# STATISTICS & ML WITH R

## Mapping causal & predictive approaches

**2024**

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# DAY 4 – LECTURE OUTLINE

## Mapping causal & predictive approaches

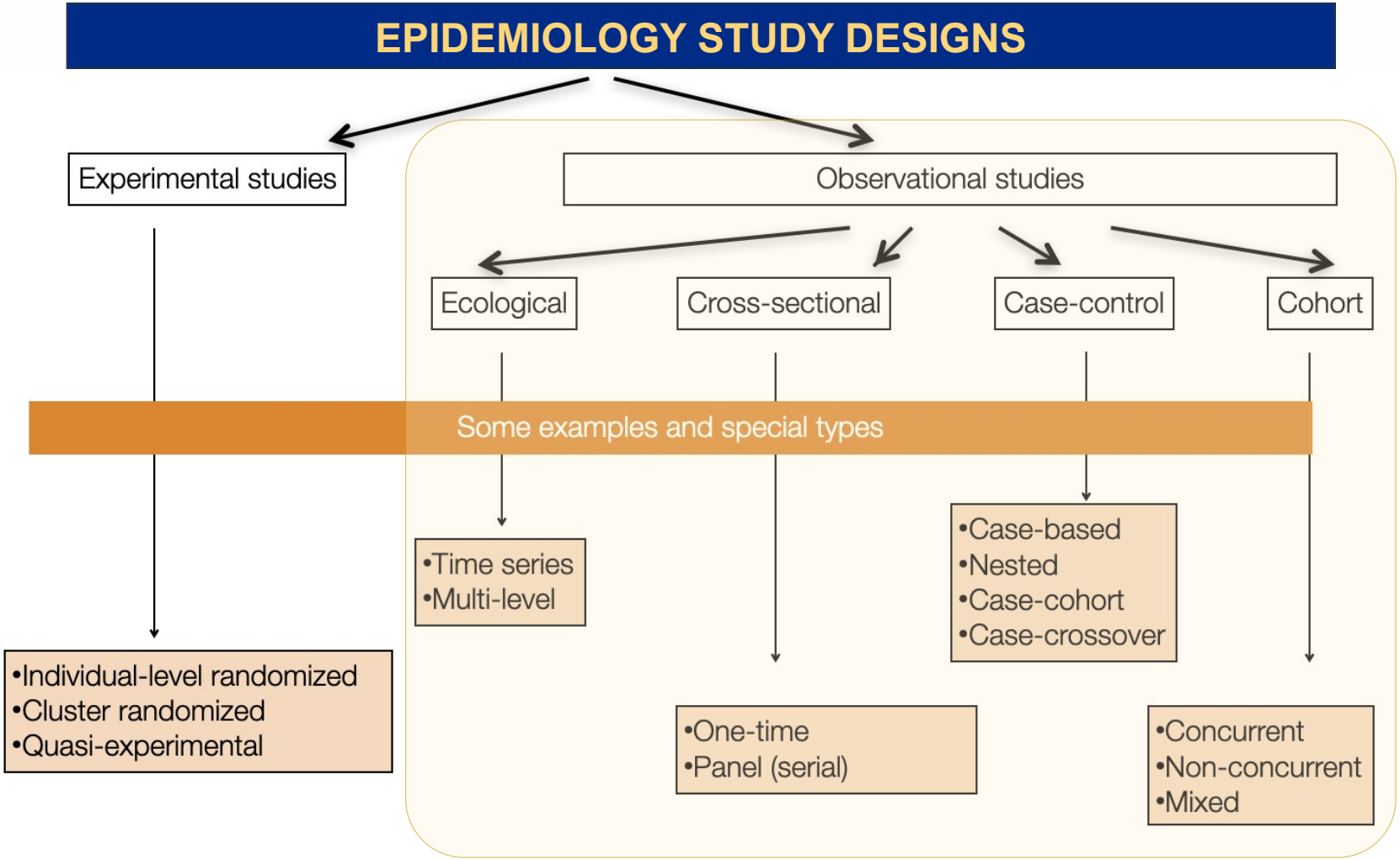
- Illustrating different study designs
- Learning the vocabulary of causal analysis
- Visual understanding of causal pathways, including:
  - Collider variables
  - Confounder variables
  - Mediator variables
- Learn how to address causal pathways in modeling, based on the research question
- Defining causal outcomes and commonly used “estimands” (ATE, ATT, ATU)
- Understand proper statistical methods to estimate ATE, ATT, ATU based on research question and target group
- Introducing Machine Learning (ML)
  - purpose
  - key algorithms’ categories

# 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...




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

# Different goals 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

# A framework for CAUSAL ANALYSIS

Key terminology and visual causal maps

# The conceptual framework for causal analysis (1/3)

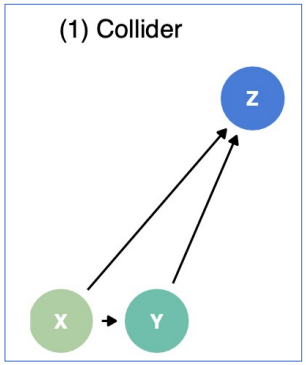
- **Fundamental vocabulary**:
  - **Intervention** decisions and actions that change the behaviors or situation of people/firms/other subjects (drug, vaccine, program participation)
    - TREATMENT = commonly used in experimental studies when researchers directly "assigns" the **causal variable**
    - 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

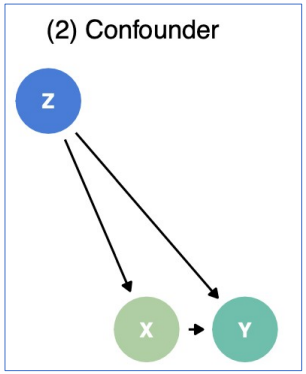
# The conceptual framework for causal analysis (2/3)

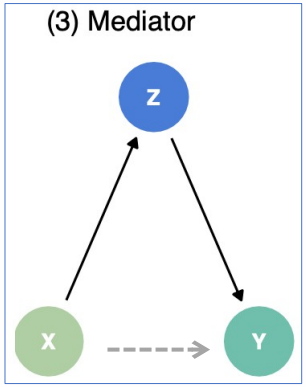
- **Fundamental vocabulary** ("*tricky ones*" 😉):
  - **Bias** = systematic error that can occur at different stages of the study: *data collection*, *analysis* or *interpretation* of the causal relationship exposure-outcome.
    - Selection bias occurs when both the exposure and the outcome affect whether an individual is included in the sampled population
    - Information bias occurs when there is misclassification or inaccurate measurement (e.g., patients underreporting smoking habits)
    - prevalence-incidence bias …
    - ecological bias

# 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



# Estimands, Estimators, Estimates

- The **estimand** is the *target of interest*
  - EXAMPLE: expected value of the difference in potential outcomes across all individuals

- The **estimator** is the method by which we approximate this estimand using data ("recipe")
  - EXAMPLE: in randomized controlled trial, our estimator could just be the average outcome among those who received the exposure A minus the average outcome among those who receive exposure B

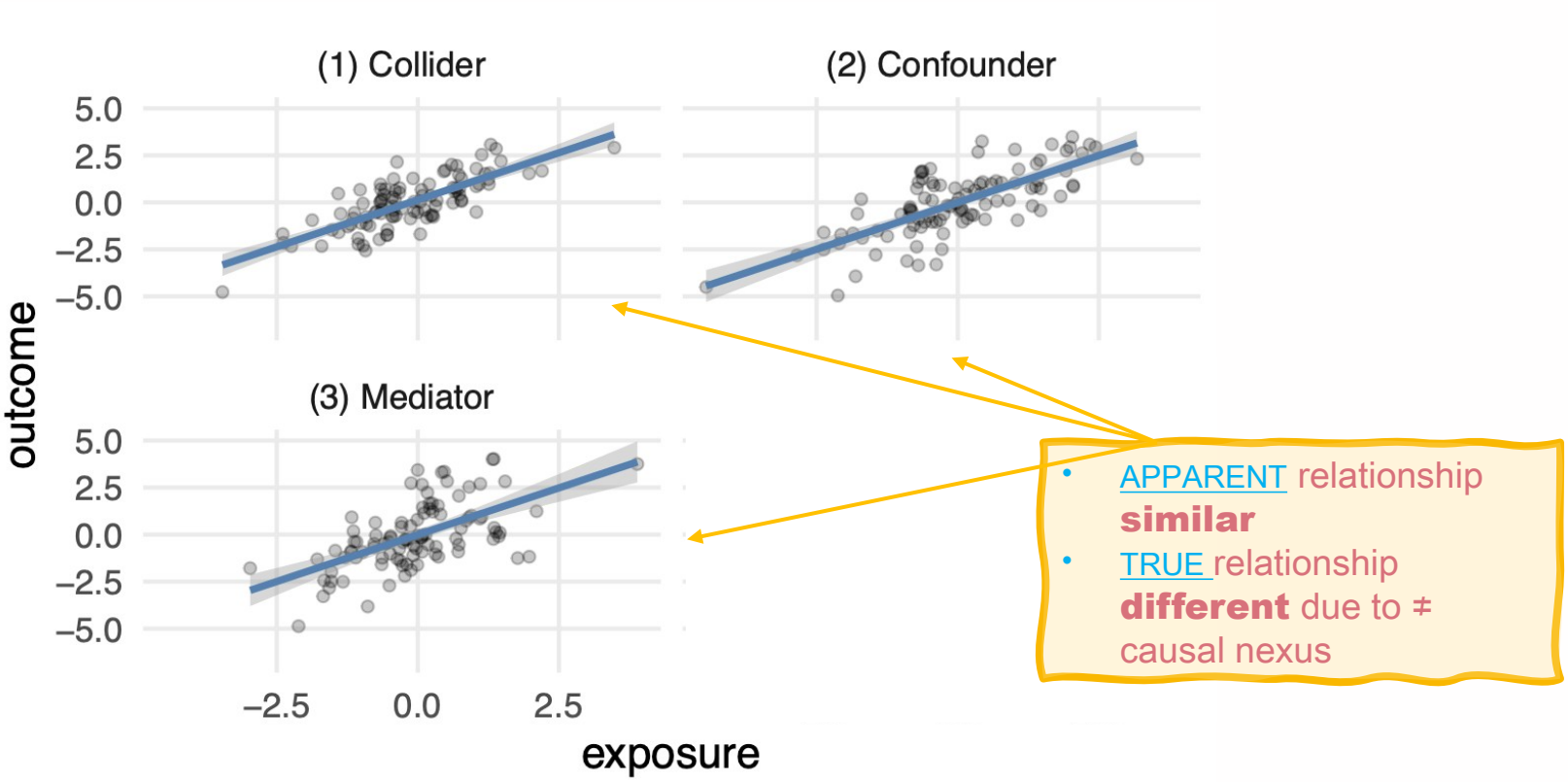
- The **estimate** is the value we get when we plug our data into the estimator
  - EXAMPLE: randomized controlled trial, our estimator could just be the average outcome among those who received the exposure A minus the average outcome among those who receive exposure B

# Visualizing causal maps

## A helpful tool in guiding statistical modeling

# Typical challenges in estimating causal effects: visual intuition

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



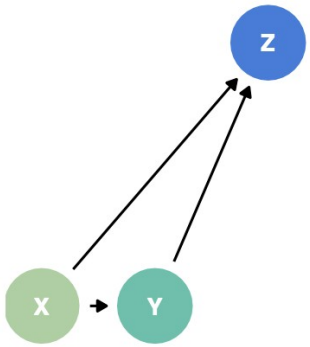

Source: Barrett, M., McGowan, L. D., & Gerke, T. (2024). *Causal Inference in R*. Retrieved from https://www.r-causal.org/

# Typical challenges in estimating causal effects: visual intuition

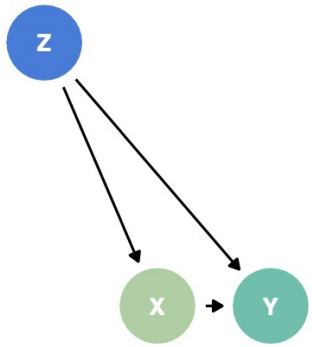
- Directed acyclic graphs (DAGs) can offer visual intuition of the causal nexus at play in the 3 datasets. Failure to adjust models to these situation leads to BIAS
  - X is some continuous exposure of interest, Y a continuous outcome, and Z a known, measured factor

(1) a "**COLLIDER**" is caused by both X and Y (it inadvertedly connects the 2). E.g.:
- X = sodium intake
- Y = systolic blood pressure
- Z = urinary protein excretion

(1) Collider



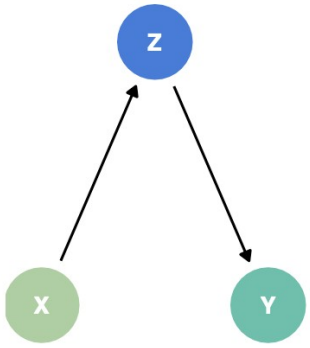

(2) Confounder




(2) a "CONFOUNDER" causes both X and Y. 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



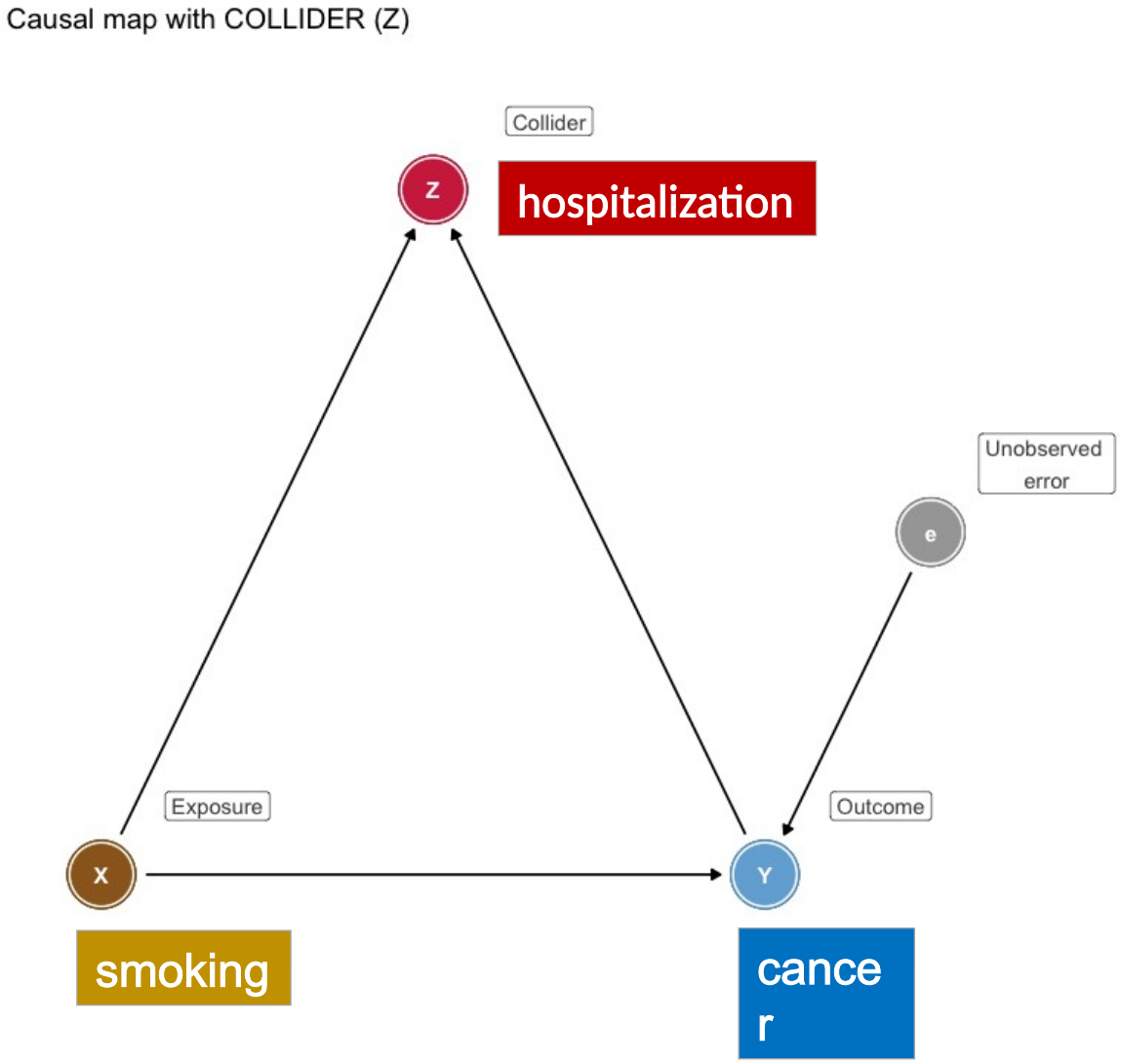

we'll revisit this later in multivariate regression…

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

# How to address causal pathways in modeling

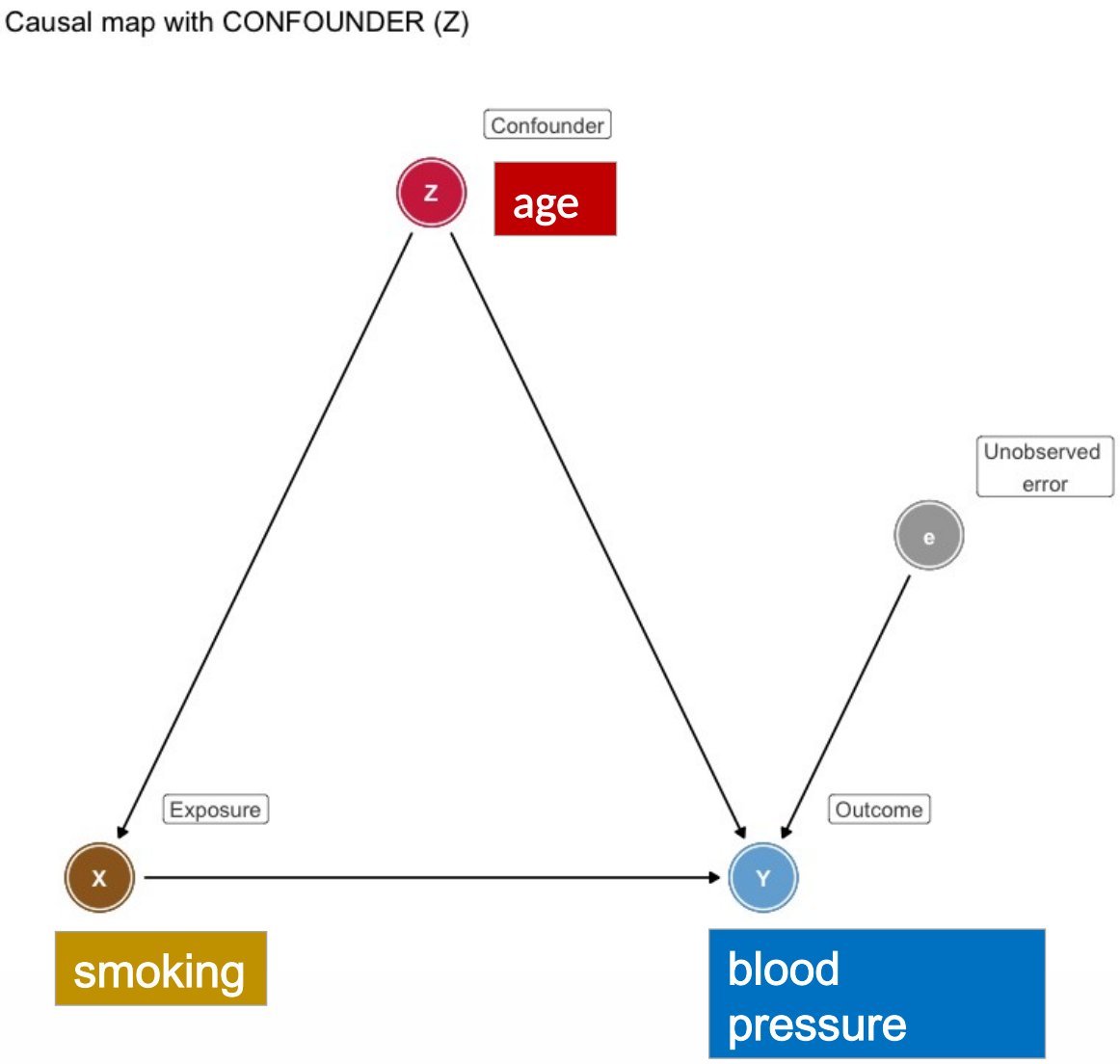
This will be re-visited through practical examples in Lab 4

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



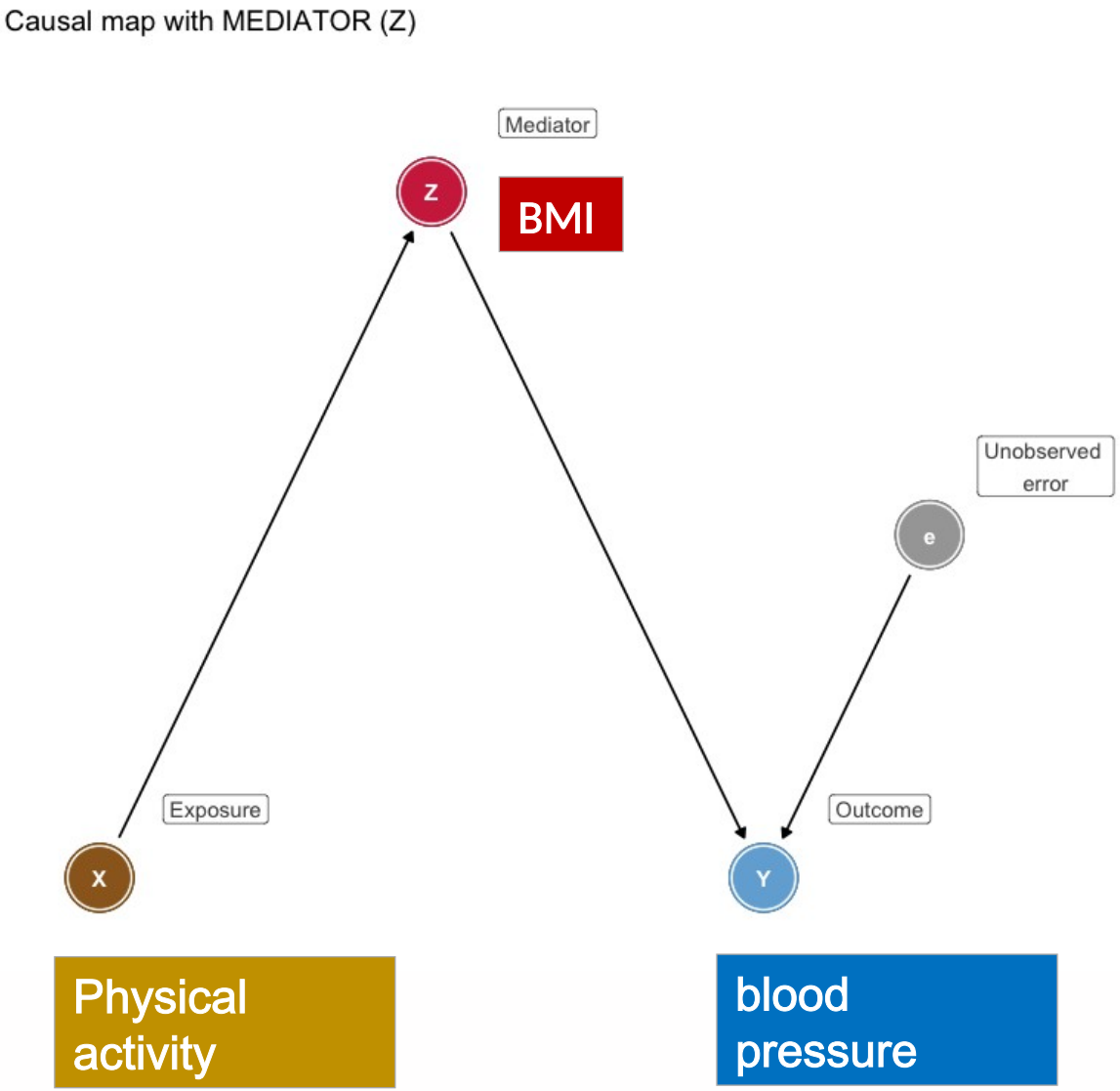

- We must **NOT** control for collider.
- **colliders CAN HIDE REAL CAUSE EFFECTS**
  - i.e., it would distort the true relationship between the exposure and the outcome

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




- We must control for a confounder, so we reduce bias, by:
  - including term in regression
  - matching observantions
  - stratifying sample

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




- We *could* control for the mediator, depending on which effect you want to focus on:
  - WITHOUT adjusting we get the total (direct + indirect) effect from X to Y
  - WITH adjusting for the mediator we can assess what part of the effect can be attributed to the mechanism

- *(normally both models are shown)*

# Measuring causal outcomes of interest

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

# Defining potential outcomes at the *subject level (experimental unit)*

- **NOTATION:**
  - and are the potential outcomes in the *absence* and *presence* of treatment
  - for patient $i$ in a study on a new drug on blood pressure,
    - 
    - = with takes new drug

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

  where treatment is

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

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

  - (*) 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 potential outcomes at the *subject level (experimental unit)*

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

]

  - This refers to the avg of the differences conditionally on the fact that both groups "received" the treatment ("" )
  - is essentially the counterfactual for 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

]

  - This time we seek the Avg of the differences ("" ) conditionally on the fact that both groups were "assigned" to the treatment
  - is essentially the counterfactual for 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 vriable
- outcome of interest is
- **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

| Ex: Does hospitalization (T) increase health (Y) ? | |
|---|---|
| (ATE) | Avg health of hospitalized group – avg health of NOT hospitalized group |
| (ATT) + … | Avg health of treated group – [counterfactual] avg health of treated group IF NOT hospitalized |
| (Selection bias) … +<br><br>*(hospitalized have worse than non hospitalized)* | Difference in [counterfactual] avg health of treated group IF NOT hospitalized - those who were NOT hospitalized |

# EXE. potential causal outcomes ( depends on patients characteristics)

| | *Confounder* | *Treatment* | *Unobservable* | | | *Realized* |
|---|---|---|---|---|---|---|
| | **Age** | **Treated** | **Potential outcomes** | | **ICE or $\delta_i$*** | **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 |

* ICE = individual causal effect

*(ATE decomposition)*

# 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 |



*+ = 4.1667*

After stratification based on the confounder we get a very close ***approximation of the ATE***

# Other ways to deal with confounders

- *GIVEN THAT IN REAL LIFE WE NEVER HAVE THE ALTERNATIVE POTENTIAL OUTCOMES FOR EACH SUBJECT $i$ , HOW DO WE DEAL?*
  - **STRATIFYING** by Age was easy, but what if there is >1 confounder? What if it is continuous?

- *WE'VE GOT TO DO SOMETHING ELSE TO GET TO COMPARABLE GROUPS:*
  - **MATCHING** methods = dropping units from the sample or partitioning units into pairs or subclasses (e.g., *Propensity Score Matching*)
  - **WEIGHTING** methods = weighting the units so that the weighted distributions are similar between treatment groups (e.g., *Inverse probability weighting*)
- After *adjustment* the treatment effect is estimated in the resulting sample (incorporating the weights resulting from the matching or weighting)

# 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?*
  - ~~Some methods, such as PSM in its most commonly used form, cannot target the ATE, and so are inappropriate when the ATE is of interest!~~

# Choosing the estimands based on the research question

BEFORE analyzing an observational 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:*<br>*- 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?*<br>*- 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?***<br>***- e.g. regulating a system-wide policy for a previously unregulated practice***<br>***- useful when treatment decisions are not well informed (ATE does not depend on current treatment assignment)***<br>***- NOT OK when patients' benefit depend on clinical judgment*** |

# EXE [see LAB 4]: how to exploit *"*matched*"* untreated observation to estimate the ATT

- …. ANDREW HEISS ESEMPIO DI PSM (uso il suo che e' troppo bello!!!!

# Shifting emphasis on empirical outcome prediction

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

# vedi

- https://statisticalhorizons.com/the-machine-learning-foundations-of-artificial-intelligence/

# 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

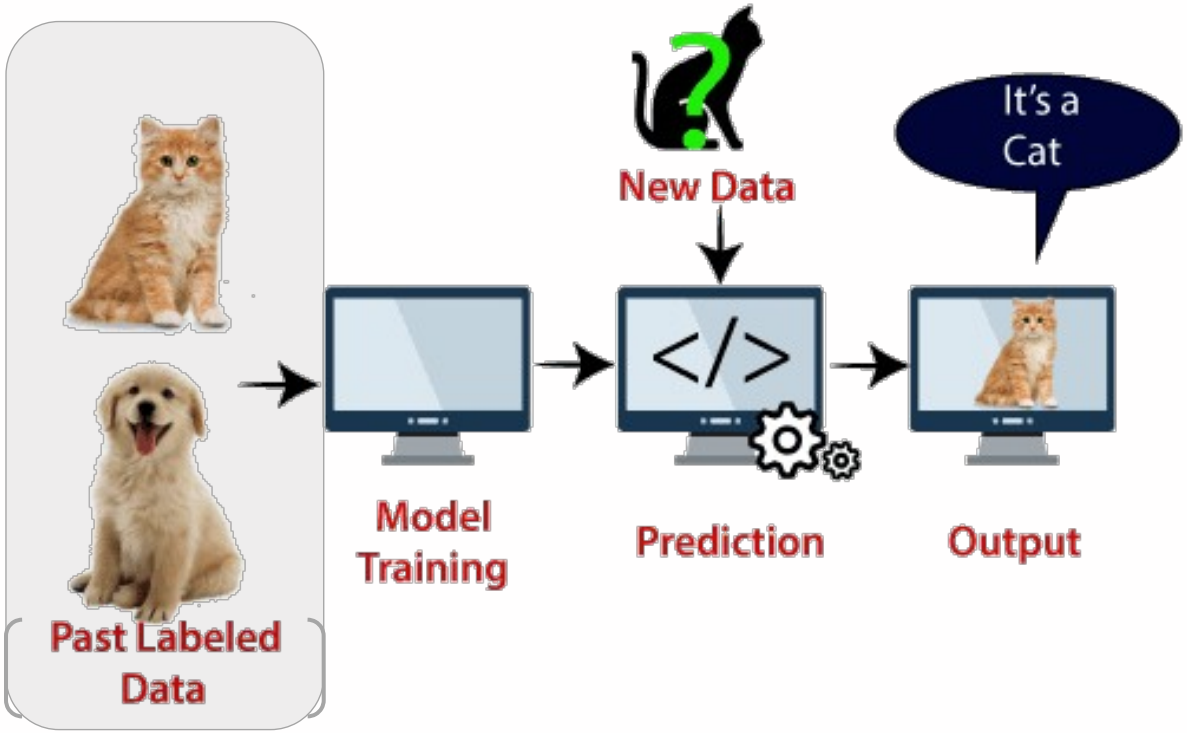
- **NOTES**:
  - ✓ "Prediction" does not necessarily refer to future events, but rather to *future* datasets that were previously unseen to the algorithm

# MACHINE LEARNING

# Defining Machine Learning (ML)

**"At its core, Machine Learning is just a "thing-labeler", taking something and telling you what label it should get."**

(Cassie Kozyrkov)




Source: Image from https://entri.app/blog/what-is-svm-algorithm-in-machine-learning/

# Defining Machine Learning (ML)

- **Machine Learning** is a broad and highly active research field. (In the life sciences, "*precision medicine*" is an application of machine learning to biomedical data)
- The **general idea** is to predict or discover outcomes from measured predictors, in problems like:
  - *Can we discover new types of cancer from gene expression profiles?*
  - *Can we predict drug response from a series of genotypes?*
  - *How do we classify a set of images/spectrometry outputs, etc.*
  - *Given various clinical parameters, how can we use them to predict heart attacks?*
- The **ML is a data-driven (inductive) approach**, where a machine **learns** the rules/patterns from a set of **training data** and (then) **validates** findings on a set of **testing data**
- In contrast with inferential statistics, **ML *doesn't worry* about assumptions on parameters** (probability distribution, error, correlation, etc.), **nor the causal nexus** between specific predictor(s) and response, **nor the data collection strategy**
- In contrast with standard statistics, **in ML the rules are not necessarily specified**… hence ML = a subfield of AI

# Stylized comparison between statistics and machine-learning

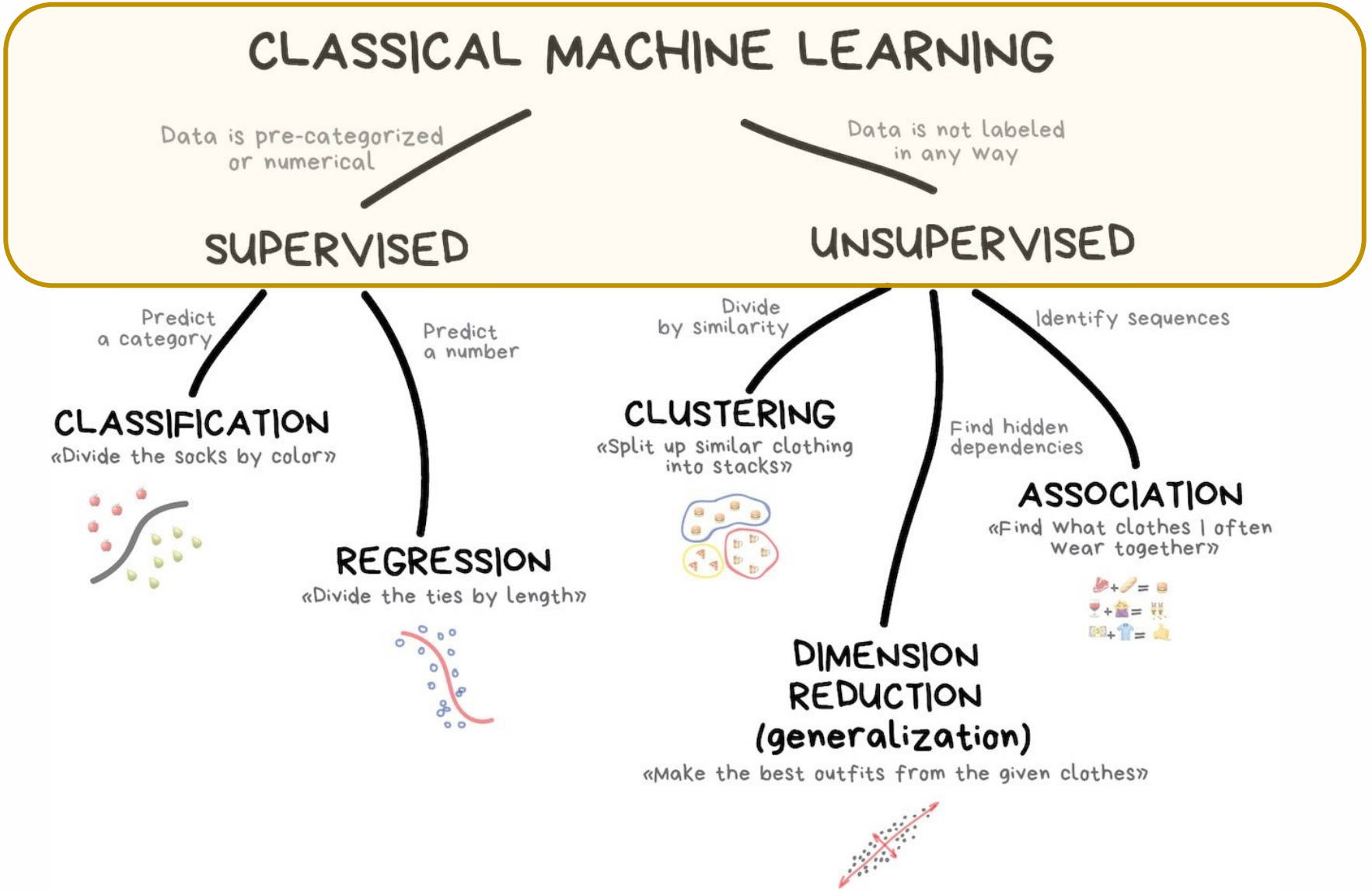
| | Standard (causal inference) Statistics | Machine Learning |
|---|---|---|
| **Typical Goal** | Explanation, uncovering causal relationships | Predicting an outcome as accurately as possible |
| **Typical Task** | Research based on a theory to identify the causal effect (better: pre-register your hypothesized model). | Try out and tune many different algorithms in order to maximize predictive accuracy in new and unseen test datasets. |
| **Data generating process** | Designed ex-ante based on study goal (e.g. randomized control trial, or observational study with statistical control variables) | Useful but not strictly necessary, and often not available |
| **Parameters of interest:** | Causal effect size and statistical significance, p-value of treatment X for outcome Y | Model's accuracy (%), precision/recall, sensitivity/specificity, in predicting Y |
| **Dataset** | Use **ALL AVAILABLE DATA** to calculate effect of interest (it was designed to be representative of a population). | It is critical to **SPLIT THE DATA** (usually 75% for training and 25% for testing the algorithms) leaving aside a sub-sample to test the model with unseen new data |

Source: Adapted from https://forloopsandpiepkicks.wordpress.com/2022/02/10/beginners-guide-to-machine-learning-in-r-with-step-by-step-tutorial/

# Supervised or Unsupervised ML algorithms?

….another conceptual framework

# A fundamental distinction: supervised and unsupervised ML




Source: Image from https://vas3k.com/blog/machine_learning/index.html

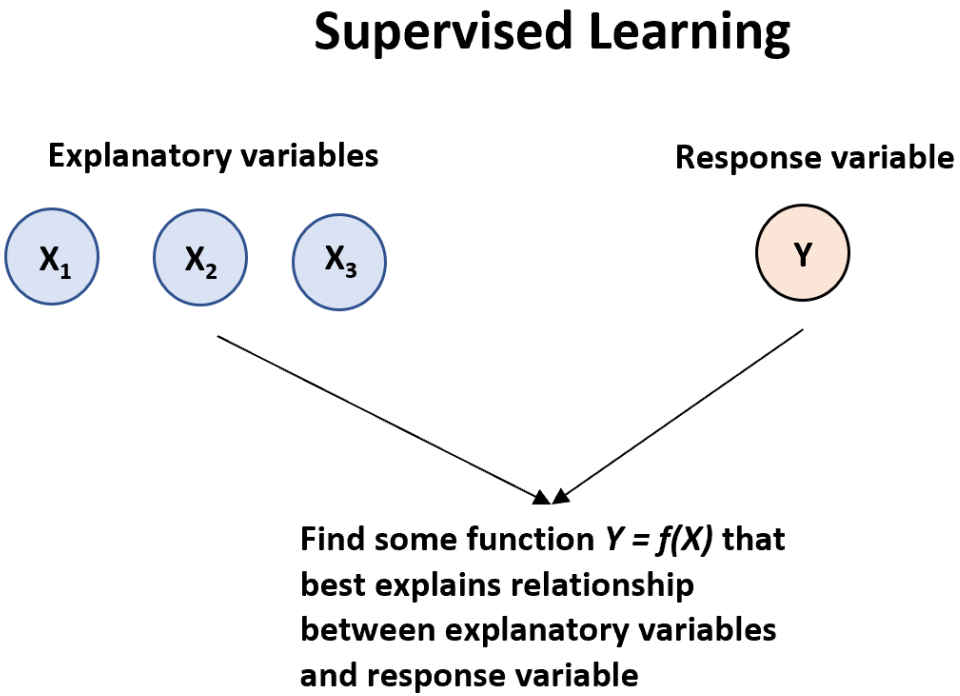
# A fundamental distinction: supervised and unsupervised ML

- ML includes many different algorithms that can be used for understanding data. These algorithms can be classified as:

- **Supervised Learning Algorithms**:
  - building a model to estimate or predict an output based on one or more inputs
    - **Regression**: Modeling a relationship, the typical output variable is continuous (e.g. weight, height, time, etc.) or dichotomous.
    - **Classification**: Splits objects based on one of the attributes known beforehand. The the typical output variable is categorical (e.g. male or female, pass or fail, benign or malignant, etc.)
- **Unsupervised Learning Algorithms**:
  - finding structure and relationships among inputs. There is no "supervising" output
    - **Clustering:** Finding "clusters" of observations in a dataset that are similar to each other (*based on unknown features)*.
    - **Association:** Finding "rules" that can be used to draw associations. For example, if a patient has a high biomarker X, he will have a low biomarker Y.
    - **Dimension reduction**: Assembling specific features into more high-level ones (e.g. PCA)

# Supervised ML algorithms

- A supervised learning algorithm can be used when we have **one or more explanatory variables** ($X_1$, $X_2$, $X_3$, ..., $X_p$) and a **response variable** (Y) and we would like to find some function that describes the relationship between the explanatory variables and the response variable:
- $Y = f(X) + \varepsilon$
- where
  - f () represents **systematic information that X provides about Y** and where
  - ε is a random error term independent of X with a mean of zero.




Source: https://www.statology.org/supervised-vs-unsupervised-learning/

# Supervised Learning Algorithms purpose

There are two main reasons to use supervised learning algorithms:

1. **Prediction**: We often use a set of explanatory variables to predict the value of some response variable (e.g. using square footage and number of bedrooms to predict home price)
2. **Inference**: We may be interested in understanding the way that a response variable is affected as the value of the explanatory variables change (e.g. how much does home price increase, on average, when the number of bedrooms increases by one?)

- *Depending on whether our goal is inference or prediction (or a mix of both), we may use different methods for estimating the function f. For example, linear models offer easier interpretation but non-linear models that are difficult to interpret may offer more accurate prediction.*

# Supervised Learning: commonly used algorithms

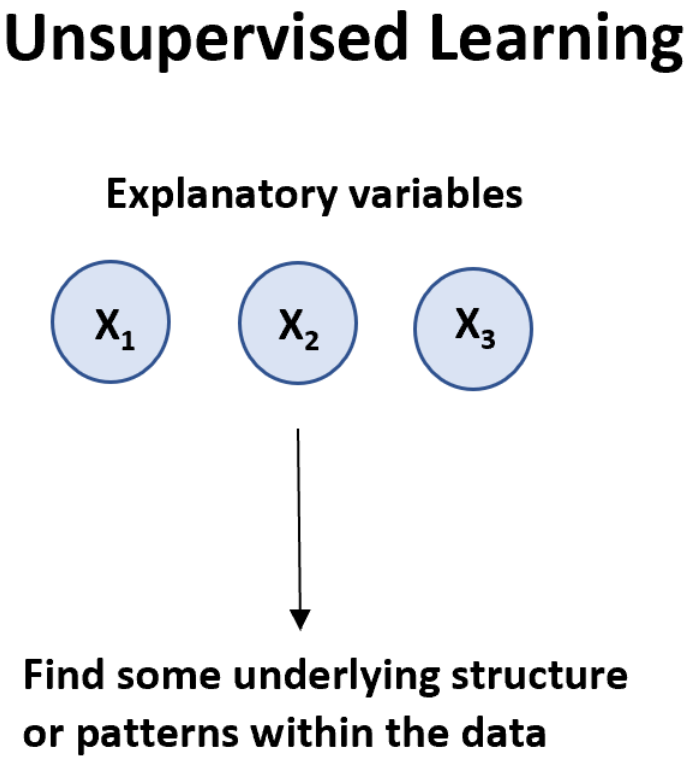
**Most commonly used supervised learning** algorithms:

- Linear regression
- Logistic regression
- Linear discriminant analysis
- Quadratic discriminant analysis
- Decision trees
- Naive bayes
- Support vector machines
- Neural networks

# Unsupervised ML algorithms

## Example of PCA

An unsupervised learning algorithm can be used when we have a list of variables ($X_1$, $X_2$, $X_3$, …, $X_p$) and we would simply like to find underlying structure or patterns within the data.




Source: https://www.statology.org/supervised-vs-unsupervised-learning/

## Unsupervised Learning Algorithms typical purpose

There are two main types of unsupervised learning algorithms:

1. **Clustering:** Using these types of algorithms, we attempt to find “clusters” of observations in a dataset that are similar to each other. This is often used in retail when a company would like to identify clusters of customers who have similar shopping habits so that they can create specific marketing strategies that target certain clusters of customers.
2. **Association:** Using these types of algorithms, we attempt to find “rules” that can be used to draw associations. For example, retailers may develop an association algorithm that says “if a customer buys product X they are highly likely to also buy product Y.”

# Unspervised Learning: commonly used algorithms

- Most commonly used unsupervised learning algorithms:
  - Principal component analysis
  - K-means clustering
  - K-medoids clustering
  - Hierarchical clustering
  - Apriori algorithm

# Summary: Supervised vs. Unsupervised Learning

- Here are the key differences between supervised and unsupervised learning algorithms:

| | Supervised Learning | Unsupervised Learning |
|---|---|---|
| **Description** | Involves building a model to estimate or predict an output based on one or more inputs. | Involves finding structure and relationships from inputs. There is no "supervising" output. |
| **Variables** | Explanatory and Response variables | Explanatory variables only |
| **End goal** | Develop model to **(1)** predict new values or **(2)** understand existing relationship between explanatory and response variables | Develop model to **(1)** place observations from a dataset into a specific cluster or to **(2)** create rules to identify associations between variables. |
| **Types of algorithms** | **(1)** Regression and **(2)** Classification | **(1)** Clustering and **(2)** Association |

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