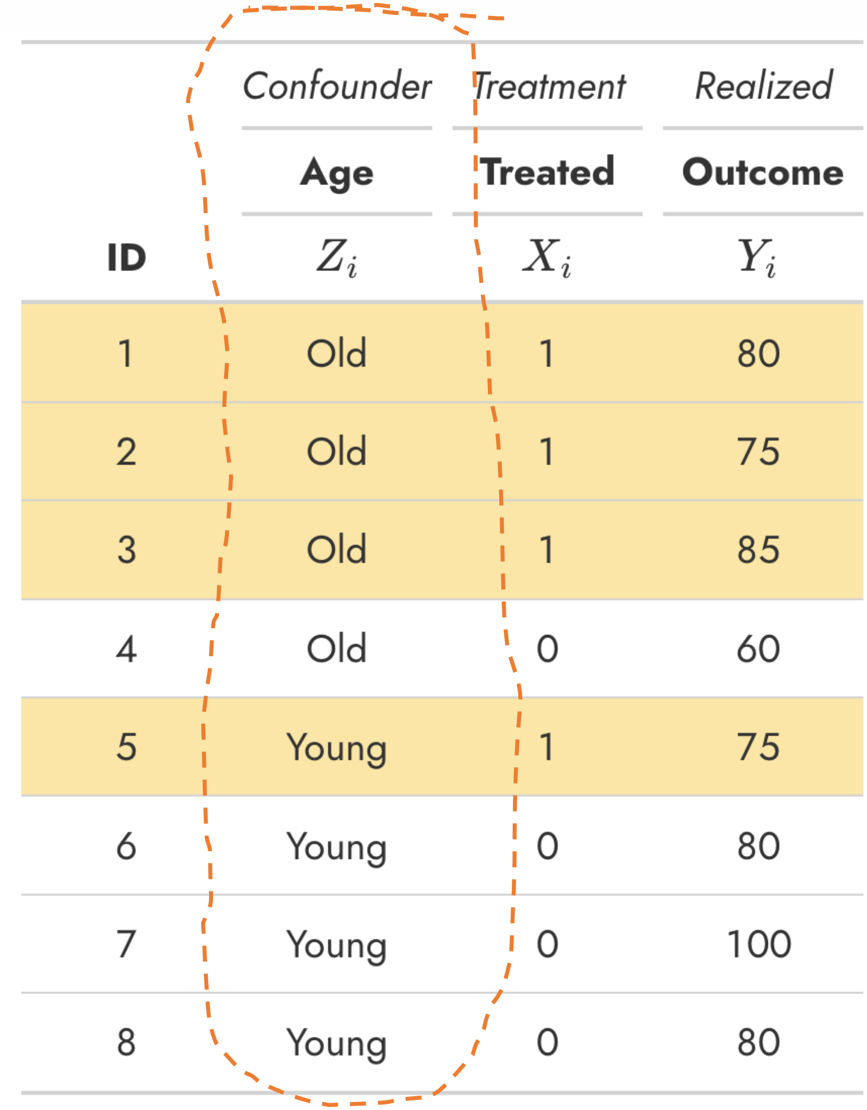
$$\text{ATE} = \frac{20+5+5+5+10+0+-10+5}{8} = \mathbf{5}$$

$$\text{ATE} = \left(\frac{4}{8} \times \mathbf{8.75}\right) + \left(\frac{4}{8} \times \mathbf{1.25}\right) = \ 4.375\ +\ 0.625 = \mathbf{5}$$ *(ATE decomposition)*

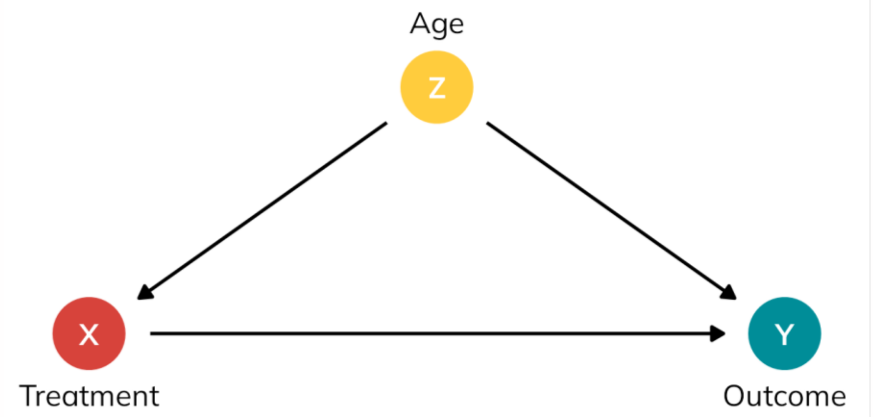
Revisiting the confounder seen in DAG visualization

Accounting for age for an accurate estimate of ATE

Acknowledging a confounder variable



	Confounder	*Treatment*	*Realized*
	Age	**Treated**	**Outcome**
ID	Z_i	X_i	Y_i
1	Old	1	80
2	Old	1	75
3	Old	1	85
4	Old	0	60
5	Young	1	75
6	Young	0	80
7	Young	0	100
8	Young	0	80

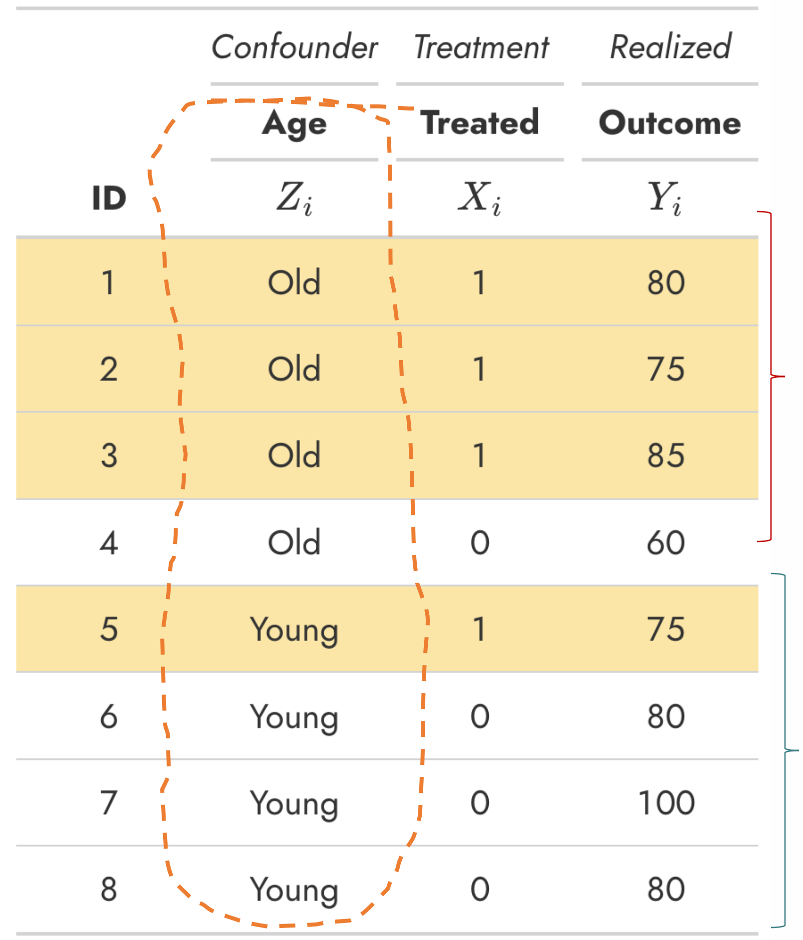


- So far, we ignored it, but:
- *AGE* seems to behave as a confounder:
  - → it is highly correlated with treatment status
  - → it also affects the ultimate value of the outcome
- *Hence, we need to account for it statistically*

How to deal with confounder variable?

- Recall that we listed different ways to *control for* a confounder (to reduce bias in estimands)
- Here, we illustrate 2 of them (feasible *at analysis stage*):
- 1) At **design** stage:
  - ○ **Random assignment**
  - ○ **Restriction** (*only participants of a certain confounder category*)
  - ○ **Matching observations** *(confounder distributed evenly by exposure)*
- 2) In **analysis** stage:
  - ✓ **Stratifying sample in subgroups** *(by confounding)*
  - ✓ **Including confounder variable as term in regression**
  - ○ **Inverse probability weighting** *(equalizing frequency of counfounder by exposure)*
  - ○ **Instrumental variable estimation**

1) Stratification to deal with confounder (i.e. combining the weighted averages for old and young people)



	Confounder	*Treatment*	*Realized*
	Age	**Treated**	**Outcome**
ID	Z_i	X_i	Y_i
1	Old	1	80
2	Old	1	75
3	Old	1	85
4	Old	0	60
5	Young	1	75
6	Young	0	80
7	Young	0	100
8	Young	0	80

$$\text{Effect}_{old} = \overline{Y}_{treated} - \overline{Y}_{untreated} =$$

$$= \frac{80+75+85}{3} - \frac{60}{1} = \mathbf{20}$$

$$\text{Effect}_{young} = \overline{Y}_{treated} - \overline{Y}_{untreated} =$$

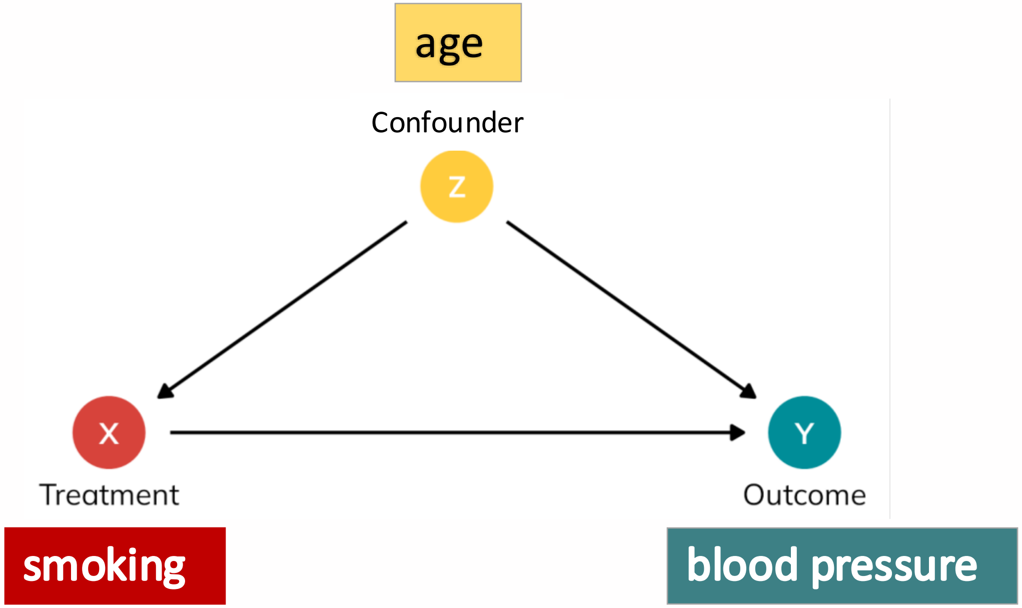
$$= \frac{75}{1} - \frac{80+100+80}{3} = \mathbf{-11.667}$$

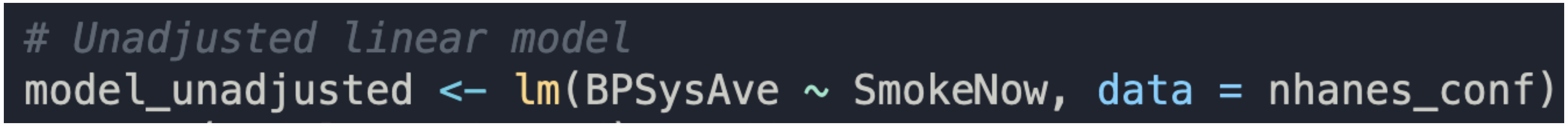
$$\text{ATE}_{stratified} = \pi_{old}\text{Effect}_{old} + \pi_{young}\text{Effect}_{young} = \left(\frac{4}{8} \times \mathbf{20}\right) + \left(\frac{4}{8} \times \mathbf{-11.667}\right) = \mathit{4.1667}$$

After stratification based on the confounder we get a very close ***approximation of the ATE*** (=5)

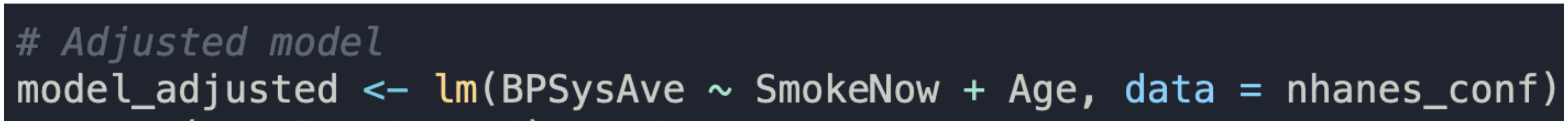
2) Introducing the confounder as term in the regression model

- Let’s consider an example (to be discussed in the Lab) based on the NHANES dataset,
- where:
  - Z = Age = confounder
  - X = SmokeNow
  - Y = BPSysAve (blood pressure)
- In the Lab, we will fit a regression model for the outcome and compare the results WITH and WITHOUT the confounder in the model





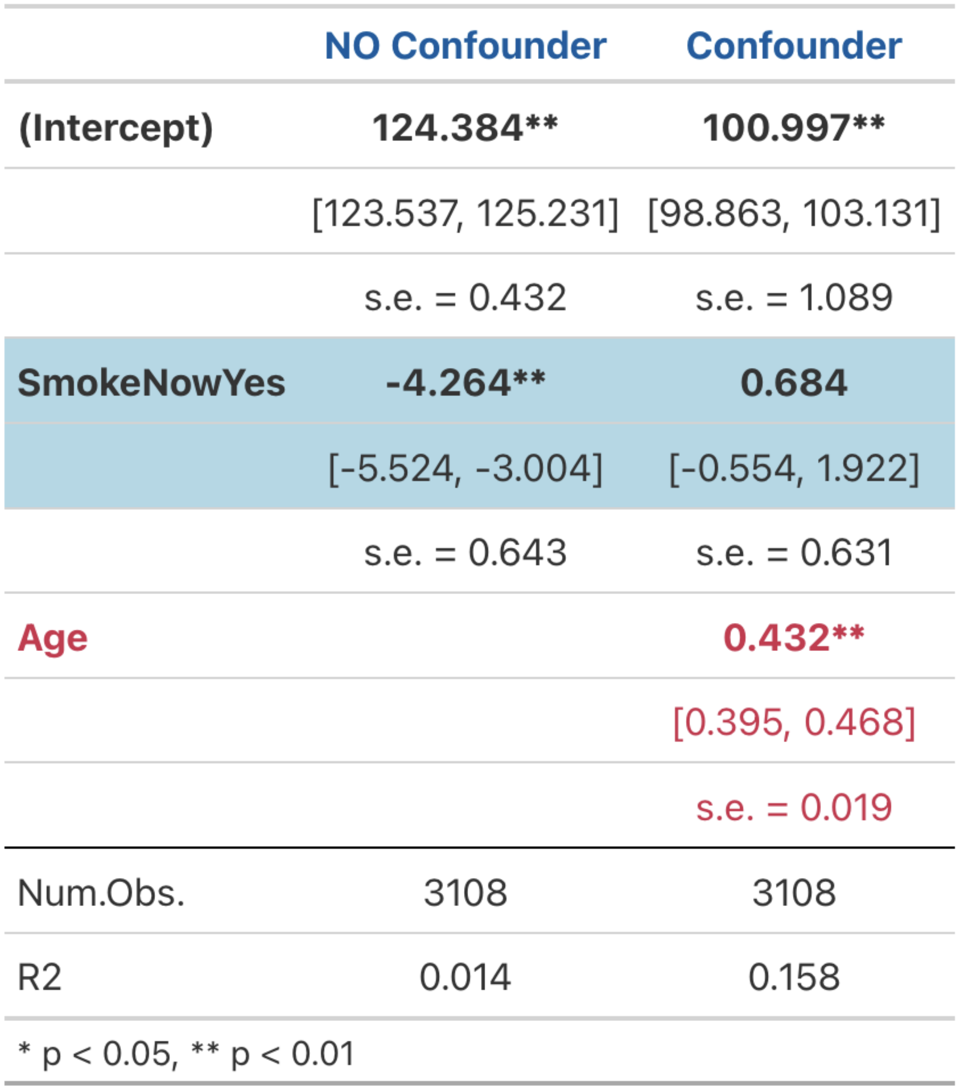
```
# Unadjusted linear model
model_unadjusted <- lm(BPSysAve ~ SmokeNow, data = nhanes_conf)
```



```
# Adjusted model
model_adjusted <- lm(BPSysAve ~ SmokeNow + Age, data = nhanes_conf)
```

2) Introducing the confounder as term in the regression model reduces bias and isolates the true effect of the X on Y

- In the **Adjusted Model** (with Age), the estimate of the causal effect of smoking (SmokeNowYes) on blood pressure (BPSysAve) is more *accurate*
  - the regression “adjusts” for the influence of Z in the causal path X → Y
  - this prevents *falsely attributing* to Smoking (X) an effect that might actually result from X



	NO Confounder	Confounder
(Intercept)	**124.384****	**100.997****
	[123.537, 125.231]	[98.863, 103.131]
	s.e. = 0.432	s.e. = 1.089
SmokeNowYes	**-4.264****	**0.684**
	[-5.524, -3.004]	[-0.554, 1.922]
	s.e. = 0.643	s.e. = 0.631
Age		**0.432****
		[0.395, 0.468]
		s.e. = 0.019
Num.Obs.	3108	3108
R2	0.014	0.158

* p < 0.05, ** p < 0.01

Ways to deal with confounders must be carefully pondered

All these solutions have pros and cons that must be considered…

DESIGN

WHAT CAN BE DONE AT DATA COLLECTION?

- **RANDOM ASSIGNMENT** to treatment exposure
- **RESTRICTION** of participants of a certain confounder category
- **MATCHING** by distributing the confounder evenly (between exposed and unexposed)

ANALYSIS

WHAT CAN BE DONE DURING ANALYSIS?

- **STRATIFICATION** (as we saw by Age) by estimating the relationship outcome within different subsets of the confounder
- **REGRESSION** (as we saw with Age) can scale to many confounders
- **INVERSE PROBABILITY WEIGHTING** to balance confounder-weighted distributions and achieve comparability between treated and untreated groups

What about the other estimands? (ATT, ATU)

Choosing the estimands and the proper statistical method to estimate the effect

- In a randomized trial, the treated and untreated groups will, on average, have the same distributions of patient characteristics, so the ATT, ATU, and ATE will be the same

- Without randomization, however, the treatment groups can have quite different distributions of characteristics, ATT, ATU, and ATE will differ when these characteristics also relate to the treatment effect
  - So, when using observational data: *for whom should the treatment effect be estimated?*

Choosing the estimands based on the research question

BEFORE analyzing a dataset, let's consider which question we are asking, and about which target population group,

THEN choose a statistical method that corresponds to the chosen estimand.

Estimands	Target Population	Example research question and research/policy addressed
ATT	Treated patients	*Examining an intervention that would only reach those currently receiving it:* *- e.g. decision to replace / withhold a treatment for currently treated patients*
ATU	Untreated patients (control)	*How would untreated patients respond to a new potential treatment/exposure?* *- e.g. decision to extend a medical practice (drug prescription/vaccine) to a group that would not otherwise receive it*
ATE	*Full sample / population*	*Should a specific policy be applied to all eligible patients? How would the outcome be on average?* *- e.g. regulating a system-wide policy for a previously unregulated practice* *- useful when treatment decisions are not well informed (ATE does not depend on current treatment assignment)* *- NOT OK when patients' benefit depend on clinical judgment*

Recapping key points of the lecture

- Capturing the **causal nexus** between a treatment and an outcome may be tricky due to:
  - constraints in study design, sampling, or data collection process
  - repeated measures over time
  - effects of *confounder*, *collider* or *mediator/mechanism* variables
  - etc.
- **Visual causal maps** may help guiding the analysis, by summarizing how variables affect each other
  - e.g. DAGs (Directed Acyclic Graphs)
- Another key step is deciding which **estimand(s)** we are seeking with reference to the specific target population:
  - ATE – if a treatment targeted to the general population (e.g. a universal policy)
  - ATT – if a treatment targeted subjects already exposed (e.g. ≠ drug for treated patients)
  - ATU – if a new treatment apply to currently untreated patients (e.g. new drug)
- Each estimand implies its own assumptions, interpretation, and **statistical methods**

- *coming up next…*

Shifting emphasis on empirical outcome prediction

Introduction to **Machine Learning (ML)** models

A conceptual framework to understand different types of statistical modeling (part 2/2)

1. **association/correlation** → observational studies
2. **causal explanation** → experimental studies
3. **empirical prediction** → algorithmic machine learning and data-mining modeling
   - aimed at **predicting new or future observations** (without necessarily explaining how)
   - relies on **big data**
   - prevalent in fields like natural language processing, bioinformatics, etc.. In epidemiology, there is more of a mix causal explanation & empirical prediction

- **NOTES**:
  - ✓ "Prediction" does not necessarily refer to future events, but rather to *future* datasets that were previously unseen to the algorithm

…stay tuned for next chapter on ML

😉