Estimands, and Causal Thinking

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Big thank you to

- Stijn Vansteelandt and Oliver Dukes (Ghent University)

Outline

Introduction

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  yet statistical developments in this field are relatively recent.
- For decades, the feeling was that in most empirical studies,
  except for randomised experiments,
  it is too ambitious to infer cause-effect relationships.

Sidestepping the causal question...

Our statistical methods are subject to debate.[17] Other more sophisticated advanced approaches, such as marginal structural models, aim to address causality but necessitate additional assumptions.[18] Our methods are correct in terms of statistical association, because they adequately acknowledge the chronological order of all factors and do not need further assumptions.

Discussion

Health-care-associated infections cause high excess mortality in critically ill patients, although antimicrobial resistance has a comparatively low additional effect.

Lancet Infect Dis 2011; 11:30-38

The need for a formal approach

- Drawing causal conclusions from data is indeed ambitious.
- But when the scientific question concerns causality, then sidestepping it, can make things worse.

The need for a formal approach (1)

- Standard statistical analyses jump right into modeling the data, e.g.

$$\lambda(t|Z, X) = \lambda_0(t) \exp(\beta Z + \gamma X)$$

- This can be useful when the aim is prediction, but does not acknowledge that our interest is only in the effect of treatment Z.

The need for a formal approach (2)

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  - our assumptions;

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    (Greenland, Robins and Pearl, 1998; Martinussen and Vansteelandt, 2013; Daniel, Zhang and Farewell, 2021)

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  (Vansteelandt, Bekaert and Claeskens, 2012; Dukes and Vansteelandt, 2020)
- In fact, the treatment effect is not even well defined when the model is wrong.

  (Vansteelandt, Dukes, Van Lancker and Martinussen, 2022)

The roadmap for causal inference

The causal inference literature advocates a formal framework for addressing scientific questions empirically:

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3. Estimate that estimand.
   Model building enters only in this final stage, to address the curse of dimensionality.

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example

If $\beta_1 \neq 0$ in

$$Y = \beta_0 + \beta_1 Z + \epsilon_y$$

then also $\alpha_1 \neq 0$ in

$$Z = \alpha_0 + \alpha_1 Y + \epsilon_z.$$

However, the statement 'Z causes Y' does not imply 'Y causes Z'.

Causal inference in search of a language

- The introduction of formal languages for communicating about causal effects,
  has revolutionized this field.
- Two popular languages: causal diagrams, and counterfactuals.

  (Pearl, 1995, 2000; Hernan, 2004; Hernan and Robins, 2020)
- These are largely interchangeable, but causal diagrams are more 'intuitive'
  and counterfactuals are more 'refined'.

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  and counterfactuals are more 'refined'.
- In this lecture, I will introduce counterfactuals,
  which express causal effects by relating to hypothetical interventions.

Outline

A simple example

- Example due to Rhian Daniel.
- 12 subjects each suffer a headache.
- Some take a potion; others don't.
- One hour later, we ask each of the 12 whether or not his/her headache has disappeared.

The observed data (1)

	Z (potion taken?)	Y (headache disappeared?)
Arianrhod	0	0
Blodeuwedd	1	0
Caswallawn	1	1
Dylan	0	0
Efnisien	0	1
Gwydion	1	0
Hafgan	1	0
Lleu	0	0
Matholwch	0	1
Pwyll	0	0
Rhiannon	0	1
Teyrnon	1	1

The observed data (2)

	Z (potion taken?)	Y (headache disappeared?)
Arianrhod	0	0
Blodeuwedd	1	0
Caswallawn	1	1
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Efnisien	0	1
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- Did the potion cause his headache to disappear?

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- Caswallawn took the potion, and his headache disappeared.
- Did the potion cause his headache to disappear?
- We don't know.
- To answer this, we need to know what would have happened had he not taken the potion.

Counterfactuals and potential outcomes

- Z is the treatment: whether or not a potion was taken.
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- Write Y^0 (or $Y(0)$) and Y^1 (or $Y(1)$) to represent the *potential outcomes* under both treatments.
- Y^0 is the outcome which would have been seen had the potion NOT been taken.
- Y^1 is the outcome which would have been seen had the potion been taken.

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- Y^1 is the outcome which would have been seen had the potion been taken.
- One of these is observed: if $Z = 0$, Y^0 is observed; if $Z = 1$, Y^1 is observed.
- The other is *counterfactual*.

Counterfactuals and potential outcomes

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- Y^0 is the outcome which would have been seen had the potion NOT been taken.
- Y^1 is the outcome which would have been seen had the potion been taken.
- One of these is observed: if $Z = 0$, Y^0 is observed; if $Z = 1$, Y^1 is observed.
- The other is *counterfactual*.
- Suppose that we can observe the unobservable. . .

The ideal data

	Y^0	Y^1
Arianrhod	0	0
Blodeuwedd	1	0
Caswallawn	0	1
Dylan	0	1
Efnisien	1	1
Gwydion	0	0
Hafgan	1	0
Lleu	0	0
Matholwch	1	0
Pwyll	0	0
Rhiannon	1	1
Teyrnon	0	1

- For Caswallawn, the potion did have a causal effect.
- He did take it, and his headache disappeared;
  but had he not taken it,
  his headache would not have disappeared.
- Thus the potion had a causal effect on his headache.
- What about Gwydion?
- and Rhiannon?
- and Matholwch?

The fundamental problem of causal inference

	Y^0	Y^1	Z	Y
Arianrhod	0	?	0	0
Blodeuwedd	?	0	1	0
Caswallawn	?	1	1	1
Dylan	0	?	0	0
Efnisien	1	?	0	1
Gwydion	?	0	1	0
Hafgan	?	0	1	0
Lleu	0	?	0	0
Matholwch	1	?	0	1
Pwyll	0	?	0	0
Rhiannon	1	?	0	1
Teyrnon	?	1	1	1

- In reality, we never observe both Y^0 and Y^1 on the same individual.
- Sometimes called the fundamental problem of causal inference.
- It is therefore over-ambitious to infer anything about individual-level causal effects.

Population-level causal effects

- A less ambitious goal is to focus on the population-level or average causal effect:

$$E\left(Y^1 - Y^0\right) \quad \text{or} \quad \frac{E\left(Y^1\right)}{E\left(Y^0\right)}.$$

- We can also define causal effects in a subpopulation, e.g. the treated:

$$E\left(Y^1 - Y^0 \,|Z = 1\right)$$

or, for precision medicine, in strata defined by pre-treatment characteristics X:

$$E\left(Y^1 - Y^0 \,|X\right)$$

Exercises

How would you express the following in counterfactuals?

- What would be the 1-year mortality risk *if all were treated?*
- How much would the hospital mortality risk decrease *if we had been able to prevent hospital-acquired infection in the infected?*
- What would be the 5-year mortality risk be *if we initiate HAART treatment when CD4 count L is below 200 cells/ml?*

Solutions

Summary so far...

- We now have notation
  to distinguish causation

$$E\left(Y^1 - Y^0\right) \quad \text{or} \quad \frac{E\left(Y^1\right)}{E\left(Y^0\right)}$$

  from association:

$$E\left(Y|Z=1\right) - E\left(Y|Z=0\right) \quad \text{or} \quad \frac{E\left(Y|Z=1\right)}{E\left(Y|Z=0\right)}.$$

- Historically, this has been key
  to the development of methods for causal inference.

causation $\neq$ association?

Id	X	Z	Y	Y^1	Y^0
Fay	0	0	0	0	0
George	0	0	0	0	0
Tom	0	0	0	0	0
Mary	0	0	0	0	0
Chris	0	0	1	0	1
Anna	0	0	1	0	1
Rose	0	1	0	0	0
Jack	0	1	0	0	0
Lee	0	1	0	0	1
Adam	1	0	0	0	0
John	1	0	1	0	1
Ian	1	0	1	1	1
Betsy	1	1	0	0	0
Claus	1	1	0	0	0
Sara	1	1	0	0	1
Lisa	1	1	0	0	1
Peter	1	1	1	1	1
Sue	1	1	1	1	1

$$\frac{P(Y^1 = 1)}{P(Y^0 = 1)} = \frac{3/18}{9/18} = \frac{1}{3}$$

$$\frac{P(Y = 1|Z = 1)}{P(Y = 1|Z = 0)} = \frac{2/9}{4/9} = \frac{1}{2}$$

Outline

The consistency assumption

- So far, we have implicitly used that:

$$Z = z \Rightarrow Y^z = Y$$

  in order to link counterfactuals to the observed data.

- This may appear logical, but is nonetheless called an assumption:
  the consistency assumption.

  (Pearl, 2000; Hernán, 2016)

- The reason is that we define 'causal effects'
  as expressing what would happen under hypothetical interventions,
  but no interventions may have been considered in the study.

Example: the effect of weight loss

Review > Nutr Res Rev. 2009 Jun;22(1):93-108. doi: 10.1017/S0954422409990035.

A review and meta-analysis of the effect of weight loss on all-cause mortality risk

Mary Harrington [1], Sigrid Gibson, Richard C Cottrell

Affiliations + expand

PMID: 19555520 DOI: 10.1017/S0954422409990035

What is meant by the effect of weight loss on mortality?
If $Z = 1$ means weight loss, then does $Y^1 = Y$ for those with $Z = 1$?

What does weight loss mean?

- Quantitative statements such as

  'Intentional weight loss had a small benefit for individuals classified as unhealthy (with obesity-related risk factors) (RR 0.87 (95% CI 0.77, 0.99); P = 0.028) ...'

  are therefore very difficult to understand:
  it is unclear precisely what intervention on weight is considered.

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- If our interest was in quantifying the effect of weight loss via physical exercise,
  then obviously the study will not help when participants lost weight via gastric bypass.

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  are therefore very difficult to understand:
  it is unclear precisely what intervention on weight is considered.

- If our interest was in quantifying the effect of weight loss via physical exercise,
  then obviously the study will not help when participants lost weight via gastric bypass.

- The consistency assumption:

$$Z = z \Rightarrow Y^z = Y$$

  then fails.

Consistency assumption

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Consistency assumption

- By forcing us to think in terms of specific interventions, causal estimands make us think and clarify what the scientific question is.
- This conceptualisation may appear as a hindrance

  (because we may not have in mind doing interventions)

  but it forces us to be precise,
  and makes us realize when results are ambiguous.

Outline

Fundamental problem of causal inference

- Since we don't know Y^1 for every subject, we can't easily estimate $E\left(Y^1\right)$ as the proportion of all subjects with $Y^1 = 1$.
- Likewise, we can't simply calculate $E\left(Y^0\right)$ as the proportion of all subjects with $Y^0 = 1$.

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- Likewise, we can't simply calculate $E\left(Y^0\right)$ as the proportion of all subjects with $Y^0 = 1$.
- Our task is therefore to choose quantities from the observed data
  (i.e. involving Z, Y and other observed variables)
  that represent reasonable substitutes for hypothetical quantities such as $E\left(Y^1 - Y^0\right)$.

Exchangeability (1)

- What might be a good substitute for $E\left(Y^1\right)$?
- *What about* $E\left(Y \,|Z=1\right)$*?*
- This is the proportion whose headache disappeared among those who actually took the potion.
- *Is this the same as* $E\left(Y^1\right)$*?*

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- *Is this the same as* $E\left(Y^1\right)$*?*
- Only if those who took the potion are **exchangeable** with those who didn't.
  Mathematically, $Z \perp\!\!\!\perp Y^0$ and $Z \perp\!\!\!\perp Y^1$.
- This would be the case if the choice to take the potion was made at random.
- This is why ideal randomised experiments are the gold standard for inferring causal effects.

Exchangeability (2)

With exchangeability, analyses of randomised experiments return causal effects

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- Those with a worse headache
  are probably more likely to take the potion.
- Suppose we asked each subject at the beginning of the study:
  "is your headache severe?".
- Then, we might propose that,
  after taking severity into account,
  the decision as to whether or not to take the potion was
  effectively taken at random.

Conditional exchangeability (2)

- Suppose X denotes severity.
- Then, under this assumption, within strata of X, the exposed and unexposed subjects are exchangeable.
- This is called **conditional exchangeability** (given Z). Mathematically, $Z \perp\!\!\!\perp Y^0 | X$ and $Z \perp\!\!\!\perp Y^1 | X$.
- We can't check this from our data; we need to believe it from a priori knowledge.

Conditional exchangeability (3)

With conditional exchangeability, regression delivers conditional causal effects

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It follows that the marginal causal effect equals

$$E(Y^1 - Y^0) = E\{E(Y|Z=1,X) - E(Y|Z=0,X)\}$$

The average treatment effect in the treated

Suppose that $Y^0 \perp\!\!\!\perp Z|X$,
then how would you identify the average treatment effect in the treated?

$$E(Y^1 - Y^0|Z = 1) \quad =$$

How would you evaluate this on data?

The hazards of hazard ratios

- Common to measure the effect of a randomized treatment Z on a time-to-event endpoint T
  in terms of the hazard ratio; e.g. in discrete time:

$$\frac{P(T = t | T \geq t, Z = 1)}{P(T = t | T \geq t, Z = 0)}$$

- By randomization, we have that $T^z \perp\!\!\!\perp Z$ for $z = 0, 1$.
- *Can you re-express this in counterfactuals?*

The hazards of hazard ratios

- $T^z \perp\!\!\!\perp Z$ for $z = 0, 1$ allows us to re-express the hazard ratio as

$$\frac{P(T = t | T \geq t, Z = 1)}{P(T = t | T \geq t, Z = 0)} = \frac{P(T^1 = t | T^1 \geq t, Z = 1)}{P(T^0 = t | T^0 \geq t, Z = 0)} = \frac{P(T^1 = t | T^1 \geq t)}{P(T^0 = t | T^0 \geq t)}$$

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- E.g., under proportional hazards, we can equivalently express the hazard ratio as

$$\frac{\log P(T \geq t | Z = 1)}{\log P(T \geq t | Z = 0)} = \frac{\log P(T^1 \geq t)}{\log P(T^0 \geq t)}$$

- Only the comparison of $P(T = t | T \geq t, Z = 1)$ and $P(T = t | T \geq t, Z = 0)$ is not causal.

Outline

Principal stratification

- Qu et al. (2020) analyze the IMAGINE-3 Study, a randomized 52-week Phase 3 study comparing basal insulin peglispro (BIL) with insulin glargine (GL) for type 1 diabetes (T1D).
- Let $A = 0$ for those who discontinue the study medication and $A = 1$ otherwise.

Principal stratification

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- Let $A = 0$ for those who discontinue the study medication and $A = 1$ otherwise.
- It would be inappropriate to exclude treatment dropouts from both arms since

$$\begin{aligned} E(Y|Z = A = 1) - E(Y|Z &= 0, A = 1) \\ &= E(Y^1|Z = 1, A^1 = 1) - E(Y^0|Z = 0, A^0 = 1) \\ &= E(Y^1|A^1 = 1) - E(Y^0|A^0 = 1) \end{aligned}$$

  is an apple versus orange comparison.
- Principal stratification focuses on 'patients who would have adhered, no matter what treatment':

$$E(Y^1 - Y^0|A^1 = A^0 = 1).$$

(Robins, 1986 Section 12.2; Robins, 1995; Rubin, 1998, 2000, 2006; Little and Rubin, 1999; Robins and

How relevant is the estimand?

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  What if other patients may potentially be harmed?
- Suppose now that I can predict that a given patient with given covariate values x
  has 80% chance to belong to that stratum.
- *Should that reassure me?*

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  What if other patients may potentially be harmed?
- Suppose now that I can predict that a given patient with given covariate values x
  has 80% chance to belong to that stratum.
- *Should that reassure me?*
  - No, if we have a strategy for predicting who it is 'worth' giving treatment to,

    (e.g., those who are predicted to adhere on treatment, based on baseline covariates)

    then we should evaluate that hypothetical dynamic strategy.

Can we identify the estimand? (1)

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- The choice of estimand should not solely be based on what we 'ideally' wish to learn,
  but also on what is feasible to learn.
- Qu et al. (2000) assume that they have access to baseline covariates X

  (age, gender, HbA1c, low density lipoprotein cholesterol (LDL-C), triglyceride (TG), fasting serum glucose (FSG), and alanine aminotransferase (ALT))

  and longitudinal data L

  (HbA1c, LDL-C, TG, FSG, and ALT at Week 12 and Week 26, and adverse events such as injection site reaction)

  so that

$$A^1 \perp\!\!\!\perp (Y^1, Y^0, L^0) | L^1, X \quad \text{and} \quad A^0 \perp\!\!\!\perp (Y^1, Y^0, L^1) | L^0, X$$

- *What does that mean? Could this be plausible?*

Can we identify the estimand? (2)

$$A^1 \perp\!\!\!\perp (Y^1, Y^0, L^0) | L^1, X \quad \text{and} \quad A^0 \perp\!\!\!\perp (Y^1, Y^0, L^1) | L^0, X$$

- *What does that mean? Could this be plausible?*

Can we identify the estimand? (2)

$$A^1 \perp\!\!\!\perp (Y^1, Y^0, L^0) | L^1, X \quad \text{and} \quad A^0 \perp\!\!\!\perp (Y^1, Y^0, L^1) | L^0, X$$

- *What does that mean? Could this be plausible?*
- This assumption is violated when adherence directly affects outcome
  (which it quite surely does)!
  (This is because adherence on treatment A^1 affects outcome on treatment Y^1.
  Note that previous assumptions instead assumed assigned treatment Z to be independent of outcome on treatment Y^1!)

Can we identify the estimand? (3)

- Qu et al. (2000) moreover assume that

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- This example reveals a danger of the language of counterfactuals:
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- Analyses based on such assumptions should not be trusted.
- This is generally the result of asking overly ambitious questions.

Outline

Conclusions

- For drawing causal conclusions,
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Conclusions

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  there is much appeal in inferring the effects of hypothetical interventions.
- Counterfactuals give us a rich language to do this, and powerful tools.
- They help to target the scientific question.
- They avoid conflating model, assumptions and estimand.
- They also come with some dangers.

The perilous power of counterfactuals

- We may not realize that the interventions are infeasible.

  (e.g., what is the effect of renal replacement therapy in critically ill patients?)

- This may happen as a result of positivity violations: that $P(Z = 1|X)$ equals 0 or 1 with positive probability.

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- Sadly, many papers 'tick the box' by stating assumptions, but not judging their plausibility in the context of the data.

Thank you for your attention!

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