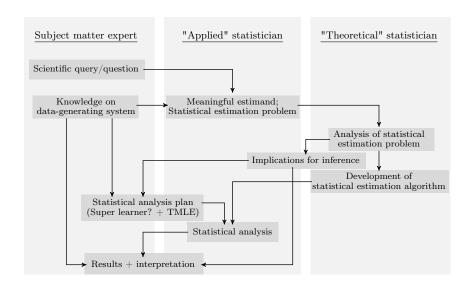
Day 3, Lecture 3

More general data settings

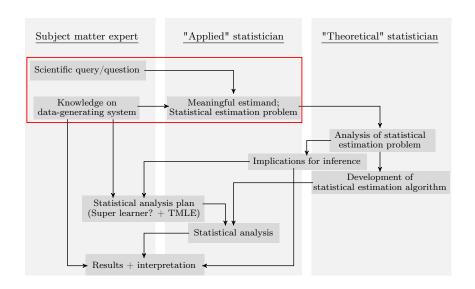
In this lecture, our goal is to:

- Identify and discuss challenges and opportunities in time-varying settings, with presence of time-varying treatments, right-censoring and death.
- Exemplify the use of counterfactuals and dynamic treatment regimes to avoid common biases in the analysis of observational data, highlighting the role of causal inference tools in defining meaningful target parameters.

Targeted learning framework



Targeted learning framework



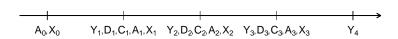
Data structure considered so far:

- $O = (X, A, Y) \in \mathbb{R}^d \times \{0, 1\} \times \{0, 1\}$
- ▶ Covariates X are measured before treatment decision A is made
- ▶ After treatment decision A, the outcome Y is observed



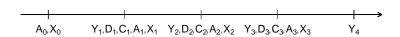
Longitudinal data structure:

- $ightharpoonup O = (X_0, A_0, ..., Y_k, D_k, C_k, X_k, A_k, ..., Y_K)$
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- 1. Dynamic treatment interventions.
- 2. Right-censoring and competing risks.
- 3. More subtleties in confounding bias.

The data setting O = (X, A, Y) may fit many problem settings

- point treatment such as planned cesarian section, or a surgery
- ▶ intention-to-treat analysis, e.g., of randomized trials

Right-censoring and death (due to other causes)

- play a big role in medical research
- sometimes in settings with point treatment

The general longtudinal data setting may involve

- treatments changing during follow-up
- right-censoring, time-to-event outcome, competing risks

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Treatment discontinuation/switching Subjects may discontinue, never take their assigned treatment, or they could start a different treatment as well.

These are different types of complications. How we handle them is reflected in our

- formulation of causal parameter;
- formulation of counterfactuals / ideal interventions / target trial.

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- formulation of causal parameter;
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This is relevant in observational studies as well as in randomized controlled trials.

From day 1

To answer a causal question, we ideally want to know

- Scenario 1 What would have happened to a subject had they been exposed?
- Scenario 2 What would have happened to the same subject had they not been exposed?

We imagine a model with two outcomes for each subject:

- \triangleright a variable Y^1 corresponding to scenario 1, and
- \triangleright a variable Y^0 corresponding to scenario 2
- = the "counterfactuals" (aka potential outcomes).

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Time-to-event data settings

- link between counterfactuals and the concept of "uncensored" event times
- 2. benefits of counterfactual reasoning (under additional treatment interventions)

In a "classical" event history (survival) analysis setting:

- ▶ $T \in \mathbb{R}_+$ time to event
- we only observe $\tilde{T} = \min(T, C)$, where $C \in \mathbb{R}_+$ is the time to right-censoring, as well as $\tilde{\Delta} = 1\{T \leq C\}$

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- ... there is a close link between handling right-censoring and imposing certain treatment interventions.
- ... basically, right-censoring can be viewed as just another time-varying treatment.

Observed data with baseline treatment:

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- we only observe $\tilde{T} = \min(T, C)$ where $C \in \mathbb{R}_+$ is the time to right-censoring, as well as $\tilde{\Delta} = 1\{T \leq C\}$
- ▶ baseline treatment $A \in \{0, 1\}$
- ▶ baseline (pre-treatment) covariates $X \in \mathbb{R}^d$

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We imagine a model with two outcomes for each subject:

- \triangleright variables T^1 if a subject was assigned treatment, and
- \triangleright variables T^0 if a subject was assigned no treatment

in the absence of censoring.

Target parameter can be defined for example as an absolute risk difference:

$$\begin{split} \Psi(P) &= \mathbb{E}_{P}[T^{1} \leq \tau] - \mathbb{E}_{P}[T^{0} \leq \tau] \\ &\stackrel{*}{=} \mathbb{E}_{P}[\mathbb{E}_{P}[T \leq \tau \mid A = 1, X] - \mathbb{E}_{P}[T \leq \tau \mid A = 0, X]] \end{split}$$

The equality * follows under causal identifiability assumptions.1

including the assumption that $T \perp C \mid A, X$.

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This is a meaningful causal parameter.

¹including the assumption that $T \perp C \mid A, X$.

Hazard ratios $\lambda(t \mid A = 1)/\lambda(t \mid A = 0)$, where

$$\lambda(t \mid A = a) = \lim_{h \to 0} \frac{1}{h} P(T \in [t, t+h) \mid T \ge t, A = a),$$

on the other hand:

- suffer interpretational difficulties due to a built-in selection bias from conditioning on different surviving groups.²
 [representing a weighted average of potentially time-varying period-specific hazard ratios, which again may be time-varying due the selection bias.]
- cannot be interpreted as a causal contrast (despite historically prevalent use in medical research).

²Hernán, M. A. (2010). The hazards of hazard ratios. Epidemiology (Cambridge, Mass.), 21(1), 13.

What is "right-censoring"?

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- loss to follow-up

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- competing risk events (death)

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A competing risk is an event that can happen to subjects/patients, after which the outcome of interest cannot happen.

Whenever the outcome of interest is not all-cause mortality (such as discharge from ICU), there can be competing risks.

A competing risk event is not a right-censoring event. We are not (rarely?) interested in reporting the treatment effect *in the absence of death*.

The "classical" event history (competing risks) analysis setting:

- ▶ $T \in \mathbb{R}_+$ time to event, $\Delta = \{1,2\}$ indicator of event or death
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We define our target parameter for example as an absolute risk difference:

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More general data settings

Example: RCT (randomized controlled trial) setting

- comparison of treatment versus placebo on discharge from the intensive care unit (ICU);
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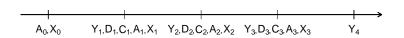
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- 1. dynamic treatment interventions
- 2. importance of being clear about what effect is targeted
- 3. longitudinal framework handling right-censoring with no new ideas (just as another time-varying treatment process)

General data structure:³

$$O = (X_0, A_0, \dots, Y_k, D_k, C_k, X_k, A_k, \dots, Y_K)$$

- Outcome process Y_k , death status D_k , censoring status C_k
- Covariates $\bar{X}_K = (X_0, X_1, \dots, X_K)$ change over time
- ▶ Treatment decisions $\bar{A}_K = (A_0, A_1, ..., A_K)$ are updated over time
- Covariates and treatment decisions interact in complex ways



³Note that this assumes a discrete underlying time-scale. This is common in causal inference.

More general data settings

This could for example be data from an RCT setting

- ► X₀ are baseline covariates (age, sex, disease/medical history, . . .)
- A₀ tells us the randomization arm (treatment/placebo):
- \triangleright Y_k is the status of a primary outcome at the kth follow-up visit
- \triangleright D_k is the survival status (competing risk) at the kth follow-up visit
- $ightharpoonup C_k$ is the censoring status at the kth follow-up visit
- \triangleright X_k are covariates measured at the kth follow-up visit
- A_k is the treatment decision made at the kth follow-up visit (adherence to randomization arm)
- Final outcome status Y_K

More general data settings

Observational data settings

- when data is not randomized (i.e., observational), the discrete time-grid may be a bit artificial.⁴
- but otherwise the difference between observational and experimental (randomized) settings mostly consists in the randomized treatment decision at baseline.

⁴any analysis involves data modeling choices to make it fit this structure.

Counterfactual outcomes

$$Y_k^{A_0 = a_0^*, A_1 = a_1^*, \dots, A_k = a_k^*}, \qquad \text{for,} \quad a_0^*, \dots, a_K^* \in \{0, 1\}$$

= defined by a sequence of treatment decision rules that we choose.

also called:

- hypothetical treatment interventions
- hypothetical treatment strategies
- hypothetical treatment regimes

"Static" regimes/interventions/strategies:

an intervention that sets a specific (deterministic) value for treatment decisions at each time-point.

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However, the latter definition of "dynamic" also fits into the former, since interventions are always *only* applied to subjects while alive and at risk. (This is hidden in the notation).

OBS: usually we further impose "no censoring"

Counterfactual outcomes

$$Y_k^{A_0=a_0^*,A_1=a_1^*,...,A_k=a_k^*,C_0=0,C_1=0,...,C_k=0}$$

for
$$a_0^*, \dots, a_K^* \in \{0, 1\}$$

Note that:

- if $Y_k = 1\{\tilde{T} \le t_k, \tilde{\Delta} = 1\}$,
- ▶ then $Y_k^{C_0=0, C_1=0,...,C_K=0} = 1\{T \le t_k, \Delta = 1\}.$

This is an example of a static intervention.

Continued treatment and never treated:

- $Y_k^{A_0=1,A_1=1,...,A_k=1}$ = outcome if treated throughout follow-up
- $Y_k^{A_0=0,A_0=0,...,A_k=0}$ = outcome if untreated throughout follow-up

The risk difference

$$\mathbb{E}\big[Y_K^{A_\mathbf{0}=1,A_\mathbf{1}=1,...,A_K=1}\big] - \mathbb{E}\big[Y_K^{A_\mathbf{0}=0,A_\mathbf{0}=0,...,A_K=0}\big]$$

is the effect of being treated versus untreated throughout follow-up.

Intention-to-treat (ITT):

- $Y_k^{A_0=1}$ = outcome if assigned to treatment arm
- $Y_k^{A_0=0}$ = outcome if assigned to placebo arm

The risk difference

$$\mathbb{E}\big[\,Y_K^{A_0=1}\,\big] - \mathbb{E}\big[\,Y_K^{A_0=0}\,\big]$$

is the effect of being assigned to the treatment versus the placebo arm.

Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease

Miguel A. Hernán^{1,2}, Alvaro Alonso³, Roger Logan¹, Francine Grodstein^{1,4}, Karin B. Michels^{1,4,5}, Meir J. Stampfer^{1,4,5}, Walter C. Willett^{1,4,5}, JoAnn E. Manson^{1,4,7}, and James M. Robin^{1,8}

Abstract

Background—The Women's Health Initiative randomized trial found greater coronary heart disease (CHD) risk in women assigned to estrogen/progestin therapy than in those assigned to placebo. Observational studies had previously suggested reduced CHD risk in hormone users.

Methods—Using data from the observational Nurses' Health Study, we emulated the design and intention-to-treat (ITT) analysis of the randomized trial. The observational study was conceptualized as a sequence of "trials" in which eligible women were classified as initiators or noninitiators of estrogen/morestin therapy.

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³Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN

⁴Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Obstetrics and Gynecology Epidemiology Center, Brigham and Women's Hospital, Harvard Medical School. Boston, MA

⁶Department of Nutrition, Harvard School of Public Health, Boston, MA

⁷Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

⁸Department of Biostatistics, Harvard School of Public Health, Boston, MA

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(and the general difficulties in analyzing observational studies).

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Background for the paper:

- An RCT found greater risk of coronary heart disease (CHD) in women assigned to hormon therapy than those assigned to placebo.
- Earlier observational studies had found reduced risk of CHD among hormon users.

The difference has been explained as due to unobserved confounding.

Conclusion: Cannot use observational data for causal inference?

The RCT results were based on an intention-to-treat⁵ (ITT) analysis

 trial participants were randomized to hormone treatment initiation or placebo at baseline

⁵Subjects are analyzed irrespective of their actual adherence to their assigned randomization arm.

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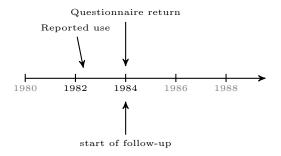
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Whereas the **observational analyses** were based on a comparison of two groups:

- "Current users"
- ▶ "Never users"

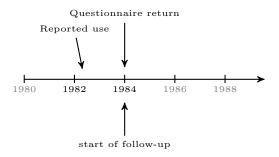
⁵Subjects are analyzed irrespective of their actual adherence to their assigned randomization arm.

- ▶ In the observational study, women answered questionnaires every two years
 - updated information on use, duration, etc, of treatment



- ▶ The start of follow-up was defined as the return of the questionnaire
 - initiaters who stopped/died before return were excluded (to define "current-users")

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Selection bias: Early (harmful) effect of treatment is not identified.

Hernán et al. reanalyze the observational data and show in their paper that:

- 1. When using the current user design (including the selection bias), the result of a **beneficial** effect from earlier observational studies was reproduced.
- 2. When imitating the analysis of the randomized trial, targeting the ITT effect, the result that the treatment has a **harmful** effect was reproduced.

The discrepancy found in the previous analyses had nothing to do with confounding.

Many such biases can be avoided by explicitly defining a "target experiment", and corresponding counterfactuals.

The current user strategy does not allow us to answer a causal question

- 1. The inclusion criterion is defined after initiation of the treatment strategy.
- 2. The current user strategy changes over the follow-up;
 - does not generally correspond to a counterfactual scenario with a sequence of treatment rules.

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The current user strategy is an attempt to estimate the effect of treatment *usage* (contrary to initiation)?

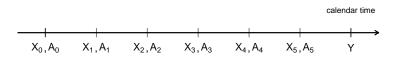
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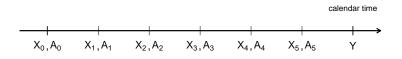
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Most appropriate summary measure would be the adherence-adjusted effect (comparing 'always treated' to 'never treated')?

Instead of the current user design, Hernán et al. divide the follow-up into monthly intervals

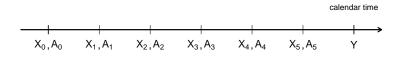


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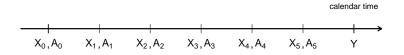
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 - 1. Intervention strategy $A_0 = 1$
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- Enforcing continued exposure (adherence-adjusted):
 - 1. Intervention strategy $A_0 = 1, A_1 = 1, A_2 = 1, \dots$
 - 2. Control strategy $A_0 = 0, A_1 = 0, A_2 = 0, ...$

- 1. When using the current user design, the result of a **beneficial** effect from earlier observational studies (due to selection bias) was reproduced.
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- 1. When using the current user design, the result of a **beneficial** effect from earlier observational studies (due to selection bias) was reproduced.
- 2. When imitating the analysis of the randomized trial, targeting the ITT effect, the result that the treatment has a **harmful** effect was reproduced.
- A larger harmful effect was found when targeting the effect of 'continued exposure', i.e., the adherence-adjusted effect.

Practical 2: Simulating longitudinal data

As part of the exercise we will —

- Simulate (simple) longitudinal data with time-varying treatment and covariates;
- 2. Approximate the true effect of different longitudinal interventions by simulating counterfactuals.
- 3. Illustrate various issues in interpreting hazard ratios.
- 4. Illustrate the benefits of targeting dynamic effects in survival settings.

The exercise is described in detail in: day3-practical2.pdf.