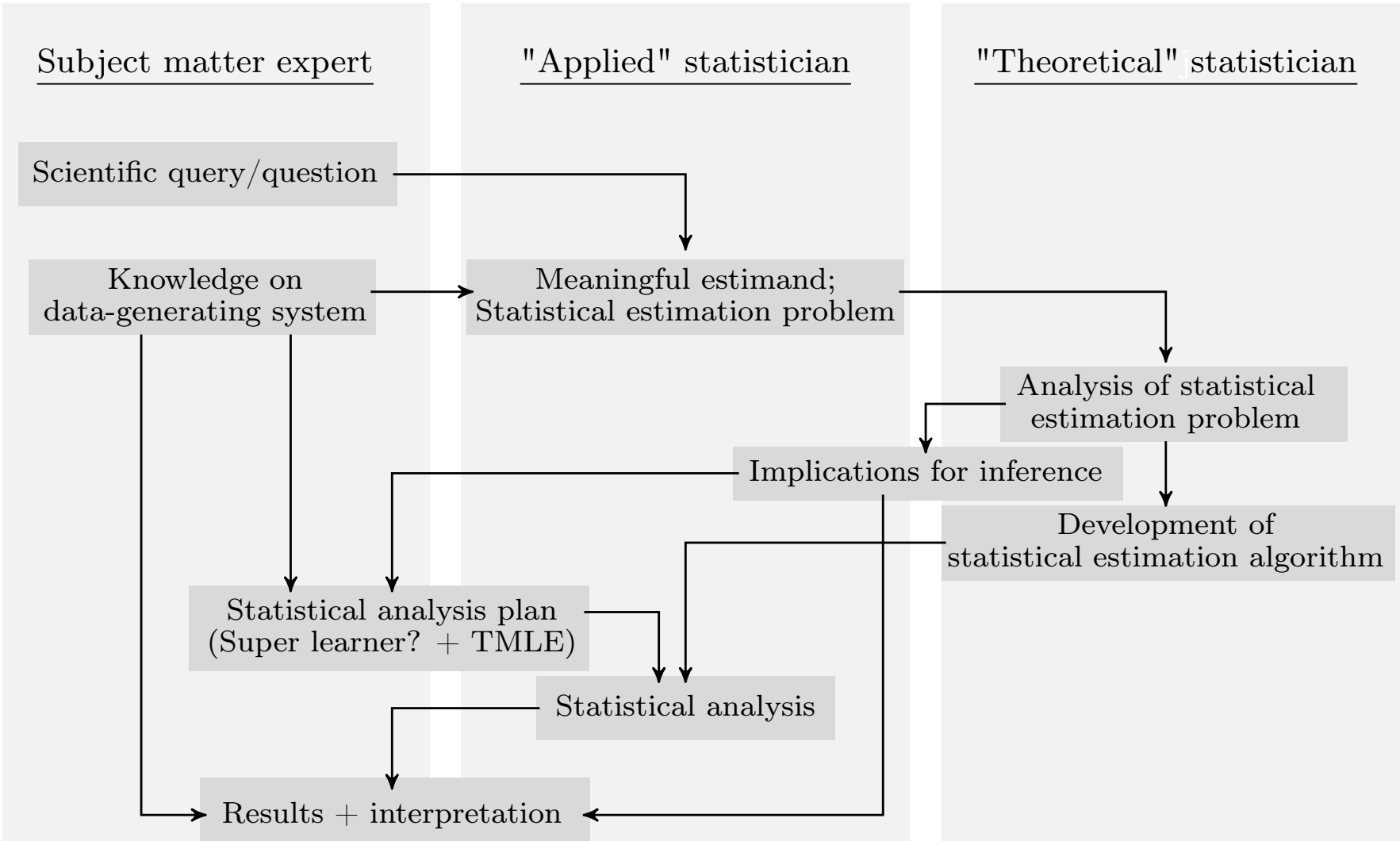
Day 3, Lecture 3

More general data settings

Targeted learning framework



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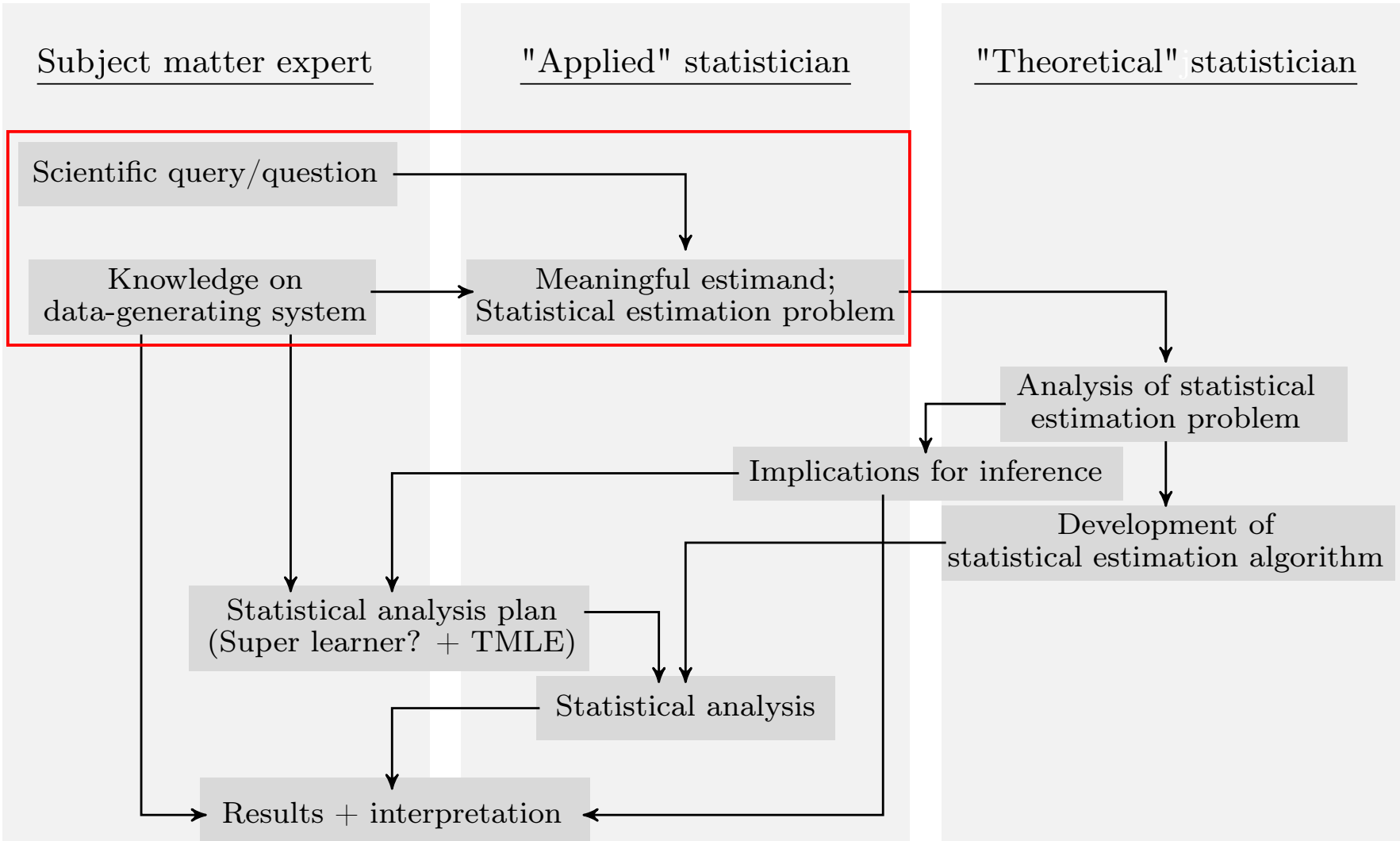
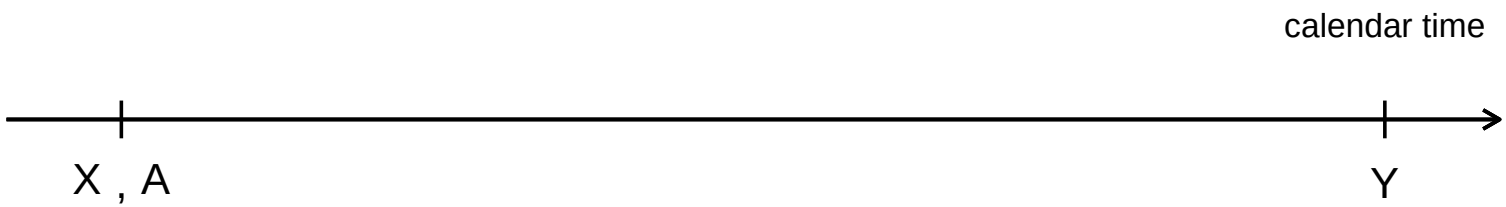


More general data settings

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



More general data settings

Longitudinal data structure:

- $O = (X_0, A_0, \ldots, Y_k, D_k, C_k, X_k, A_k, \ldots, Y_K)$
- Outcome process Y_k, death status D_k, censoring status C_k
- Covariates $\bar{X}_K = (X_0, X_1, \ldots, X_K)$ change over time
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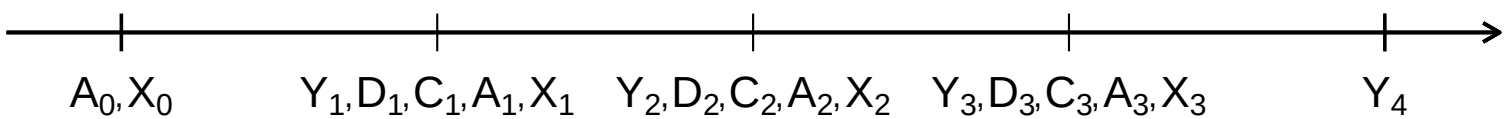

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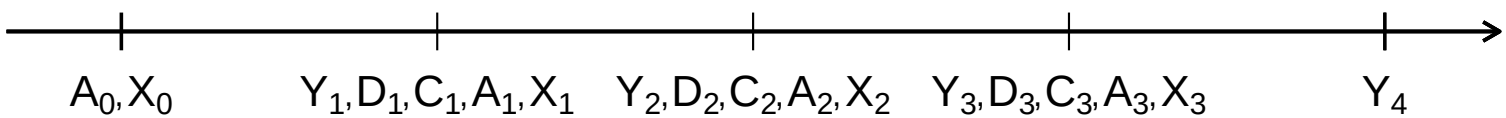

1. Dynamic treatment interventions.
2. Right-censoring and competing risks.
3. More subtleties in confounding bias.

⋮

More general data settings

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

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

More general data settings

Over the course of time of a study, we are typically not able to observe the outcome of interest due to:

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Presence of competing risk events No one cannot get experience the outcome event of interest if they already died.

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

More general data settings

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.

More general data settings

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:

- a variable Y^1 corresponding to scenario 1, and
- a variable Y^0 corresponding to scenario 2

= the "counterfactuals" (aka potential outcomes).

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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Time-to-event data settings

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

Time-to-event settings

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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So this is really a counterfactual as well.

. . . there is a close link between handling right-censoring and imposing certain treatment interventions.

. . . in essence, right-censoring can be viewed as just another time-varying treatment.

Time-to-event settings

Observed data with baseline treatment:

- $T \in \mathbb{R}_+$ 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 $\tilde{\Delta} = 1\{T \leq C\}$
- 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:

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

in the absence of censoring.

Time-to-event settings

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

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

The equality $\stackrel{*}{=}$ follows under causal identifiability assumptions.[1]

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

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$F(\tau \mid A=a, X)$ is the absolute risk function, which can be identified by cause-specific hazards.

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

Time-to-event settings

Hazard ratios $\lambda^1(t)/\lambda^0(t)$, where

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

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.]

- is therefore not recommendable as a causal contrast (despite historically prevalent use in medical research).

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

Time-to-event settings

What is "right-censoring"?

- administrative censoring
- loss to follow-up

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Whenever the outcome of interest is not all-cause mortality, 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*.

Time-to-event settings

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:

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

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Time-varying treatments

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)

Time-varying treatments

General data structure:[3]

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

- Outcome process Y_k, death status D_k, censoring status C_k
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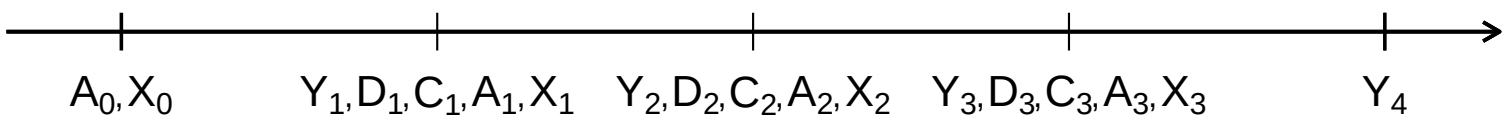

[3]Note that this assumes a discrete underlying time-scale. This is common in causal inference.

More general data settings

This could for example be data from an RCT setting

- X_0 are baseline covariates (age, sex, disease/medical history, ...)
- A_0 tells us the randomization arm (treatment/placebo)

  ⋮

- Y_k is the status of a primary outcome at the kth follow-up visit
- D_k is the survival status (competing risk) at the kth follow-up visit
- C_k is the censoring status at the kth follow-up visit
- 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.

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

Time-varying treatments

Counterfactual outcomes

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

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

also called:

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

Time-varying treatments

"Static" regimes/interventions/strategies:

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

Time-varying treatments

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"Dynamic" treatment regimes/interventions/strategies:

- in causal inference literature, "dynamic" is used to refer specifically to interventions depending on (past) covariates,
- but in other (survival) contexts, "dynamic" is used to indicate that the interventions are applied over time.

Time-varying treatments

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- but in other (survival) contexts, "dynamic" is used to indicate that the interventions are applied over time.

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).

Time-varying treatments

OBS: usually we further impose "no censoring"

Counterfactual outcomes

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

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

Note that:

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

This is an example of a static intervention.

Time-varying treatments

Continued treatment and never treated:

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

The risk difference

$$\mathbb{E}[\,Y_K^{A_0=1,A_1=1,\ldots,A_K=1}] - \mathbb{E}[\,Y_K^{A_0=0,A_0=0,\ldots,A_K=0}]$$

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

Time-varying treatments

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

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

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

Hernán et al., 2008

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

Miguel A. Hernán[1,2], **Alvaro Alonso**[3], **Roger Logan**[1], **Francine Grodstein**[1,4], **Karin B. Michels**[1,4,5], **Meir J. Stampfer**[1,4,6], **Walter C. Willett**[1,4,6], **JoAnn E. Manson**[1,4,7], and **James M. Robins**[1,8]

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[2]Harvard-MIT Division of Health Sciences and Technology, University of Minnesota, Minneapolis, MN

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

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

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

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

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

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

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/progestin therapy.

Hernán et al., 2008

An example of the importance of being clear about what effect we are targeting...

(and the general difficulties in analyzing observational studies).

Hernán et al., 2008

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(and the general difficulties in analyzing observational studies).

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?*

Hernán et al., 2008

The **RCT results** were based on an intention-to-treat[5] (ITT) analysis

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

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

Hernán et al., 2008

The **RCT results** were based on an intention-to-treat[5] (ITT) analysis

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

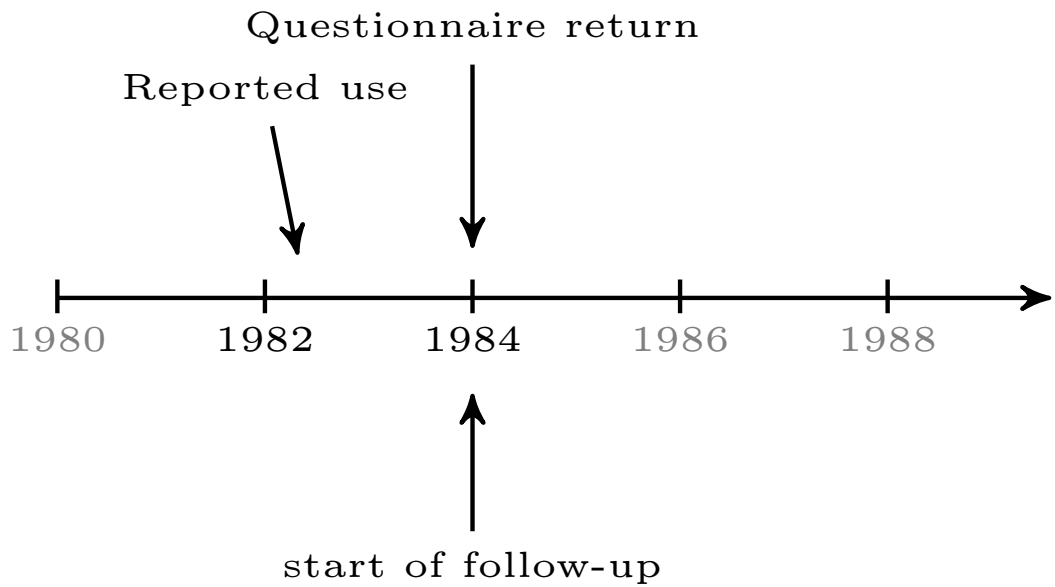
Whereas the **observational analyses** were based on a comparison of two groups:

- "Current users"
- "Never users"

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

Hernán et al., 2008

- 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
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Hernán et al., 2008

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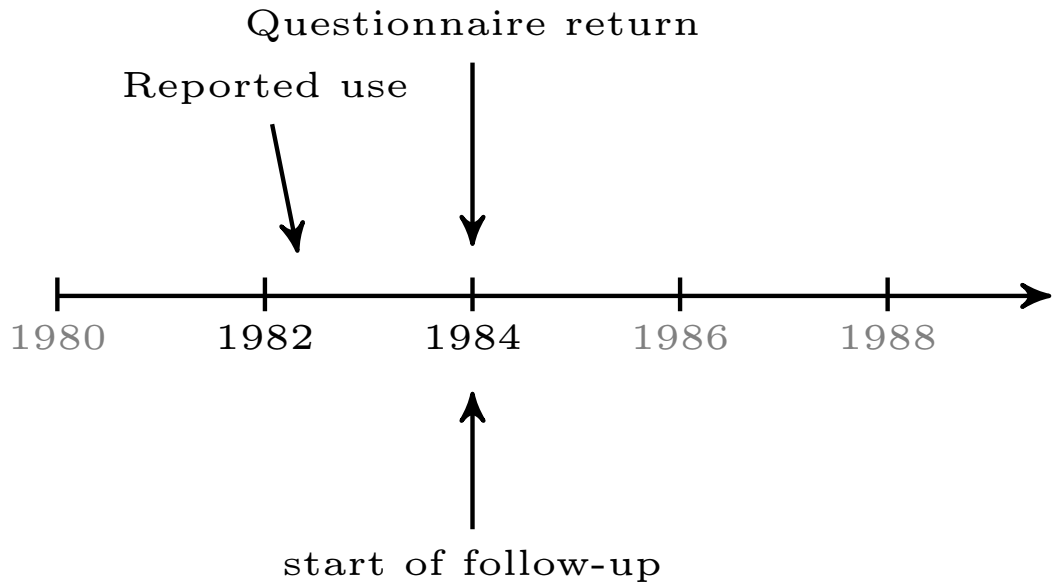

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Selection bias: Early (harmful) effect of treatment *is not identified*.

Hernán et al., 2008

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.

Hernán et al., 2008

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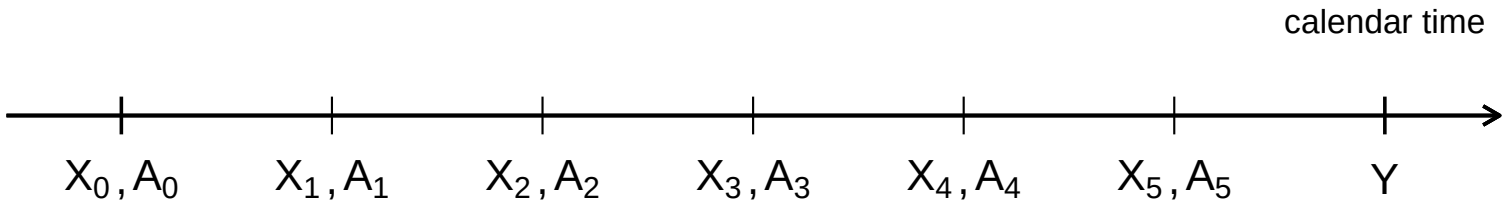
The current user strategy is an attempt to estimate the effect of treatment *usage* (contrary to initiation)?

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

Hernán et al., 2008

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



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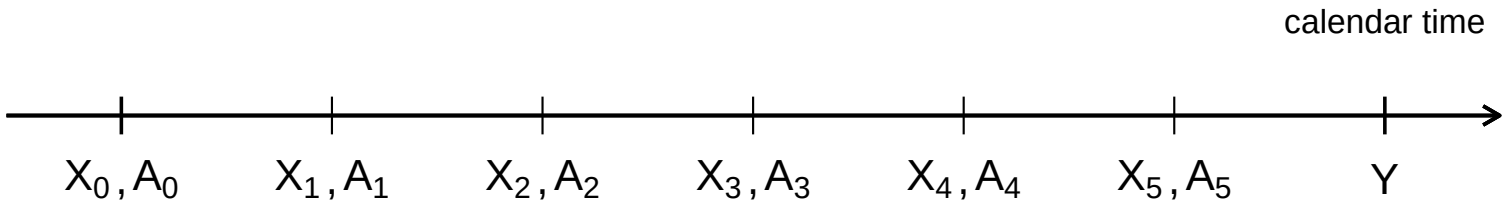

- A_k = reported use of hormone therapy between month k and month $k+1$.

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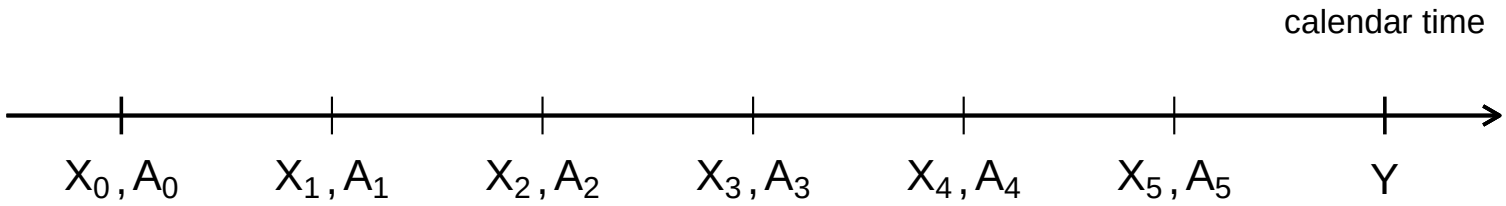

- A_k = reported use of hormone therapy between month k and month $k+1$.
- ITT treatment strategies:
  1. Intervention strategy $A_0 = 1$
  2. Control strategy $A_0 = 0$

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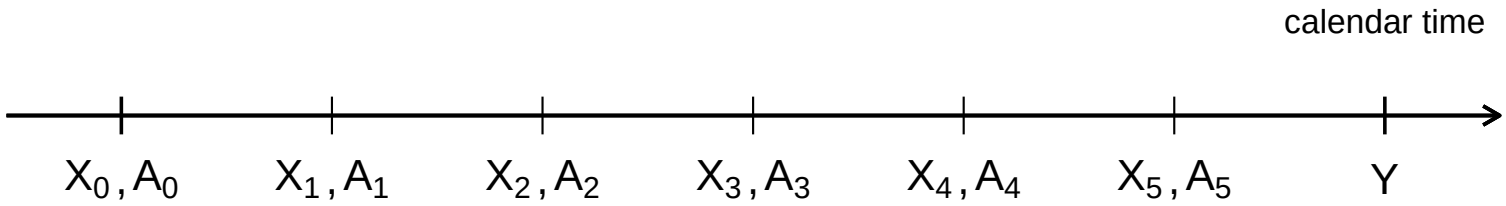

- A_k = reported use of hormone therapy between month k and month $k+1$.
- ITT treatment strategies:
  1. Intervention strategy $A_0 = 1$
  2. Control strategy $A_0 = 0$
- Enforcing continued exposure (adherence-adjusted):
  1. Intervention strategy $A_0 = 1, A_1 = 1, A_2 = 1, \ldots$
  2. Control strategy $A_0 = 0, A_1 = 0, A_2 = 0, \ldots$

Hernán et al., 2008

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.

Hernán et al., 2008

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.
3. 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 —

1. 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**.