

Estimands, and Causal Thinking

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Big thank you to

- Stijn Vansteelandt and Oliver Dukes (Ghent University)

Outline

- 1 Introduction
- 2 Counterfactuals
- 3 The consistency assumption
- 4 Exchangeability
- 5 ICH E9 addendum:
principal stratification
- 6 Conclusions

Introduction

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- Causal questions have been posed for centuries, 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)

- As we start building the model, each change of model **changes**

- our **assumptions**;

(Van Lancker, Dukes and Vansteelandt, 2021)

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- our 'definition' of **treatment effect** (cfr. non-collapsibility);

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

- This does not make sense: it leads to biased estimates and confidence intervals.

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- This does not make sense: it leads to biased estimates and confidence intervals.

(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:

- 1 **Translate** the scientific question into a **model-free estimand**.

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- 1 **Translate** the scientific question into a **model-free estimand**.
- 2 **Identify** that estimand
(i.e., 'link' it to a quantity we can calculate based on the observed data distribution)
and be clear about the required assumptions.
- 3 **Estimate** that estimand.
Model building enters only in this final stage, to address the **curse of dimensionality**.

Causal inference in search of a language

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

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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
Teyrnnon	1	1

The observed data (2)

	Z (potion taken?)	Y (headache disappeared?)
Arianrhod	0	0
Blodeuwedd	1	0
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Dylan	0	0
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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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- 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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- 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

	γ^0	γ^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
Teyrnnon	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
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- 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:

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

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

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

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

$$E(Y^1 - Y^0 | X)$$

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?*

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$$P(Y^1 = 1 | Z = 1) - P(Y^0 = 1 | Z = 1)$$

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$$E(Y^{I(L < 200)})$$

$I(L < 200)$ is an indicator function which is 1 if the condition, $L < 200$, is met, and 0 otherwise.

Summary so far...

- We now have notation to distinguish causation

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

from association:

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

- 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

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

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

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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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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

- By forcing us to think in terms of specific interventions, causal estimands make us think and clarify what the scientific question is.

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.

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Fundamental problem of causal inference

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

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- Likewise, we can't simply calculate $E(Y^0)$ 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 $E(Y^1 - Y^0)$.

Exchangeability (1)

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

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- This is the proportion whose headache disappeared among those who actually took the potion.
- *Is this the same as $E(Y^1)$?*
- 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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Conditional exchangeability (1)

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- In observational data, exchangeability is usually **implausible**.
- 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

$$E(Y^1 - Y^0|X) = E(Y^1|X) - E(Y^0|X)$$

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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?

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

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

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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.

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- 1 Introduction
- 2 Counterfactuals
- 3 The consistency assumption
- 4 Exchangeability
- 5 ICH E9 addendum:
principal stratification**
- 6 Conclusions

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.

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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':

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

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- 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**.

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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?*

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- *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 !)

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- This example reveals a **danger of the language of counterfactuals**:
it enables one to make assumptions that make no biological sense.
(this is more likely to happen when cross-world assumptions are made)
- Analyses based on such assumptions should not be trusted.
- This is generally the result of asking overly ambitious questions.

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Conclusions

- For drawing causal conclusions, 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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- Such violations are not uncommon in settings with **treatment cross-over, rescue treatment, ...**
- We may not even understand the assumptions (cfr., principal stratification).
- 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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