Mediation Analysis in Epidemiology:
Counterfactual and Causal Inference

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CounterFactuals and Causal Inference

- Suppose that we are interested in the relation between an exposure, *A*, and a disease outcome, *Y.*
- We assume for simplicity that both *A* and *Y* are binary (0,1)
- We assume that population data is available (infinite sample size).
- These assumptions are often unrealistic, but are useful for pedagogical purposes.

Independence/Association

A and *Y* are independent if the risk for disease is the same among the unexposed and exposed:

$$\Pr(Y=1 \mid A=1) = \Pr(Y=1 \mid A=0) = \Pr(Y=1)$$

→ We sometimes write this as

$$Y \coprod A$$

A and *Y* are associated if the risk for disease is different among the unexposed and exposed:

$$\Pr(Y=1 \mid A=1) \neq \Pr(Y=1 \mid A=0)$$

→ We sometimes write this as $Y \not\coprod A$

Remark on association

- There may be many explanations to an association between *A* and *Y.*
  - →*A* causes *Y*
  - →*Y* causes *A* ("reverse causation")
  - →*A* and *Y* have common causes ("confounding")
  - →etc
- That *A* and *Y* are associated only means that certain values of *A* and *Y* tend to "appear together".
  - → **Why** this happens is a completely different question.

The most common association measures for binary variables

- The *risk difference*: $RD = \Pr(Y=1 \mid A=1) - \Pr(Y=1 \mid A=0)$

  $Y \coprod A \Leftrightarrow$ RD = 0

- The *risk ratio*: $RR = \dfrac{\Pr(Y=1 \mid A=1)}{\Pr(Y=1 \mid A=0)}$

  $Y \coprod A \Leftrightarrow$ RR = 1

- The *odds ratio*: $OR = \dfrac{\Pr(Y=1 \mid A=1)}{\Pr(Y=0 \mid A=1)} / \dfrac{\Pr(Y=1 \mid A=0)}{\Pr(Y=0 \mid A=0)}$

  $Y \coprod A \Leftrightarrow$ OR = 1

Note: frequently, the log RR and log OR are reported.

Conditional association/independence

- Sometimes we analyze subgroups of the population separately.

  Eg: *L* = “sex” (0 for male, 1 for female).

  Pr(*Y*=1|*A*=1,*L*=1) is the conditional probability of disease, for an exposed woman.

- **Def**:

  A and *Y* are conditionally independent, given *L*, if

$$\Pr(Y=1 \mid A=1, L) = \Pr(Y=1 \mid A=0, L) \quad \Leftrightarrow \quad Y \coprod A \mid L$$

A and *Y* are conditionally associated, given *L*, if

$$\Pr(Y=1 \mid A=1, L) \neq \Pr(Y=1 \mid A=0, L) \quad \Leftrightarrow \quad Y \not\coprod A \mid L$$

Measures of conditional association

- All measures of association generalizes directly
  - Conditional RD:

$$RD(L) = \Pr(Y = 1 \mid A = 1, L) - \Pr(Y = 1 \mid A = 0, L)$$

  - Conditional RR:

$$RR(L) = \frac{\Pr(Y = 1 \mid A = 1, L)}{\Pr(Y = 1 \mid A = 0, L)}$$

  - Conditional OR:

$$OR(L) = \frac{\Pr(Y = 1 \mid A = 1, L)}{\Pr(Y = 0 \mid A = 1, L)} / \frac{\Pr(Y = 1 \mid A = 0, L)}{\Pr(Y = 0 \mid A = 0, L)}$$

Causal Models

- The sufficient-component cause model (Rothman).
- *Potential outcomes, counterfactuals (Rubin, Robins)*
- *Structural equations, causal diagrams (Pearl)*

Relation between models

- All common causal models are essentially equivalent, from a mathematical perspective (different languages, same content)

- *To define 'causation', we will mostly rely on the potential outcome model, but we can borrow from the other models as well*

Causation

- August has been smoking 5 cigs/day since he was 15 years old. At the age of 60 he develops lung cancer

- *Did the smoking cause the cancer?*

- *What do we mean, more exactly, when we say that "smoking caused August's illness"?*

Human reasoning for causal inference

- We compare
  - the outcome *Y* when exposure *A* is present with
  - the outcome *Y* when exposure *A* is absent
  - all other things equal

- If the two outcomes differ, we say that the exposure *A* has a causal effect.
  - causative or preventative

- Note: often (always?), the comparison is only hypothetical.

Ideal data

- Y^a = the outcome that we would observe, for a given subject, if the subject was hypothetically exposed to level *a*.
  - We call this a **potential** outcome.
  - Y^1 = the potential outcome under exposure
  - Y^0 = the potential outcome under non-exposure
  - Ideally - and very unrealistically - we could observe both potential outcomes for any given subject

ID	Y^1	Y^0
August	1	0
Ylva	0	0

Subject Specific causal effect

ID	Y^1	Y^0
August	1	0
Ylva	0	0

- We say that *A* has an effect on *Y*, for a given subject, if the potential outcomes under exposure and non-exposure differ for the subject: $Y^1 \neq Y^0$.
  - For August, the exposure has an effect; $Y^1 \neq Y^0$.
  - For Ylva, the exposure has no effect; $Y^1 = Y^0$.

- **Sharp causal null hypothesis:** $Y^1 = Y^0$ **for all subjects**.

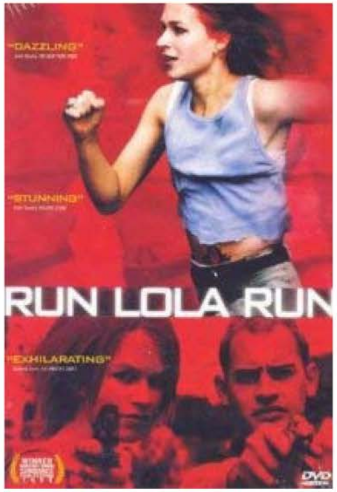
Observed Data

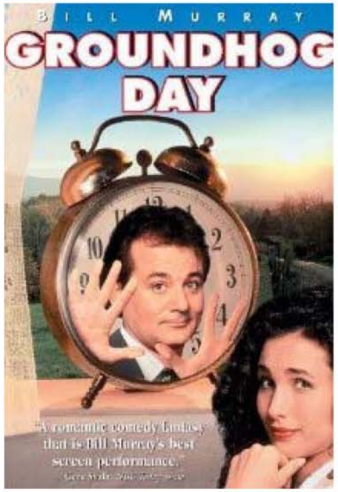
- August is exposed (A=1). Thus, for August
  - Y^1 is observed (realized) and equal to the factual outcome Y.
  - Y^0 is unobserved, or **counterfactual**.

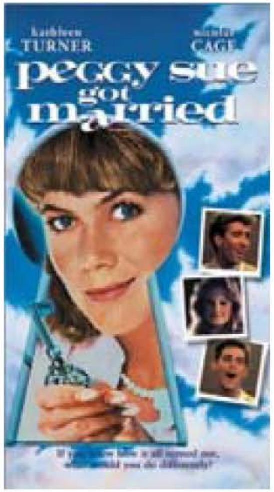
- Ylva is not exposed (A=0). Thus, for Ylva
  - Y^0 is observed (realized) and equal to the factual outcome Y.
  - Y^1 is unobserved, or **counterfactual**.

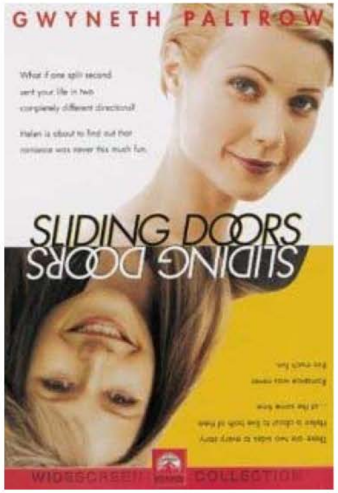
ID	A	Y	Y^1	Y^0
August	1	1	1	?
Selma	0	0	?	0

Counterfactuals in Popular Culture









Population causal effect

- Pr(Y^a=1) is the proportion of subjects that would develop disease, **if everybody would receive level *a*** (0/1).
  - the **probability** of developing disease if everybody would receive *a*.
- *A* has a population causal effect on *Y* if

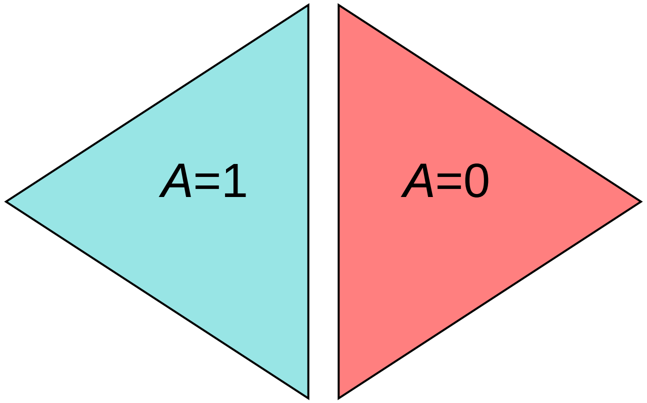
$$\Pr(Y^1 = 1) \neq \Pr(Y^0 = 1)$$

- *A* has no population causal effect on *Y* if

$$\Pr(Y^1 = 1) = \Pr(Y^0 = 1)$$

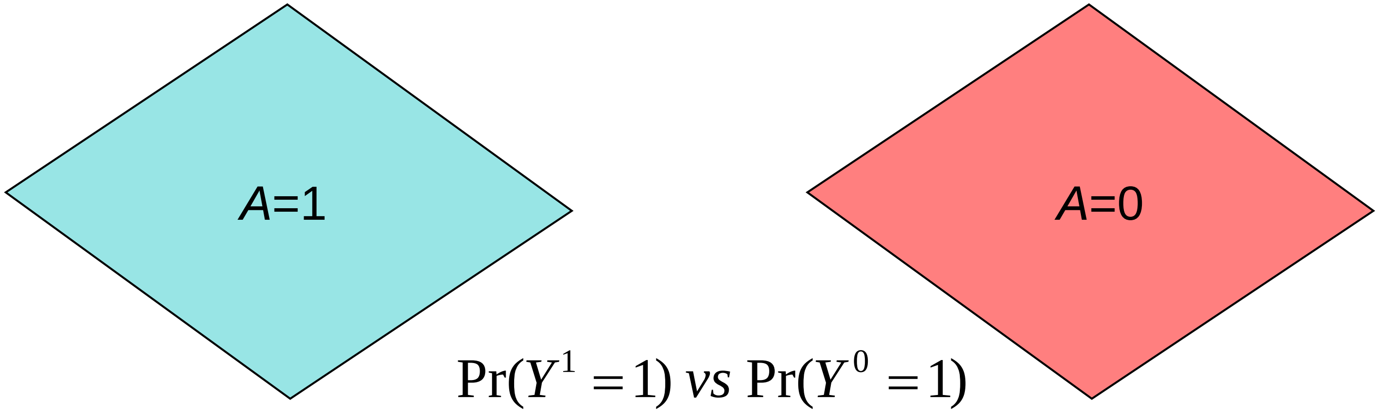
Association vs causation

- Association:



$$\Pr(Y=1 \mid A=1) \text{ } vs \text{ } \Pr(Y=1 \mid A=0)$$

- Causation:



$$\Pr(Y^1=1) \text{ } vs \text{ } \Pr(Y^0=1)$$

Measures of causal effects

- The *causal risk difference*:

$$CRD = \Pr(Y^1 = 1) - \Pr(Y^0 = 1)$$

  - Causal null hypothesis $\Leftrightarrow$ CRD = 0.
- The *causal risk ratio*:

$$CRR = \frac{\Pr(Y^1 = 1)}{\Pr(Y^0 = 1)}$$

  - Causal null hypothesis $\Leftrightarrow$ CRR = 1.
- The *causal odds ratio*:

$$COR = \frac{\Pr(Y^1 = 1)}{\Pr(Y^1 = 0)} / \frac{\Pr(Y^0 = 1)}{\Pr(Y^0 = 0)}$$

  - Causal null hypothesis $\Leftrightarrow$ COR = 1.

Conditional causal effects

- All effect-measures generalized directly:
  - Conditional causal RD:

$$CRD(l) = \Pr(Y^1 = 1 \mid L = l) - \Pr(Y^0 = 1 \mid L = l)$$

  - Conditional causal RR:

$$CRR(l) = \frac{\Pr(Y^1 = 1 \mid L = l)}{\Pr(Y^0 = 1 \mid L = l)}$$

  - Conditional causal OR:

$$COR(l) = \frac{\Pr(Y^1 = 1 \mid L = l)}{\Pr(Y^1 = 0 \mid L = l)} \Bigg/ \frac{\Pr(Y^0 = 1 \mid L = l)}{\Pr(Y^0 = 0 \mid L = l)}$$

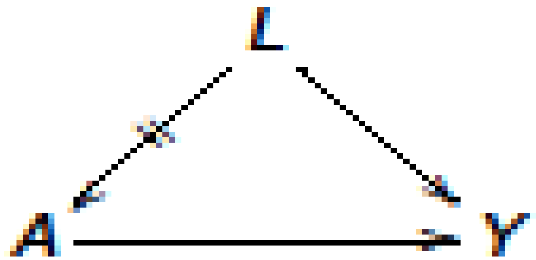
An important difference between association and causation

- In order for the causal effect of A on Y to be well defined we require that
  (i) we can tell whether an observed subject has A = 1 or A = 0
  (ii) we agree on what it means that an observed subject with A = 0 **would have had** A = 1, and vice versa
- In order for the association between A and Y to be well defined, only the first condition is required
  (i) Because the concept of association is only based on factual observations, not on counterfactuals

Estimation of causal effects

- Exchangeability
  - Randomization
  - Confounding Adjustment

Confounding adjustment - the main idea



- When A is randomized, all confounders become independent of A

$$Y \coprod A$$

- We can eliminate the influence of a potential confounder L by artificially breaking the association between L and A in the analysis

Several methods - often combined

- Stratification
- Matching
- Standardization
- Propensity scores
- Regression modeling
- Inverse probability weighting

Facts:

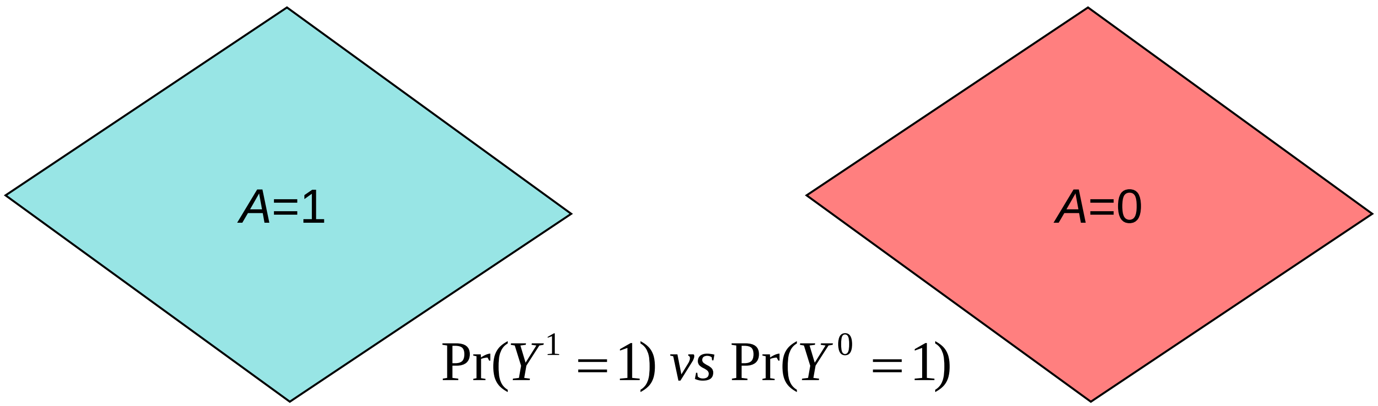
- Under exchangeability, association is equal to causation
- Exchangeability follows by randomization

- Exchangeability can be achieved by confounding adjustment
  - but is untestable

- Stratification produces subpopulation (conditional) Effects

- We use standardization to calculate population (marginal) effects

Population causal effects

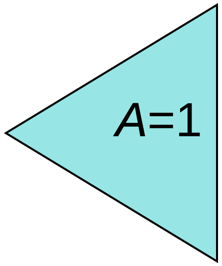


$$\Pr(Y^1 = 1) \; vs \; \Pr(Y^0 = 1)$$

- The definition of population causal effects calls for a comparison between
  - **the whole population** under exposure
  - **the whole population** under non-exposure
- But just like for separate individuals, we cannot in general observe whole populations under both exposure levels.

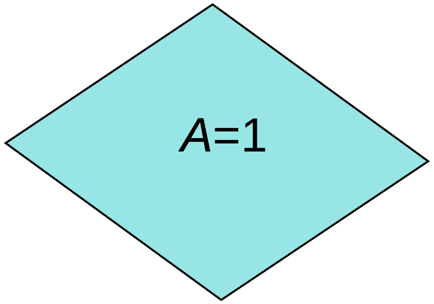
Tentative strategy

- To solve this problem we may attempt use the group of those who are **factually** exposed



$$\Pr(Y=1 \mid A=1)$$

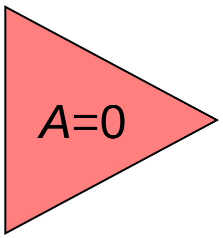
as a surrogate for the whole population under exposure:



$$\Pr(Y^1=1)$$

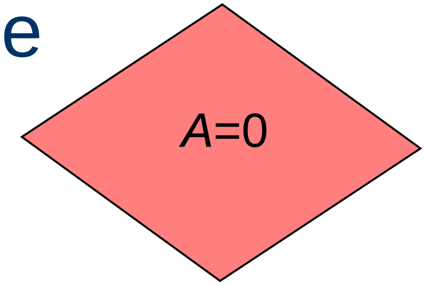
Tentative strategy, cont'd

- Similarly, we may attempt to use the group of those who are **factually** unexposed



$$\Pr(Y = 1 \mid A = 0)$$

as a surrogate for the whole population under non-exposure



$$\Pr(Y^0 = 1)$$