Causal Inference for Observational Longitudinal Survival Data

Mark Bech Knudsen

Thesis written in blocks 1 & 2 autumn 2022, supervised by Torben Martinussen & Helene Rytgaard @ Biostatistics KU.

Thesis written in blocks 1 & 2 autumn 2022, supervised by Torben Martinussen & Helene Rytgaard @ Biostatistics KU.

Thesis explores 3 topics relating to causal inference for non-randomized survival data:

Thesis written in blocks 1 & 2 autumn 2022, supervised by Torben Martinussen & Helene Rytgaard @ Biostatistics KU.

Thesis explores 3 topics relating to causal inference for non-randomized survival data:

• Do hazard ratio estimates from the Cox model have a causal interpretation for a time-dependent treatment?

Thesis written in blocks 1 & 2 autumn 2022, supervised by Torben Martinussen & Helene Rytgaard @ Biostatistics KU.

Thesis explores 3 topics relating to causal inference for non-randomized survival data:

- Do hazard ratio estimates from the Cox model have a causal interpretation for a time-dependent treatment?
- A problem with Markov models for survival data with time-dependent covariates.

Thesis written in blocks 1 & 2 autumn 2022, supervised by Torben Martinussen & Helene Rytgaard @ Biostatistics KU.

Thesis explores 3 topics relating to causal inference for non-randomized survival data:

- Do hazard ratio estimates from the Cox model have a causal interpretation for a time-dependent treatment?
- A problem with Markov models for survival data with time-dependent covariates.
- Causal inference in continuous-time using inverse probability of treatment weights.

Assume a binary treatment $A \in \{0,1\}$ that is given at time t=0. Wish to infer the effect of treatment on survival.

Assume a binary treatment $A \in \{0, 1\}$ that is given at time t = 0. Wish to infer the effect of treatment on survival.

For each person, suppose there exists two potential outcomes T^0 and T^1 :

Assume a binary treatment $A \in \{0, 1\}$ that is given at time t = 0. Wish to infer the effect of treatment on survival.

For each person, suppose there exists two potential outcomes T^0 and T^1 :

• T^0 is the survival time if the person *does not* receive treatment.

Assume a binary treatment $A \in \{0, 1\}$ that is given at time t = 0. Wish to infer the effect of treatment on survival.

For each person, suppose there exists two potential outcomes T^0 and T^1 :

- T^0 is the survival time if the person *does not* receive treatment.
- T^1 is the survival time if the person receives treatment.

Assume a binary treatment $A \in \{0, 1\}$ that is given at time t = 0. Wish to infer the effect of treatment on survival.

For each person, suppose there exists two potential outcomes T^0 and T^1 :

- T^0 is the survival time if the person *does not* receive treatment.
- T^1 is the survival time if the person receives treatment.

The effect of treatment could then be defined as

$$P(T^1 > t) - P(T^0 > t)$$

i.e. how much more likely is it for the person to survive if they receive treatment vs. if they do not?

Assume a binary treatment $A \in \{0, 1\}$ that is given at time t = 0. Wish to infer the effect of treatment on survival.

For each person, suppose there exists two potential outcomes T^0 and T^1 :

- T^0 is the survival time if the person *does not* receive treatment.
- T^1 is the survival time if the person receives treatment.

The effect of treatment could then be defined as

$$P(T^1 > t) - P(T^0 > t)$$

i.e. how much more likely is it for the person to survive if they receive treatment vs. if they do not?

Or on the population scale: What would the survival rate be if we treated everyone vs. if we did not treat anyone?

Assume a binary treatment $A \in \{0, 1\}$ that is given at time t = 0. Wish to infer the effect of treatment on survival.

For each person, suppose there exists two potential outcomes T^0 and T^1 :

- T^0 is the survival time if the person *does not* receive treatment.
- T^1 is the survival time if the person receives treatment.

The effect of treatment could then be defined as

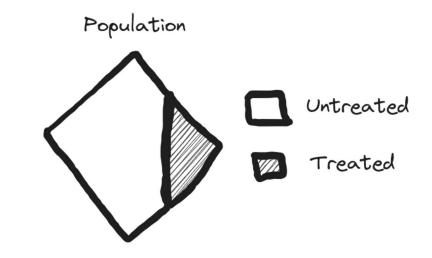
$$P(T^1 > t) - P(T^0 > t)$$

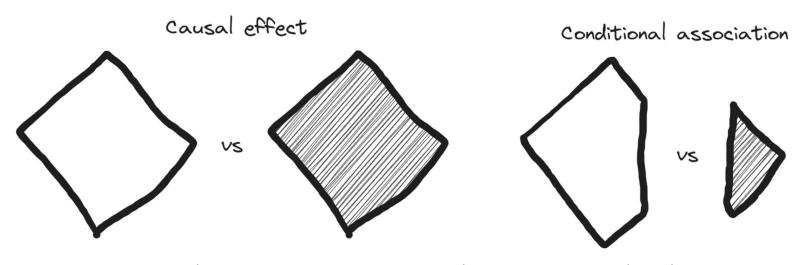
i.e. how much more likely is it for the person to survive if they receive treatment vs. if they do not?

Or on the population scale: What would the survival rate be if we treated everyone vs. if we did not treat anyone?

Different from the conditional association $P(T > t \mid A = 1) - P(T > t \mid A = 0)$.

Causal vs. conditional effects





*Inspired by Miguel A. Hernán: A definition of causal effect for epidemiological research (2004)

Assume a randomized treatment A. Then the subpopulation with A=a is representative of what would have happened to the rest of the population, had they been treated.

Assume a randomized treatment A. Then the subpopulation with A = a is representative of what would have happened to the rest of the population, had they been treated.

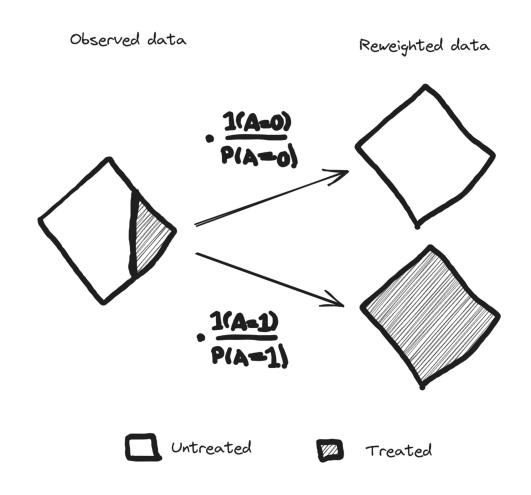
Scale up subpopulation to full population size with weights

$$W_i^a = \frac{1(A_i = a)}{P(A = a)}$$

Assume a randomized treatment A. Then the subpopulation with A = a is representative of what would have happened to the rest of the population, had they been treated.

Scale up subpopulation to full population size with weights

$$W_i^a = \frac{1(A_i = a)}{P(A = a)}$$



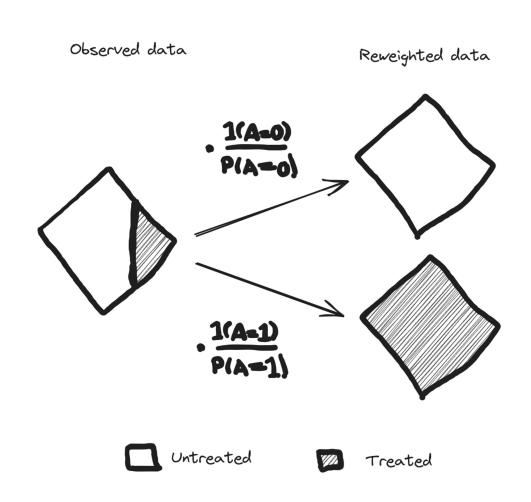
Assume a randomized treatment A. Then the subpopulation with A = a is representative of what would have happened to the rest of the population, had they been treated.

Scale up subpopulation to full population size with weights

$$W_i^a = \frac{1(A_i = a)}{P(A = a)}$$

An estimate of the probability of survival, had everyone received treatment *a*:

$$P(T^{a} > t) = \frac{1}{n} \sum_{i=1}^{n} W_{i}^{a} 1(T_{i} > t)$$



Assume a randomized treatment A. Then the subpopulation with A = a is representative of what would have happened to the rest of the population, had they been treated.

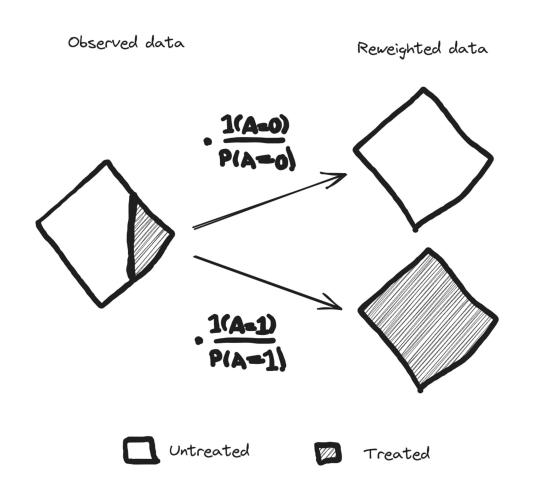
Scale up subpopulation to full population size with weights

$$W_i^a = \frac{1(A_i = a)}{P(A = a)}$$

An estimate of the probability of survival, had everyone received treatment *a*:

$$P(T^{a} > t) = \frac{1}{n} \sum_{i=1}^{n} W_{i}^{a} 1(T_{i} > t)$$

The W_i^a are referred to as *inverse* probability of treatment weights (IPTW).



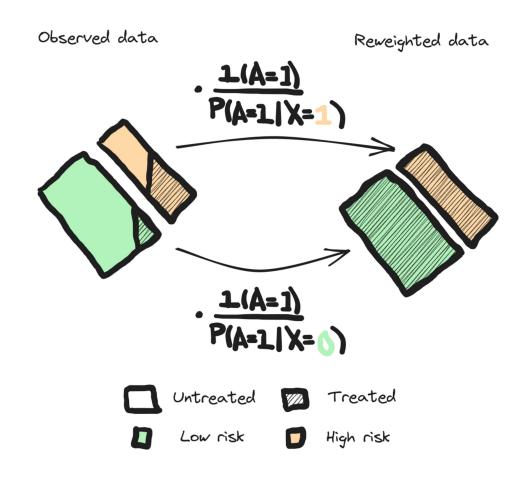
Suppose now that a $confounder X \in \{0,1\}$ (low/high risk) affects both treatment and outcome (non-randomized data).

Suppose now that a *confounder* $X \in \{0, 1\}$ (low/high risk) affects both treatment and outcome (non-randomized data).

If *X* is the *only* confounder, then we still have representativity *within levels of X*. So we can pretend randomized treatment within levels of *X*.

Suppose now that a *confounder* $X \in \{0, 1\}$ (low/high risk) affects both treatment and outcome (non-randomized data).

If *X* is the *only* confounder, then we still have representativity *within levels of X*. So we can pretend randomized treatment within levels of *X*.

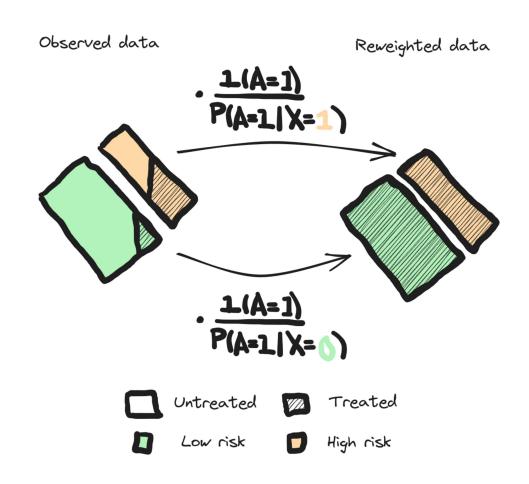


Suppose now that a *confounder* $X \in \{0, 1\}$ (low/high risk) affects both treatment and outcome (non-randomized data).

If *X* is the *only* confounder, then we still have representativity *within levels of X*. So we can pretend randomized treatment within levels of *X*.

So we assign different weights depending on *X*:

$$W_i^a = \frac{1(A_i = a)}{P(A = a \mid X_i)}$$



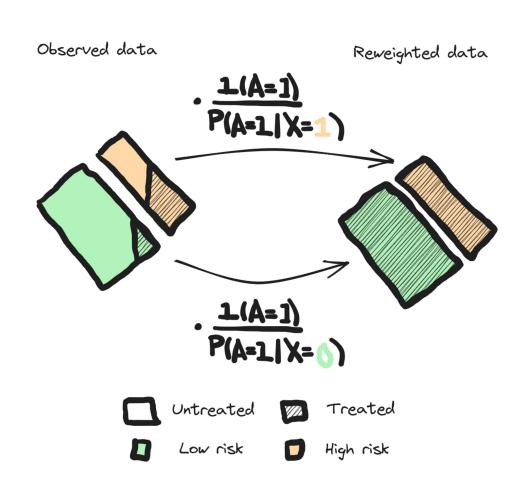
Suppose now that a *confounder* $X \in \{0, 1\}$ (low/high risk) affects both treatment and outcome (non-randomized data).

If *X* is the *only* confounder, then we still have representativity *within levels of X*. So we can pretend randomized treatment within levels of *X*.

So we assign different weights depending on *X*:

$$W_i^a = \frac{1(A_i = a)}{P(A = a \mid X_i)}$$

This works regardless of the dimension of X, and also for continuous covariates.



Consider a case where treatment is a binary counting process A(t) that starts at 0 and jumps to 1 at time au when a treatment is undertaken (e.g. surgery).

Consider a case where treatment is a binary counting process A(t) that starts at 0 and jumps to 1 at time τ when a treatment is undertaken (e.g. surgery).

Covariates X(t) are also time-dependent.

Consider a case where treatment is a binary counting process A(t) that starts at 0 and jumps to 1 at time τ when a treatment is undertaken (e.g. surgery).

Covariates X(t) are also time-dependent.

Can generalize to a weight *process*

$$W_i(t) = \frac{1}{\lambda^A (\tau \mid \mathcal{F}_{\tau^-})^{A(t)} e^{-\Lambda^A (t \wedge \tau)}}$$

where λ^A is the hazard/rate of treatment initiation and

$$\Lambda^{A}(t) = \int_{0}^{t} \lambda^{A}(s \mid \mathcal{F}_{s-}) ds$$

Consider a case where treatment is a binary counting process A(t) that starts at 0 and jumps to 1 at time τ when a treatment is undertaken (e.g. surgery).

Covariates X(t) are also time-dependent.

Can generalize to a weight *process*

$$W_i(t) = \frac{1}{\lambda^A (\tau \mid \mathcal{F}_{\tau^-})^{A(t)} e^{-\Lambda^A (t \wedge \tau)}}$$

where λ^A is the hazard/rate of treatment initiation and

$$\Lambda^{A}(t) = \int_{0}^{t} \lambda^{A}(s \mid \mathcal{F}_{s-}) ds$$

The processes $W_i(t)$ are quite nice (exponential martingales), and can be estimated from data.

Consider a case where treatment is a binary counting process A(t) that starts at 0 and jumps to 1 at time τ when a treatment is undertaken (e.g. surgery).

Covariates X(t) are also time-dependent.

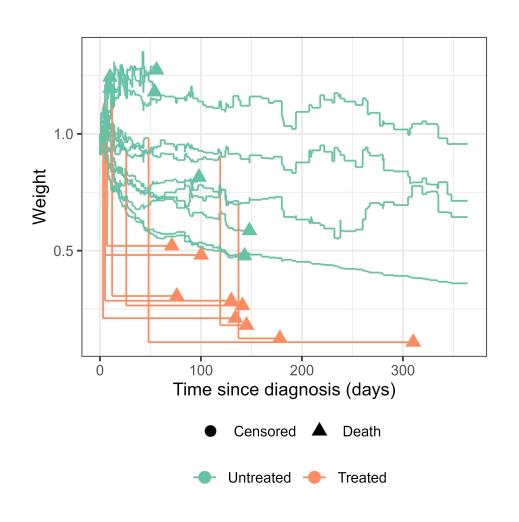
Can generalize to a weight *process*

$$W_i(t) = \frac{1}{\lambda^A(\tau \mid \mathcal{F}_{\tau^-})^{A(t)} e^{-\Lambda^A(t \wedge \tau)}}$$

where λ^A is the hazard/rate of treatment initiation and

$$\Lambda^{A}(t) = \int_{0}^{t} \lambda^{A}(s \mid \mathcal{F}_{s-}) ds$$

The processes $W_i(t)$ are quite nice (exponential martingales), and can be estimated from data.



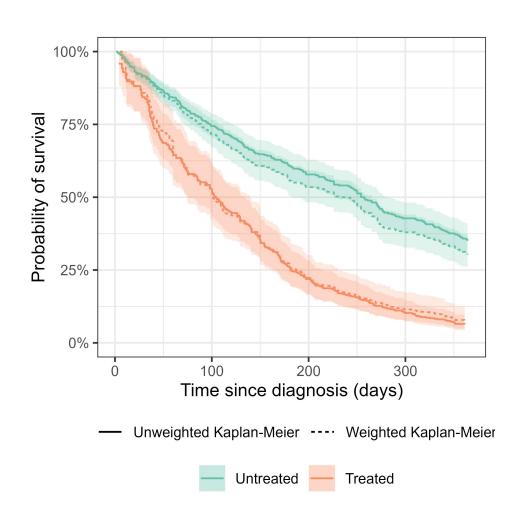
Observational data (n=601) from oncologists at Rigshospitalet.

Observational data (n = 601) from oncologists at Rigshospitalet.

- *T* time from diagnosis of incurable throat cancer to death.
- *A*(*t*) insertion of metalic tube (stent) into throat.
- A bunch of covariates X(t), mostly measured at baseline.

Observational data (n = 601) from oncologists at Rigshospitalet.

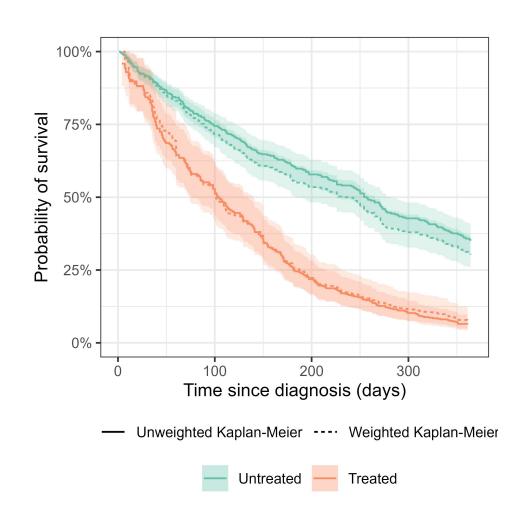
- *T* time from diagnosis of incurable throat cancer to death.
- *A*(*t*) insertion of metalic tube (stent) into throat.
- A bunch of covariates X(t), mostly measured at baseline.



Observational data (n = 601) from oncologists at Rigshospitalet.

- *T* time from diagnosis of incurable throat cancer to death.
- *A*(*t*) insertion of metalic tube (stent) into throat.
- A bunch of covariates X(t), mostly measured at baseline.

Weighting does not change the conclusion much. But we did not have enough information about *time-dependent* confounders.



Thank you!

And good luck when you write your thesis.