Association vs causation

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Causal Inference for Epidemiological Research

Outline

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Preliminaries

- Suppose we are interested in the relation between an exposure, X, and an outcome, Y
- We assume for simplicity that both X and Y are binary
  - we use ‘0’ for ‘unexposed/no outcome’, and ‘1’ for ‘exposed/outcome’
- We assume that population data are available (infinite sample size)
  - no need for p-values, confidence intervals etc
- These conditions are often unrealistic, but are useful for pedagogical purposes
  - will be relaxed later

Joint probability

- Suppose that the population proportions of X and Y are given by

	$Y=0$	$Y=1$
$X=0$	0.88	0.02
$X=1$	0.09	0.01

- Among all subjects, 1% are both exposed and have the outcome
- We say that the **joint probability** of $(X=1, Y=1)$ is 0.01
- We denote this as $p(X=1, Y=1)=0.01$

Marginal probability

	$Y=0$	$Y=1$
$X=0$	0.88	0.02
$X=1$	0.09	0.01
$\sum$	0.97	0.03

- Among all subjects, 3% have the outcome
- We say that the **marginal probability** of $Y=1$ is 0.03
- We denote this as $p(Y=1)=0.03$

Conditional probability

	$Y=0$	$Y=1$
$X=0$	0.88	0.02
$X=1$	0.09	0.01

- Among the exposed subjects, $\frac{0.01}{0.01+0.09}=10\%$ have the outcome
- We say that the **conditional probability** of having the outcome, for exposed subjects, is 0.1
- We denote this as $p(Y=1|X=1)=0.1$

A note on terminology

- In this course we use the terms ‘probability’, ‘risk’, and ‘chance’ as synonyms for the same thing
- For instance, $p(Y=1|X=1)$ is
  - the probability of the outcome, among the exposed
  - the risk of the outcome, among the exposed
  - the chance of the outcome, among the exposed
- We may also think of it as the proportion of subjects who have the outcome, among those that are exposed

Independence and association

- We say that X and Y are **independent** if the risk of the outcome is the same for exposed and unexposed:

$$p(Y=1|X=0) = p(Y=1|X=1) = p(Y=1)$$

We sometimes write this as

$$Y \perp\!\!\!\perp X$$

- We say that X and Y are **associated** if the risk of the outcome is different for exposed and unexposed:

$$p(Y=1|X=0) \neq p(Y=1|X=1) \neq p(Y=1)$$

We sometimes write this as

$$Y \not\!\perp\!\!\!\perp X$$

Example

	$Y=0$	$Y=1$
$X=0$	0.88	0.02
$X=1$	0.09	0.01

- *Are X and Y independent or associated in the table?*

Solution

Remark

- There may be several explanations for an association between X and Y
  - X causes Y
  - Y causes X ('reverse causation')
  - X and Y have common causes ('confounding')
- That X and Y are associated only means that certain values of X and Y tend to 'appear together'
  - why this happens is a different question

Measures of association

- The risk difference

$$p(Y = 1|X = 1) - p(Y = 1|X = 0)$$

$Y \perp\!\!\!\perp X \Leftrightarrow$ risk difference = 0

- The risk ratio

$$\frac{p(Y = 1|X = 1)}{p(Y = 1|X = 0)}$$

$Y \perp\!\!\!\perp X \Leftrightarrow$ risk ratio = 1

- The odds ratio

$$\frac{p(Y = 1|X = 1)}{p(Y = 0|X = 1)} \Big/ \frac{p(Y = 1|X = 0)}{p(Y = 0|X = 0)}$$

$Y \perp\!\!\!\perp X \Leftrightarrow$ odds ratio = 1

Example

	$Y = 0$	$Y = 1$
$X = 0$	0.88	0.02
$X = 1$	0.09	0.01

- *Compute the risk difference, the risk ratio, and the odds ratio*

Solution

Subgroups of the population

- Sometimes we wish to consider subgroups of the population
- Let Z be a covariate that defines these subgroups, e.g Z = sex (0=male, 1=female)
- $p(Y = 1|X, Z)$ is the conditional probability of the outcome, for those with a given level of exposure X and covariate Z
  - e.g. $p(Y = 1|X = 1, Z = 1)$ is the conditional probability of the outcome, for exposed women, and
  - $p(Y = 1|X = 0, Z = 1)$ is the conditional probability of the outcome, for unexposed women

Conditional independence and association

- We say that X and Y are conditionally independent, given Z, if

$$p(Y=1|X=0,Z) = p(Y=1|X=1,Z) = p(Y=1|Z)$$

$$Y \perp\!\!\!\perp X \mid Z$$

- We say that X and Y are conditionally associated, given Z, if

$$p(Y=1|X=0,Z) \neq p(Y=1|X=1,Z) \neq p(Y=1|Z)$$

$$Y \not\!\perp\!\!\!\perp X \mid Z$$

Technical note

- In principle, we could have that
  - $p(Y=1|X=0,Z) = p(Y=1|X=1,Z)$ for some values of Z, and
  - $p(Y=1|X=0,Z) \neq p(Y=1|X=1,Z)$ for other values of Z
- When we write $Y \perp\!\!\!\perp X \mid Z$, we mean that $p(Y=1|X=1,Z) = p(Y=1|X=0,Z)$ for **all** values of Z
- When we write $Y \not\!\perp\!\!\!\perp X \mid Z$, we mean that $p(Y=1|X=0,Z) \neq p(Y=1|X=1,Z)$ for **at least one** value of Z

Measures of conditional association

- Conditional risk difference, given Z

$$p(Y=1|X=1,Z) - p(Y=1|X=0,Z)$$

- Conditional risk ratio, given Z

$$\frac{p(Y=1|X=1,Z)}{p(Y=1|X=0,Z)}$$

- Conditional odds ratio, given Z

$$\frac{p(Y=1|X=1,Z)}{p(Y=0|X=1,Z)} \Big/ \frac{p(Y=1|X=0,Z)}{p(Y=0|X=0,Z)}$$

Outline

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 borrow from the other models as well

Motivating example

- 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?*

Human reasoning about cause and effects

- We mentally compare two scenarios:
  - the outcome when the exposure is present
  - the outcome when the exposure is absent

  everything else equal
- If the two outcomes differ, then we say that the exposure has a causal effect
  - causative or preventative

Ideal data

- Let Y_x be the outcome that we would observe, for a given subject, if the subject potentially received exposure level x
  - Y_0 is the outcome when not exposed
  - Y_1 is the outcome when exposed
- Y_0 and Y_1 are referred to as **potential outcomes**
- Ideally - **and very unrealistically** - we could observe both potential outcomes for any given subject

subject	Y_0	Y_1
August	0	1
Selma	0	0
Fjodor	1	1

Subject-specific causal effects

subject	Y_0	Y_1
August	0	1
Selma	0	0
Fjodor	1	1

- X has a causal effect on Y, for a given subject, if the potential outcomes Y_0 and Y_1 differ for this subject
  - for August, the exposure has an effect: $Y_0 \neq Y_1$
  - for Selma and Fjodor, the exposure has no effect; $Y_0 = Y_1$

Observed data

- August is exposed ($X = 1$). Thus, for August
  - Y_1 is observed and equal to the factual outcome Y
  - Y_0 is unobserved, or **counterfactual**
- Selma and Fjodor are unexposed ($X = 0$). Thus, for Selma and Fjodor
  - Y_0 is observed and equal to the factual outcome Y
  - Y_1 is unobserved, or **counterfactual**

subject	X	Y	Y_0	Y_1
August	1	1	?	1
Selma	0	0	0	?
Fjodor	0	1	1	?

A fundamental problem of causation

- It is very difficult to say whether the exposure causes the outcome for a specific subject
  - because we cannot observe the same subject under two exposure levels simultaneously

From subjects to populations

- Fortunately, it is much easier to justify causal claims on population levels
  - e.g. ‘if nobody would smoke, then the incidence of liver cancer would be 15% less than if everybody would smoke’
  - more later

Population causal effects

- $p(Y_x = 1)$ is the probability of the outcome if **everybody** would receive exposure level x
  - alternatively, the proportion of subjects that would develop the outcome, if everybody would receive x
- X has a population causal effect on Y if

$$p(Y_0 = 1) \neq p(Y_1 = 1)$$

- X has no population causal effect on Y if

$$p(Y_0 = 1) = p(Y_1 = 1)$$

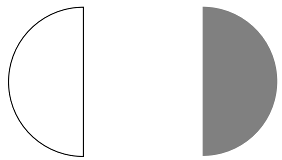
Technical note

- In statistics, we use
  - upper case letters (e.g. X, Y) for random variables
  - lower case letters (e.g. x, y) for fixed numbers
- When writing Y_x, we consider the exposure to be fixed to x (0 or 1)
- When writing $p(Y_x = 1)$, we consider a scenario where the exposure is fixed to x for everybody

Association vs Causation

- Association:

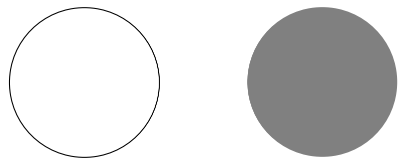
Factually unexposed Factually exposed



$$p(Y = 1|X = 0) \text{ vs } p(Y = 1|X = 1)$$

- Causation:

Everybody unexposed Everybody exposed



$$p(Y_0 = 1) \text{ vs } p(Y_1 = 1)$$

Measures of causal effects

- The causal risk difference

$$p(Y_1 = 1) - p(Y_0 = 1)$$

no causal effect of X on Y $\Leftrightarrow$ causal risk difference = 0

- The causal risk ratio

$$\frac{p(Y_1 = 1)}{p(Y_0 = 1)}$$

no causal effect of X on Y $\Leftrightarrow$ causal risk ratio = 1

- The causal odds ratio

$$\frac{p(Y_1 = 1)}{p(Y_1 = 0)} \Big/ \frac{p(Y_0 = 1)}{p(Y_0 = 0)}$$

no causal effect of X on Y $\Leftrightarrow$ causal odds ratio = 1

Example

subject	Y_0	Y_1
1	0	0
2	0	1
3	0	0
4	1	1
5	0	0
6	1	1
7	1	1
8	1	1
9	0	0
10	0	1

- *Compute the causal risk difference, the causal risk ratio, and the causal odds ratio*

Solution

Conditional causal effects

- Conditional causal risk difference, given Z

$$p(Y_1 = 1|Z) - p(Y_0 = 1|Z)$$

- Conditional causal risk ratio, given Z

$$\frac{p(Y_1 = 1|Z)}{p(Y_0 = 1|Z)}$$

- Conditional causal odds ratio, given Z

$$\frac{p(Y_1 = 1|Z)}{p(Y_1 = 0|Z)} \Big/ \frac{p(Y_0 = 1|Z)}{p(Y_0 = 0|Z)}$$

Brief remark 1

- We have seen that both association and causation can be quantified with risk differences, risk ratios, and odds ratios
- For convenience, we will mostly focus on risk ratios
- Everything that we say holds for risk differences and odds ratios as well

Brief remark 2

- We have considered binary variables and defined the (population) causal effect as

$$p(Y_0 = 1) \text{ vs } p(Y_1 = 1)$$

- When the outcome is non-binary we may define the causal effect as

$$E(Y_0) \text{ vs } E(Y_1)$$

- When the exposure is non-binary as well, we may define the causal effect of an increase from $X = 0$ to $X = x$ as

$$E(Y_0) \text{ vs } E(Y_x)$$

Outline

When is a counterfactual well defined?

- Some people have argued that counterfactuals are not always well defined
  - i.e. we don't have a uniform agreement on what the counterfactual represents 'in real life'
- If these people are correct, then causal effects based on these counterfactuals are not well defined either

Example

- Define $X = 1$ if BMI>30, and $X = 0$ if BMI<30
- Cardiovascular disease (Y) is more common among obese than among non-obese, i.e.

$$p(Y = 1|X = 1) > p(Y = 1|X = 0)$$

- Does 'obesity' have a causal effect on the risk of cardiovascular disease?

$$p(Y_1 = 0) \neq p(Y_1 = 1)?$$

Quite a vague question

- Translated into plain English, the counterfactual comparison reads
  - 'what would the risk be if everybody had BMI<30 compared to if everybody had BMI>30?'
- But what does 'if everybody had BMI>30' really mean?
  - fat or muscles?
  - belly fat or hips fat?
- The outcome is probably very different under these alternative counterfactual scenarios
  - thus, the counterfactuals that we wish to compare are not well defined

An important difference between association and causation

- The association between X and Y is well defined if we agree on
  - who is factually exposed (e.g. BMI>30), and
  - who does factually have the outcome (e.g. cardiovascular disease)
- This is typically not difficult
- The causal effect of X on Y is well defined if we also agree on
  - the counterfactual scenario where all subjects are exposed
  - the counterfactual scenario where all subjects are unexposed
- This is often not trivial

Refining the research question

- To reduce vagueness in the counterfactuals we may refine the research question
  - e.g. 'what is the causal effect on the risk of cardiovascular disease, of having 20% body fat as compared to 10% body fat, when 30% of all body fat is located on the belly and 30% is located on the hips?
- But refining the research question quickly limits
  - the relevance of it, since it becomes 'too narrow' for general interest
  - the possibility to answer it, since very few people would 'match' our inclusion criteria
- A trade-off between preciseness and relevance/feasibility

Some counterfactuals are ill-defined, most are somewhat vague, but many are useful

Lewis, 1973

Summary

- Association is not equal to causation
- To define causation, we use potential outcomes and counterfactuals
- Beware: not all counterfactuals (and causal effects) are well defined