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Time-varying Cox

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IP weighting

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oooooooooooo

Reference

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Time-varying exposure in registry data analysis: pitfalls and solutions

Brice Ozenne (brice.ozenne@nru.dk)

¹ Neurobiology Research Unit, University Hospital of Copenhagen, Rigshospitalet.

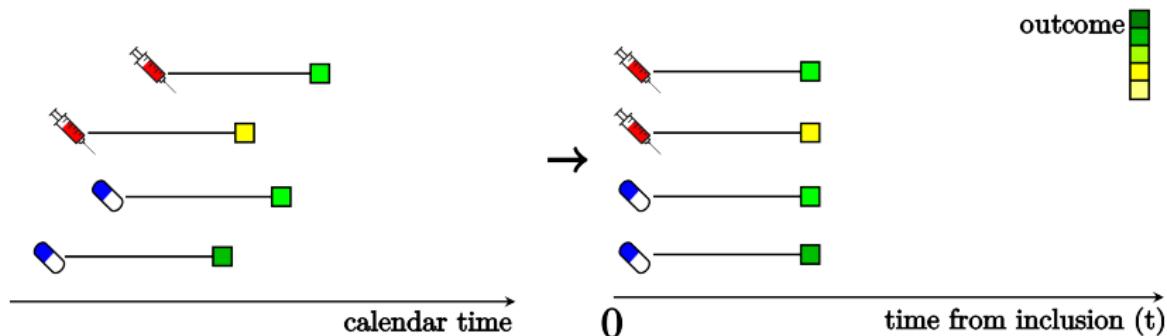
² Section of Biostatistics, Department of Public Health, University of Copenhagen.

November 3rd, 2022 - ECF meeting

"Traditional" NRU studies: experimental design

Controlled exposure, e.g.:

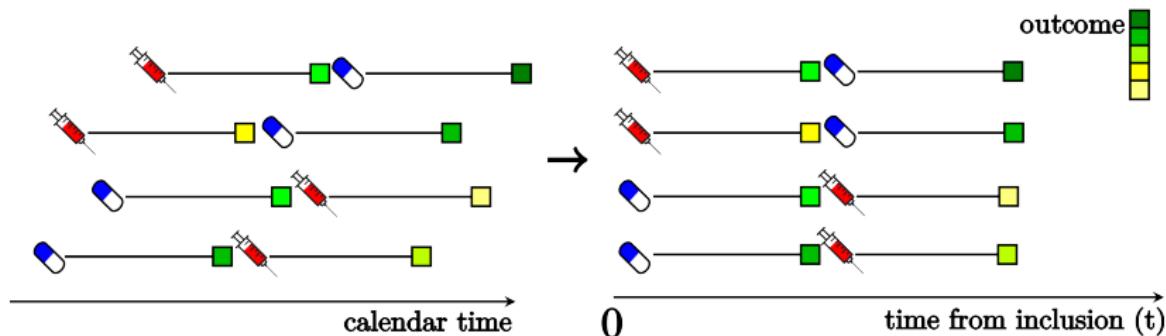
- one shot treatment just after baseline
- continuous treatment from after baseline until end of follow-up



"Traditional" NRU studies: experimental design

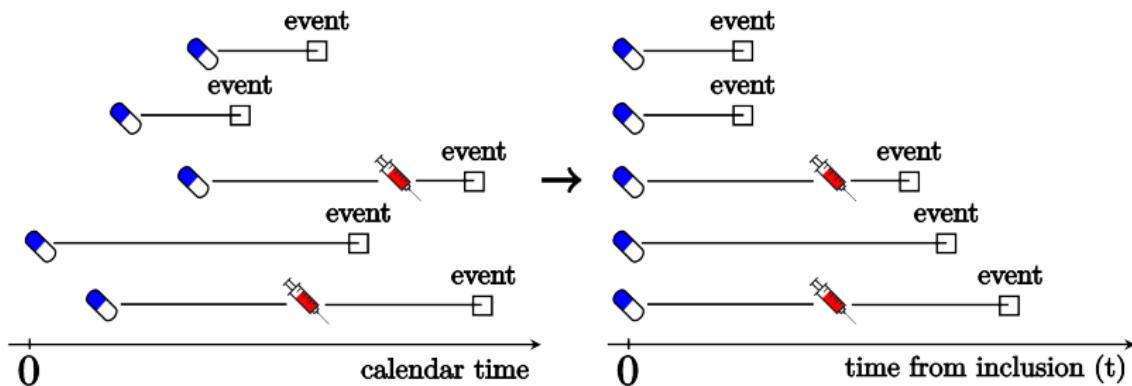
Controlled exposure, e.g.:

- one shot treatment just after baseline
- continuous treatment from after baseline until end of follow-up
- switch between treatment every week (cross over)



BrainDrugs: toward registry data

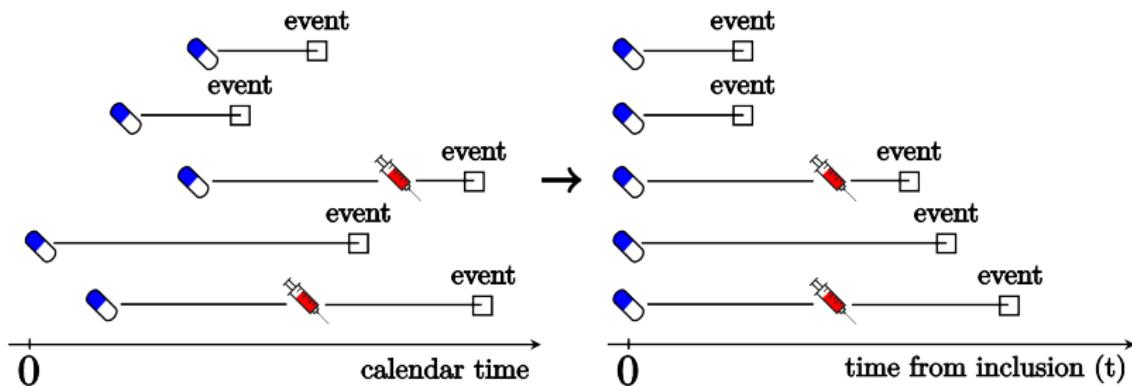
Naturalistic design:



BrainDrugs: toward registry data

Naturalistic design:

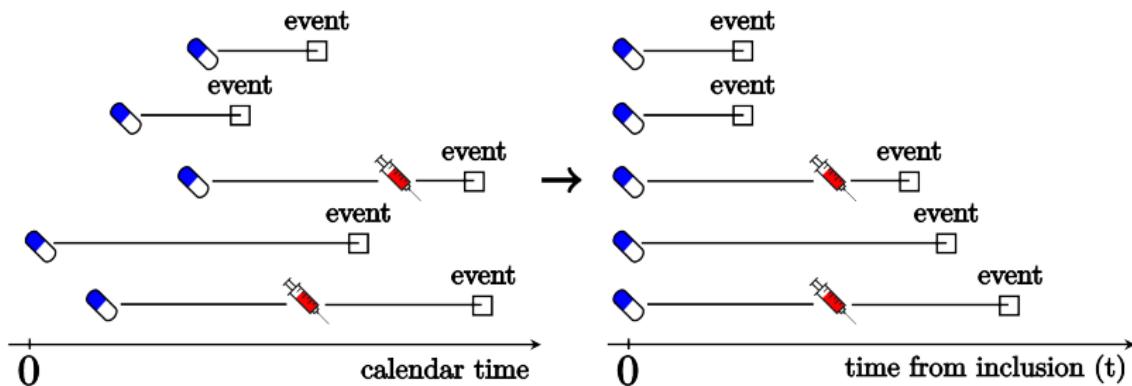
- patients may switch treatment, e.g. patient 2 and 3.



BrainDrugs: toward registry data

Naturalistic design:

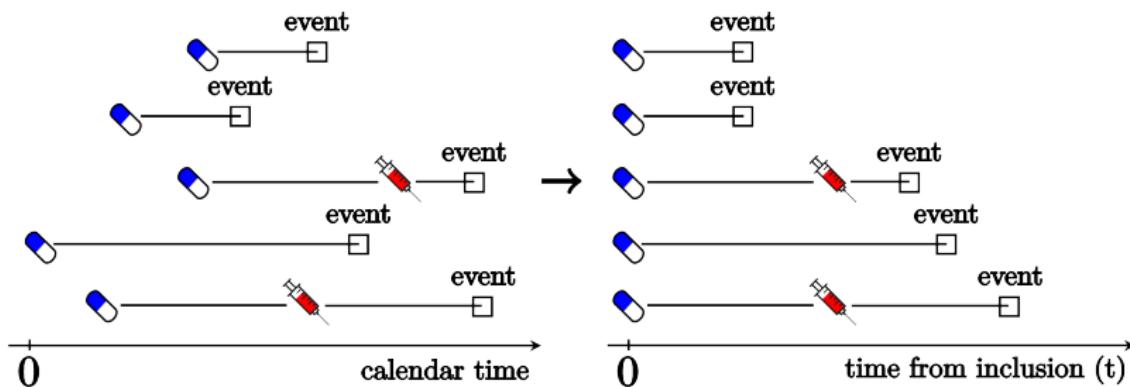
- patients may switch treatment, e.g. patient 2 and 3.
- planned treatment is unknown, e.g. was patient 1 committed to injection or was it planned that he will later switch to pill?



BrainDrugs: toward registry data

Naturalistic design:

- patients may switch treatment, e.g. patient 2 and 3.
- planned treatment is unknown, e.g. was patient 1 committed to injection or was it planned that he will later switch to pill?
- reasons for switching treatment are unknown, e.g. did patient 3 switch to injection because pill was working poorly? Or because no pill was available?



Short litterature review

Traditional analyzes method

e.g. group comparison using t-test,
logistic regression or a Cox model
are not reliable!

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→ Lange and Keiding (2014)

International Journal of Epidemiology, 2014, 971

doi: 10.1093/ije/dyu100

Letters to the Editor



Brøndum-Jacobsen *et al.* recently published in this journal¹ analyses of Danish register data concerning myocardial infarction, hip fracture and death from any cause, using incidence of skin cancer as indicator of high exposure to sunlight. The basic idea in the paper is that those who get a skin cancer diagnosis at any age are supposed to have been more exposed to the sun during their life than those who do not, and apparently the authors find it relevant to use ordinary prospective survival analysis to compare incidence of myocardial infarction, hip fracture and death from any cause between the two groups: those who (at some point) get a skin cancer diagnosis and those who do not.

Unfortunately, such an analysis is seriously flawed, because the definition of one of the two groups to be compared conditions on the future

Short litterature review

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e.g. group comparison using t-test,
logistic regression or a Cox model

are not reliable!

→ Lange and Keiding (2014)

Widely spread issue:

→ Suissa (2007)

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY
2007; **16**: 241–249
DOI: 10.1002/pds.1357

ORIGINAL REPORT

SUMMARY

Purpose Recent observational studies suggest that various drugs are remarkably effective at reducing morbidity and mortality.

These cohort studies used a **flawed approach to design and data analysis** which can lead to immortal time bias.

We describe the bias from 20 of these studies and illustrate it by showing that **unrelated drugs can be made to appear effective** at treating cardiovascular disease (CVD).

Short litterature review

Traditional analyzes method

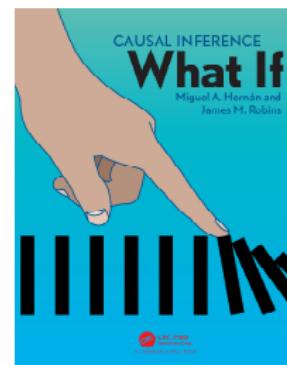
e.g. group comparison using t-test,
 logistic regression or a Cox model
 are not reliable!

→ [Lange and Keiding \(2014\)](#)

Widely spread issue:

→ [Suisa \(2007\)](#)

New, complicated,
 statistical tools have been developed to fix this issue
 such as G-computation, IP weighting,
 TMLE



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Plan for today

Focus on handling time varying exposure:¹

¹ There are many other challenges with registry data: confounding, measurement error, competing risks, censoring ...

Plan for today

Focus on handling time varying exposure:¹

 This is a difficult topic!

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Plan for today

Focus on handling time varying exposure:¹

😱 This is a difficult topic!

I'll will:

- exemplify the challenges:
 - immortal time bias
- introduce 2 methods to meet those challenges
 - Cox model with time varying covariate
 - Inverse probability weighting (IPW)

¹ There are many other challenges with registry data: confounding, measurement error, competing risks, censoring ...

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Time-varying Cox

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IP weighting

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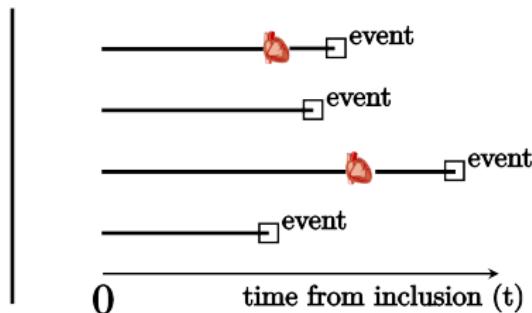
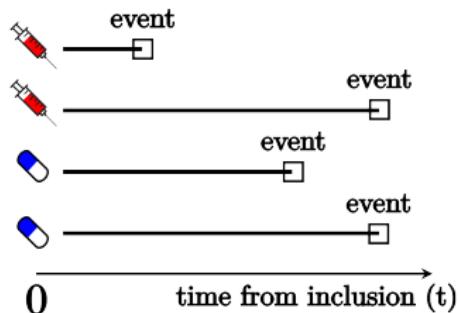
Reference

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Examples

Warm-up

Consider the following two toy studies (event = death):



Ignoring statistical uncertainty, decide:

- whether the injection is better than the pill
- whether the heart transplant improves survival

What "statistical unit" do you consider?

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Examples

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Time-varying Cox

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IP weighting

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Hint

Statistical unit: at risk time

Estimate: difference or ratio of incidence rates of the event

$$\text{incidence rate } \lambda = \frac{\text{number of events}}{\text{number of person-time}}$$

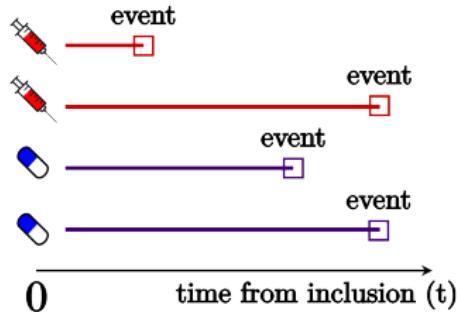
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Statistical unit: at risk time

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- study 1: equal number of events for each treatment.
Pill is better as it is associated to a longer at risk time.



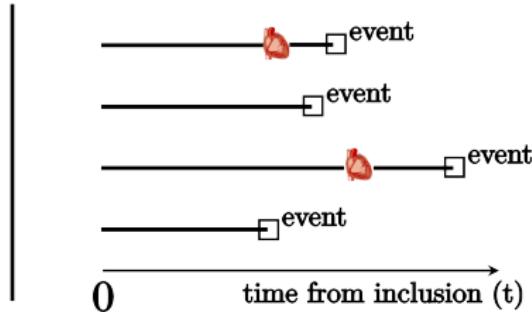
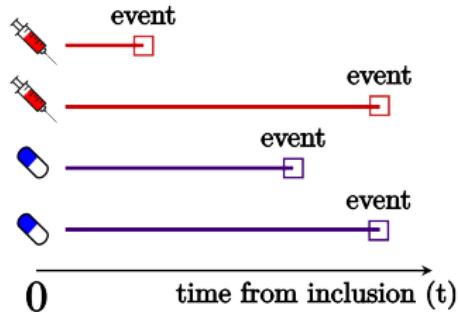
Hint

Statistical unit: at risk time

Estimate: difference or ratio of incidence rates of the event

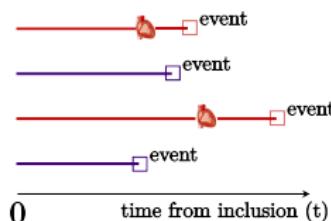
$$\text{incidence rate } \lambda = \frac{\text{number of events}}{\text{number of person-time}}$$

- study 1: equal number of events for each treatment.
Pill is better as it is associated to a longer at risk time.
- what about study 2?

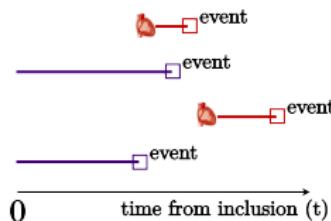


Possibilities

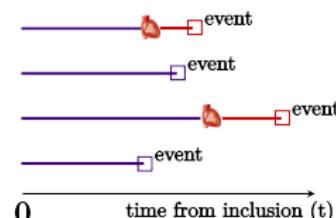
Solution 1:



Solution 2:



Solution 3:

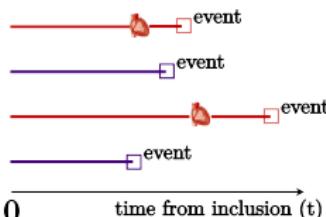


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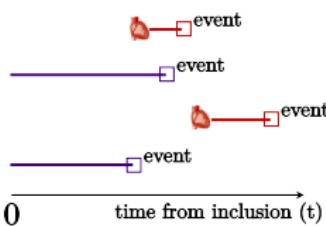


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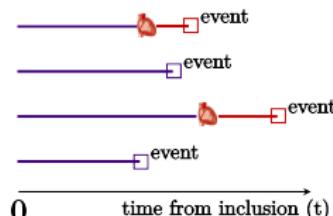
- unrealistic: use future information to define exposure
- immortal time bias: baseline-transplant



Solution 2:



Solution 3:

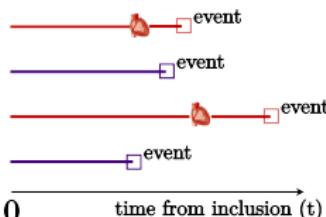


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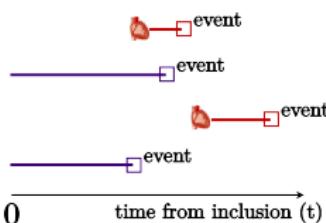
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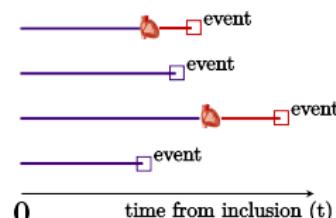


Solution 2:

- unrealistic: use future information to remove data
- biased against no transplant



Solution 3:

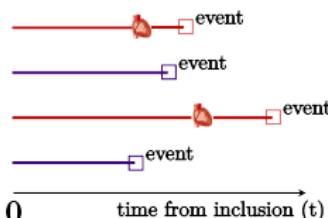


Possibilities



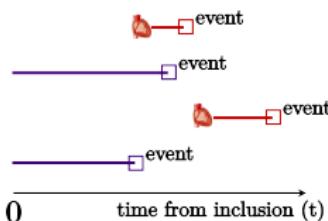
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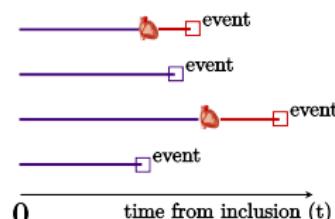
Solution 2:

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- biased against no transplant



Solution 3:

- realistic: time-varying exposure
- ⚠️ how to carry-out the analysis?



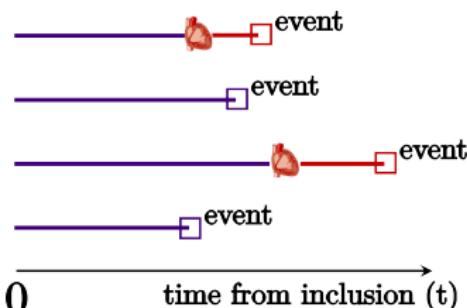
From person to person-time

- ✗ Same person is **not** treated or untreated

```
id event time transplant
1 TRUE 5.0      TRUE
2 TRUE 4.5      FALSE
3 TRUE 7.0      TRUE
4 TRUE 3.0      FALSE
```

- ✓ Same person experiences treated and untreated person-time

```
id event start stop transplant
1 FALSE 0.0 4.0    FALSE
1 TRUE 4.0 5.0    TRUE
2 TRUE 0.0 4.5    FALSE
3 FALSE 0.0 5.5    FALSE
3 TRUE 5.5 7.0    TRUE
4 TRUE 0.0 3.0    FALSE
```



Solution 0 - by hand

Given person-time and events associated to each intervention:

<code>id</code>	<code>event</code>	<code>start</code>	<code>stop</code>	<code>transplant</code>
1	FALSE	0.0	4.0	FALSE
1	TRUE	4.0	5.0	TRUE
2	TRUE	0.0	4.5	FALSE
3	FALSE	0.0	5.5	FALSE
3	TRUE	5.5	7.0	TRUE
4	TRUE	0.0	3.0	FALSE

we can compute the incidence:

```
c(waiting = (0+1+0+1)/(4+4.5+5.5+3) ,  
  transplant = (1+1)/(1+1.5))
```

`waiting` `transplant`
0.1176471 0.8000000

Assumptions:

Solution 0 - by hand

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waiting transplant
0.1176471 0.8000000

Assumptions:

- no time effect
- random heart transplant allocation

Back to the Melanoma study

Letters to the Editor

Skin cancer as a marker of sun exposure: a case of serious immortality bias

From Theis Lange* and Niels Keiding

Department of Biostatistics, Institute of Public Health, University of Copenhagen, Denmark

Brøndum-Jacobsen *et al.* recently published in this journal¹ analyses of Danish register data concerning myocardial infarction, hip fracture and death from any cause, using incidence of skin cancer as indicator of high exposure to sunlight. The basic idea in the paper is that those who get a skin cancer diagnosis at any age are supposed to have been more exposed to the sun during their life than those who do not, and apparently the authors find it relevant to use ordinary prospective survival analysis **to compare incidence** of myocardial infarction, hip fracture and death from any cause **between the two groups: those who (at some point) get a skin cancer diagnosis and those who do not.**

Unfortunately, such an analysis is seriously flawed, because **the definition of one of the two groups to be compared conditions on the future: in order to get a skin cancer**

diagnosis, and thus become a member of the skin cancer group, it is at least necessary to survive until age of diagnosis, but the authors' analysis does not take this conditioning into account. Put another way: for those in the skin cancer group it is impossible to die until the age of diagnosis of the cancer, the so-called immortal person-time.²

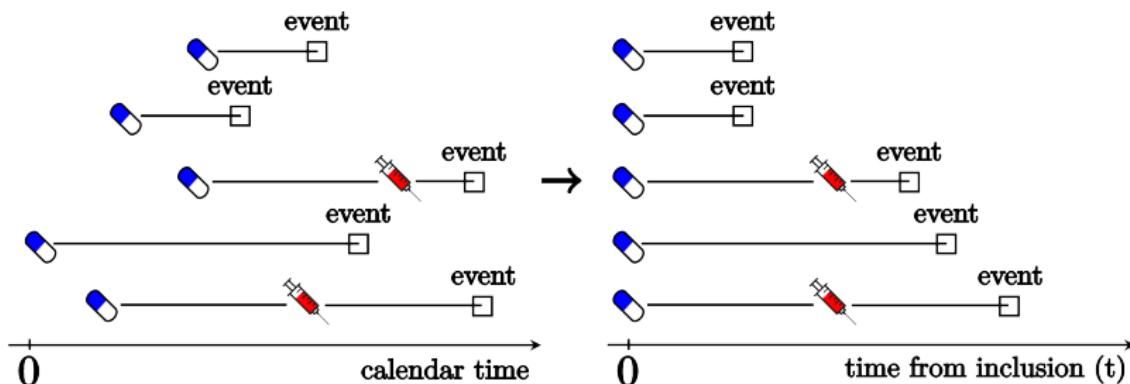
It is seen in the lower left panel of Figure 2¹ that those who get non-melanoma skin cancer at some age have a hazard ratio of dying from any cause in the age interval 40–49 years of about 0.2 vs those who never get a non-melanoma skin cancer diagnosis. A main reason for this is probably that very few of those with non-melanoma skin cancer are at all at risk for dying—**most of the members of this group get their skin cancer diagnosis at ages >50 years and are therefore by design immortal in the age interval 40–49.**

Multi-therapy

Consider a randomized clinical trial comparing:

- group 1: staying on a fixed therapy
- group 2: switching therapy

Do we have evidence for a positive effect of switching?

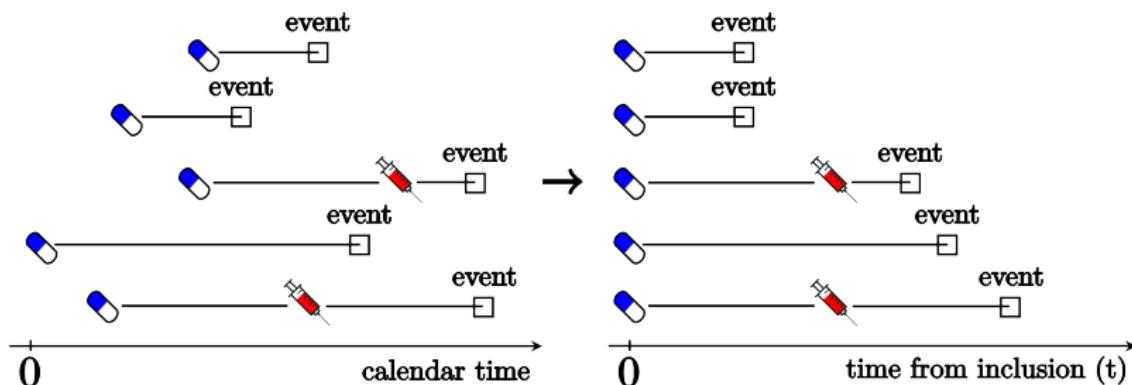


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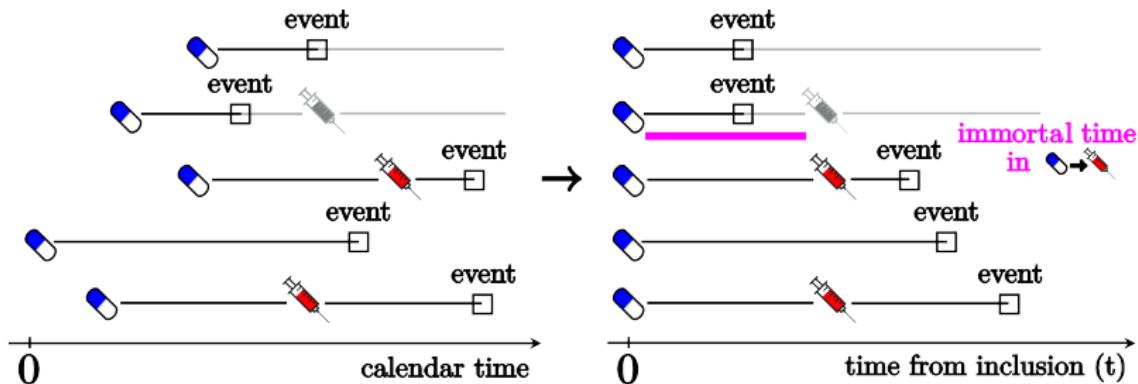
Hint: to which group belongs subject 1?

Multi-therapy - dilemma

Assessing the effect of switching is easy when knowing the intended treatment.

Otherwise, e.g. with observational data, it is not trivial!

⚠ attributing patients who did not switch to group 1 leads to immortal time bias



Multi-therapy - example

From Shariff et al. (2008)

In the March 2007 issue of *JASN*, Hemmelgarn *et al.*¹ reported a 50% reduction in the risk for all-cause mortality for patients who had chronic kidney disease (CKD) and attended multidisciplinary care (MDC) clinics compared with those who received usual care. Their survival curves showed a clear divergence in rates of death between the two groups in the first 6 months of follow-up. We suggest that it is less plausible from a biologic perspective that use of MDC clinics immediately reduces the short-term risk for death. Rather, much of the early observed effect may be due to survivor treatment selection bias, also known as immortal time bias.

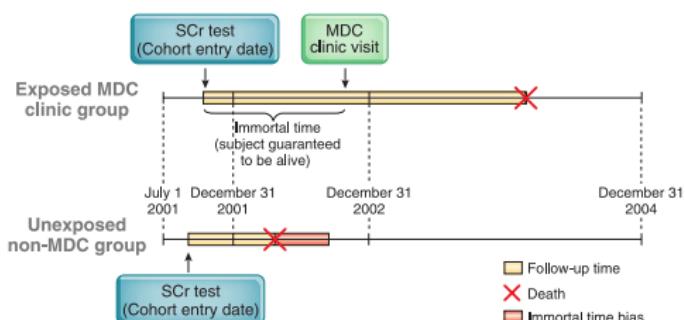


Figure 3. Immortal time bias. Situation in which MDC clinic visit occurred after serum creatinine test. Exposed patient was guaranteed to be alive between the test date and the clinic visit, resulting in a period of "immortal time."

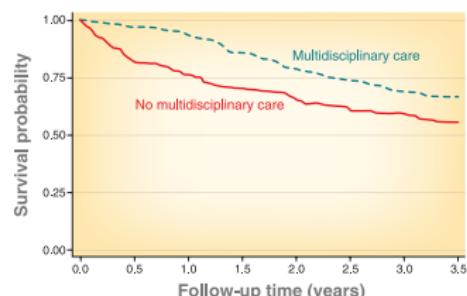


Figure 2. Kaplan-Meier survival curve

Summary - analyzing registry data

Incorrect handling of time-varying exposure likely lead to bias:

- irrespective to the sample size!
- can have dramatic consequences

There is a rich and accessible litterature on the subject!

General advice:

- do not condition on the future ([Andersen and Keiding, 2012](#))
- emulate a feasible trial ([Hernán and Robins, 2016](#))
- look at the data (Lexis diagram, survival curves)
- discuss plausibility of the results with experts

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Lexis diagram

Example from Hanley et al. (2006)

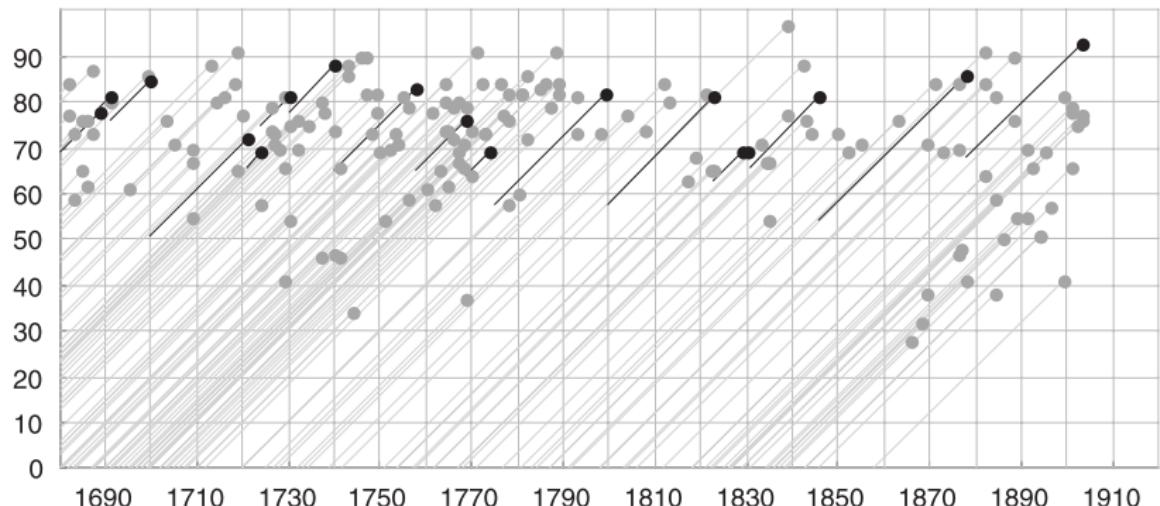


Figure 1 Lexis diagram, with age on vertical, and calendar time on the horizontal axis.
Pope-years (i.e. those post election) shown as black lines and artist-years as grey lines.
Age of/year at death indicated by circle

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IP weighting

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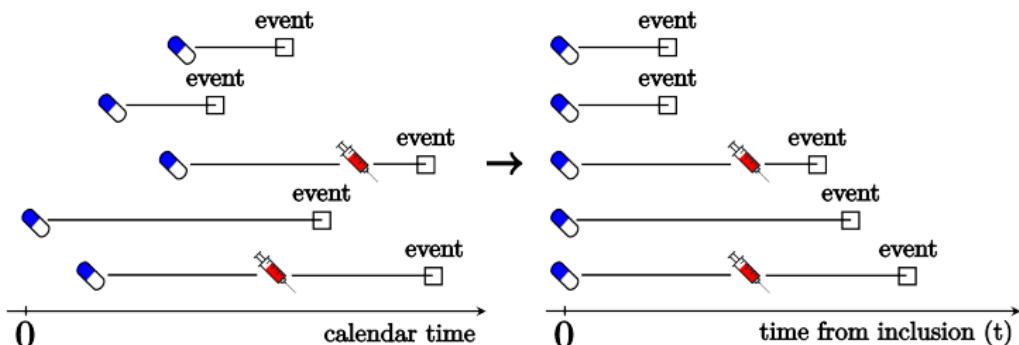
Reference

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Cox with time-varying covariates

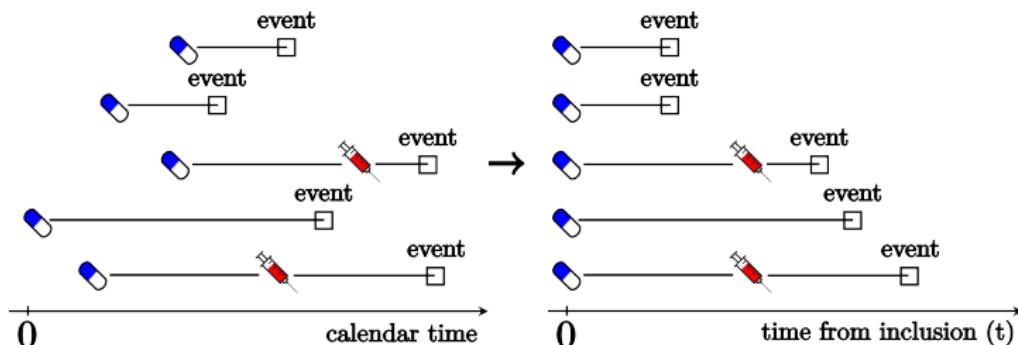
Improving on solution 0

We can handle time-varying treatments by splitting the follow-up:



Improving on solution 0

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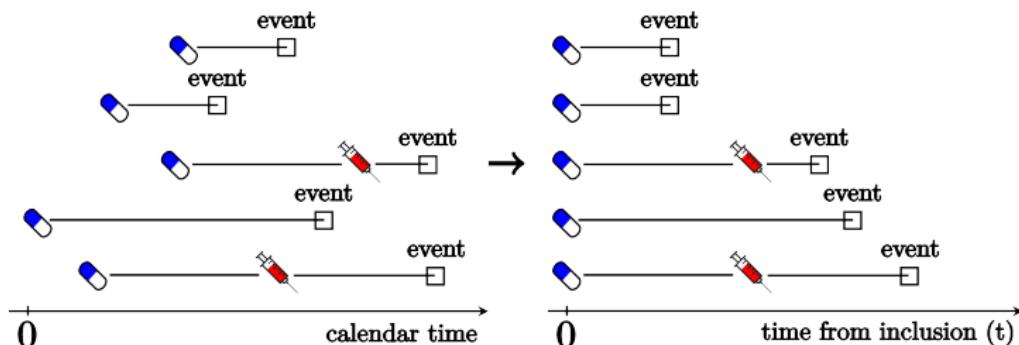


Previously, we compared the treatments assuming:

- no time effect
- switching treatment independently of the event

Improving on solution 0

We can handle time-varying treatments by splitting the follow-up:



Previously, we compared the treatments assuming:

- no time effect
- switching treatment independently of the event

How can we relax the first assumption?

Accounting for time-varying rates

Matching: compare individuals at risk at the same time

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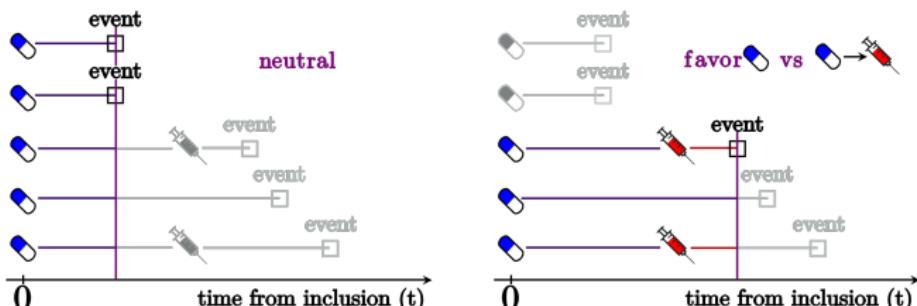
Time-varying Cox
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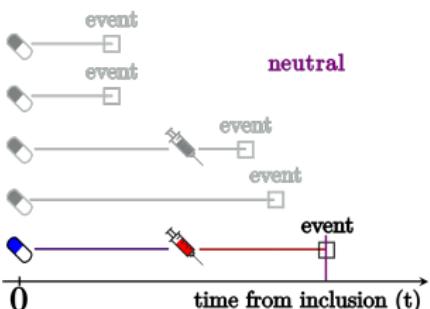
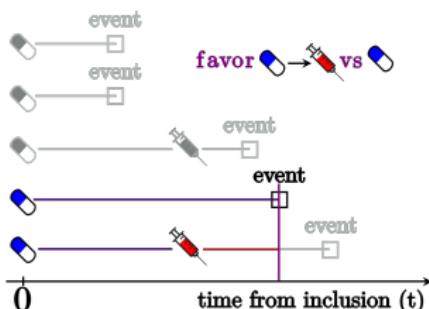
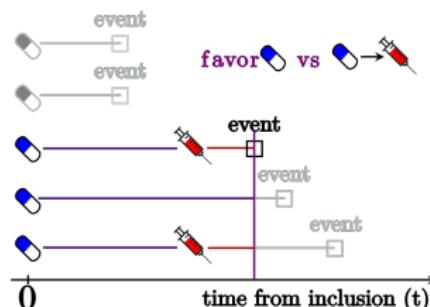
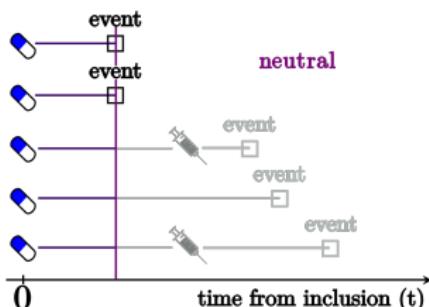
Accounting for time-varying rates

Matching: compare individuals at risk at the same time

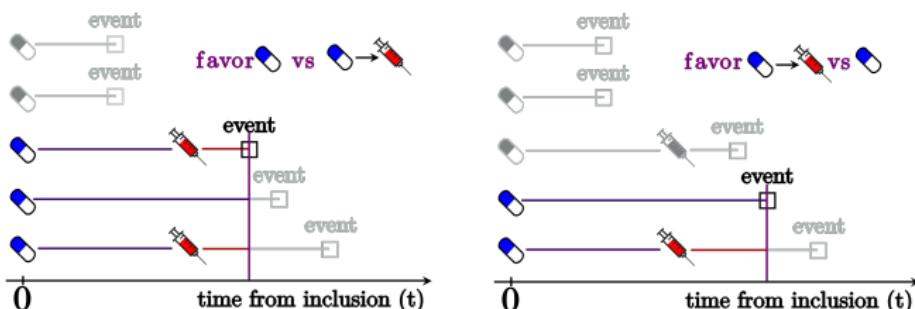


Accounting for time-varying rates

Matching: compare individuals at risk at the same time



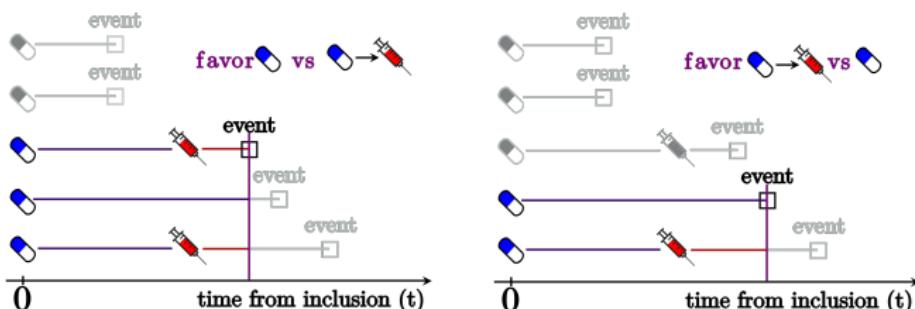
Quantification using a (simple) Cox model



At each event time:

- $n_{\text{blue}} + n_{\text{red}}$ individuals still event-free

Quantification using a (simple) Cox model



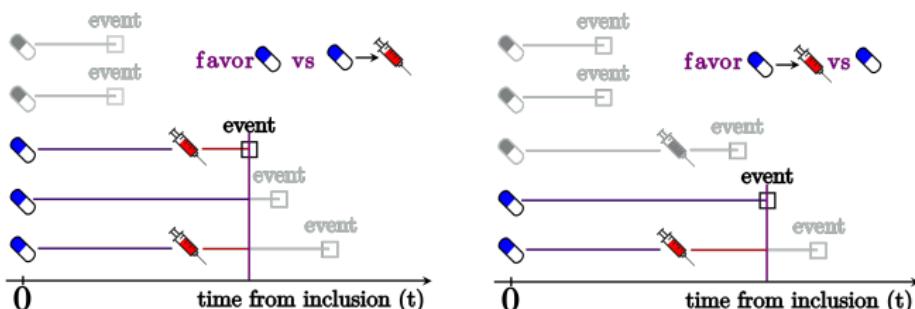
At each event time:

- $n_0 + n_\downarrow$ individuals still event-free

- grade

$$\begin{cases} n_0 + n_\downarrow \theta & \text{if event in } \text{blue capsule} \\ n_0 / \theta + n_\downarrow & \text{if event in } \text{red syringe} \end{cases}$$

Quantification using a (simple) Cox model

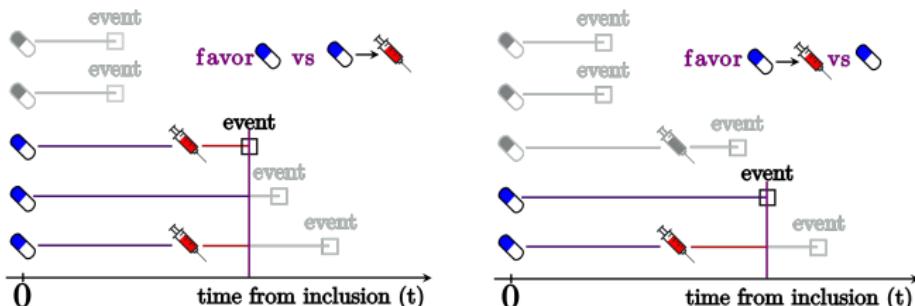


At each event time:

- $n_0 + n_\theta$ individuals still event-free
- grade
$$\begin{cases} n_0 + n_\theta \theta & \text{if event in } \text{blue capsule} \\ n_0/\theta + n_\theta & \text{if event in } \text{red syringe} \end{cases}$$

Find $\theta \in [0, \infty]$ minimizing the product of grades across timepoints

Quantification using a (simple) Cox model



At each event time:

- $n_0 + n_\theta$ individuals still event-free
- grade

$$\begin{cases} n_0 + n_\theta \theta & \text{if event in } \text{blue capsule} \\ n_0/\theta + n_\theta & \text{if event in } \text{red capsule with needle} \end{cases}$$

Grade:

$$(1/\theta + 2)(1 + \theta)$$

min at $\theta = 1/\sqrt{2}$

Find $\theta \in [0, \infty]$ minimizing the product of grades across timepoints

Cox: on the computer

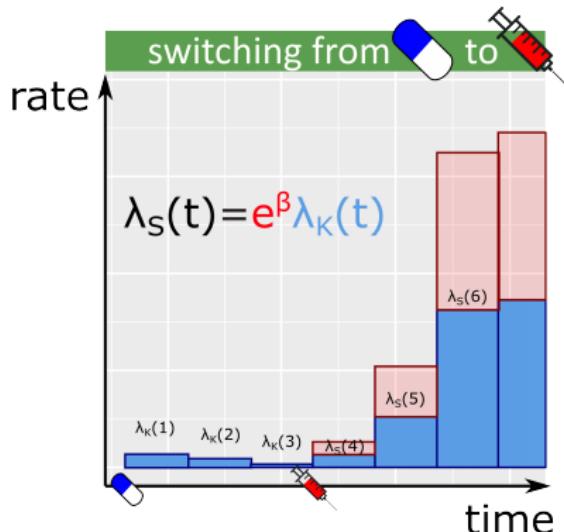
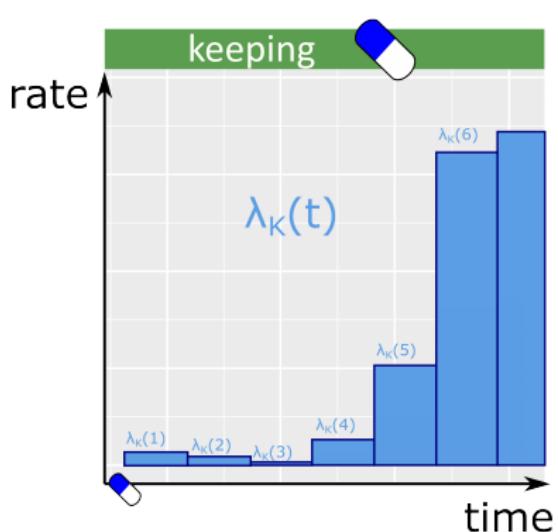
```
print(df.switch, row.names = FALSE)
```

	id	event	start	stop	switch
1	TRUE	0.0	3.0		FALSE
2	TRUE	0.0	3.0		FALSE
3	FALSE	0.0	4.0		FALSE
3	TRUE	4.0	5.0		TRUE
4	FALSE	0.0	4.5		FALSE
4	TRUE	4.5	6.0		TRUE
5	TRUE	0.0	5.5		FALSE

```
library(survival)
e.cox <- coxph(Surv(start, stop, event) ~ switch,
                  data = df.switch)
exp(c(coef(e.cox), confint(e.cox)))
```

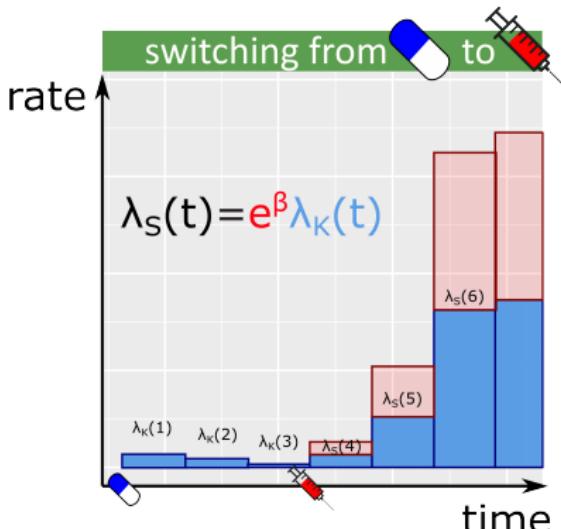
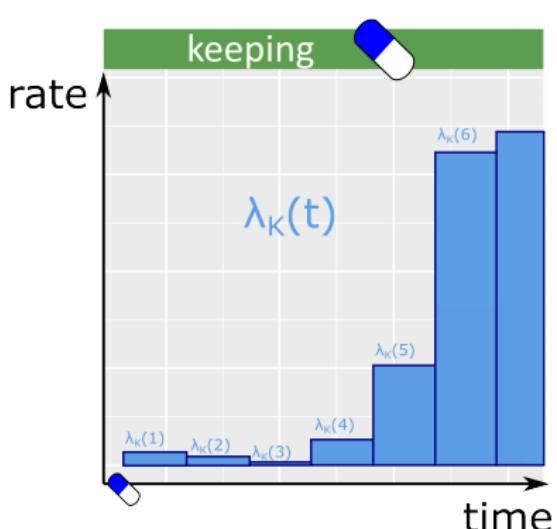
```
switchTRUE
0.70710678 0.04242142 11.78649820
```

Underlying model



Multiplicative effect of the treatment (e^β) on the rates ($\lambda(t)$):

Underlying model



Multiplicative effect of the treatment (e^β) on the rates ($\lambda(t)$):

- same at all follow-up times
- same regardless to when the treatment was initiated

Both can be relaxed with more "advanced" Cox models

Software output

If the model is correct:

- 🎉 we get a p-value testing the existence of a treatment effect
- 😱 but the estimate that can be hard to interpret

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Software output

If the model is correct:

- 🎉 we get a p-value testing the existence of a treatment effect
- 😱 but the estimate that can be hard to interpret

e^β is the *instantaneous* rate ratio between exposures

- quite different from a (long-term) risk ratio

Software output

If the model is correct:

- 🎉 we get a p-value testing the existence of a treatment effect
- 😱 but the estimate that can be hard to interpret

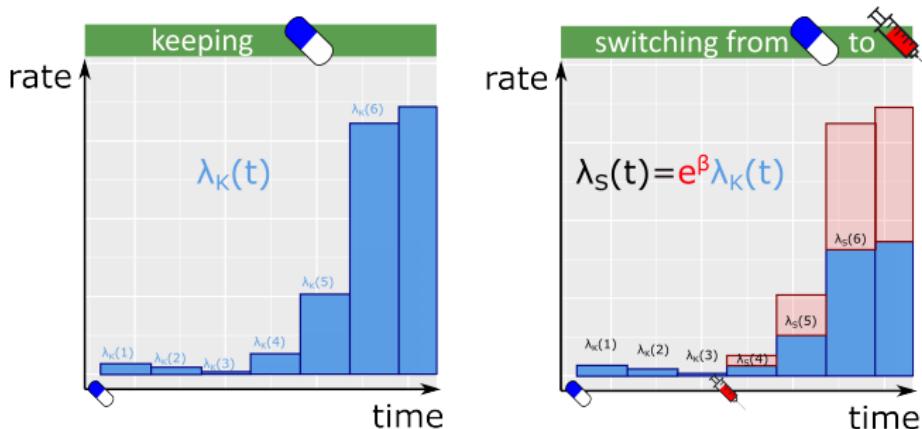
e^β is the *instantaneous* rate ratio between exposures

- quite different from a (long-term) risk ratio

Usually with Cox models $\beta > 0$ means harmful
 $\beta < 0$ means protective

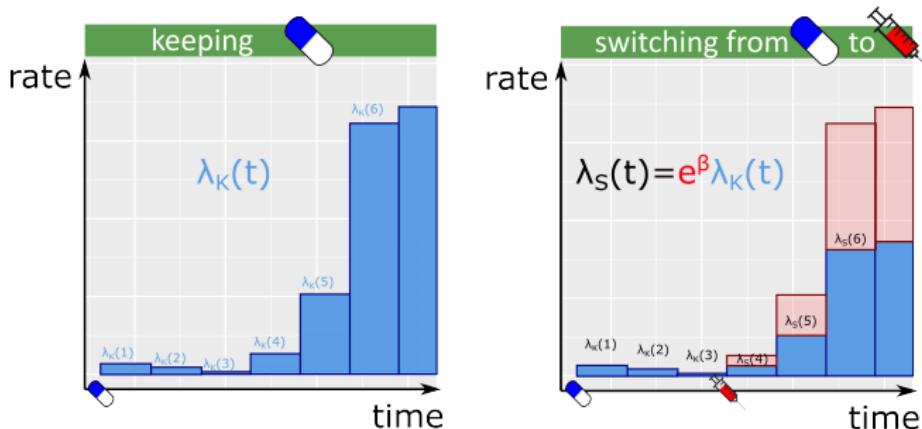
- not always true with time varying exposures!

Reminder (1/2): what are we modeling?



With Cox, we model the *instantaneous* rate $\lambda(t)$

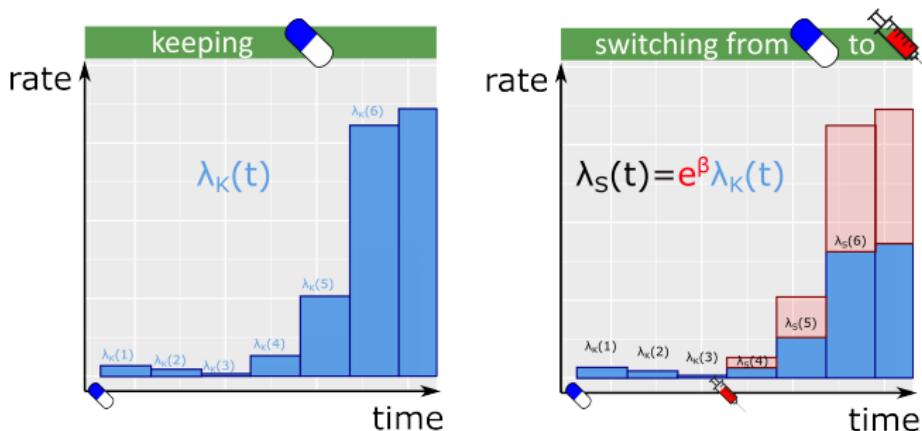
Reminder (1/2): what are we modeling?



With Cox, we model the *instantaneous* rate $\lambda(t)$

- also called hazard, hazard rate, intensity

Reminder (1/2): what are we modeling?



With Cox, we model the *instantaneous* rate $\lambda(t)$

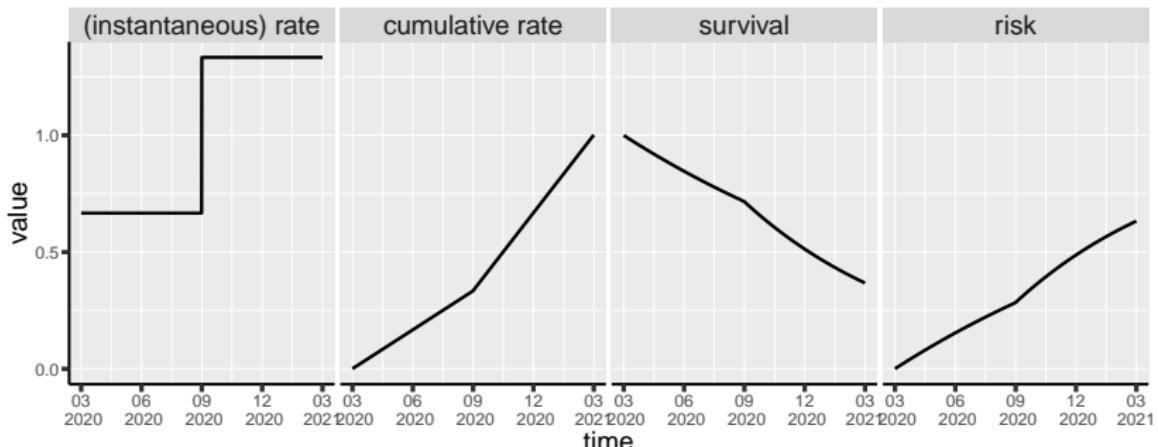
- also called hazard, hazard rate, intensity

Estimate:

- log hazard ratio β
hazard ratio $\theta = e^\beta$
- ratio between the *instantaneous* rate under different exposures

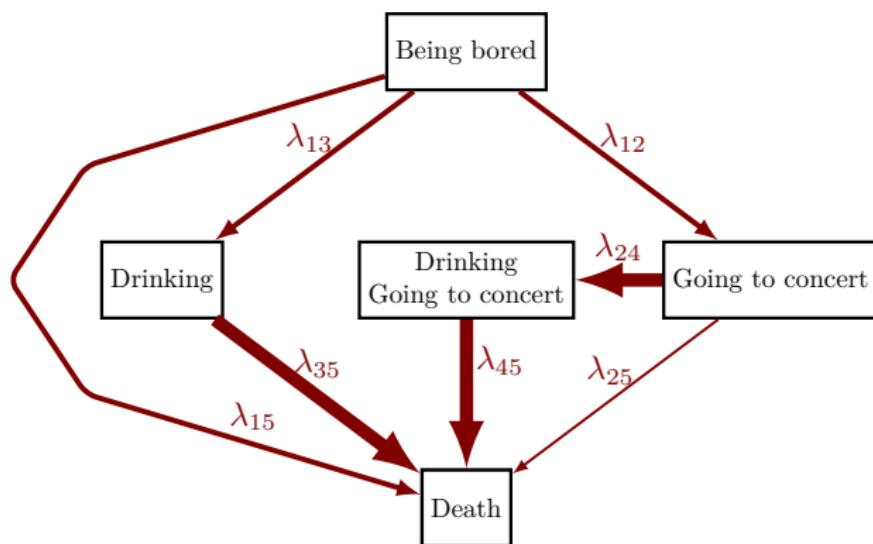
Reminder (2/2): rate - risk relationship

- cumulative rate $\Lambda(t) = \int \lambda(s)ds$
- survival $\approx \exp(-\text{cumulative rate})$ $P[T > t] = \exp(-\Lambda(t))$
- risk = 1 - survival $P[T \leq t] = 1 - \exp(-\Lambda(t))$



What can go wrong?

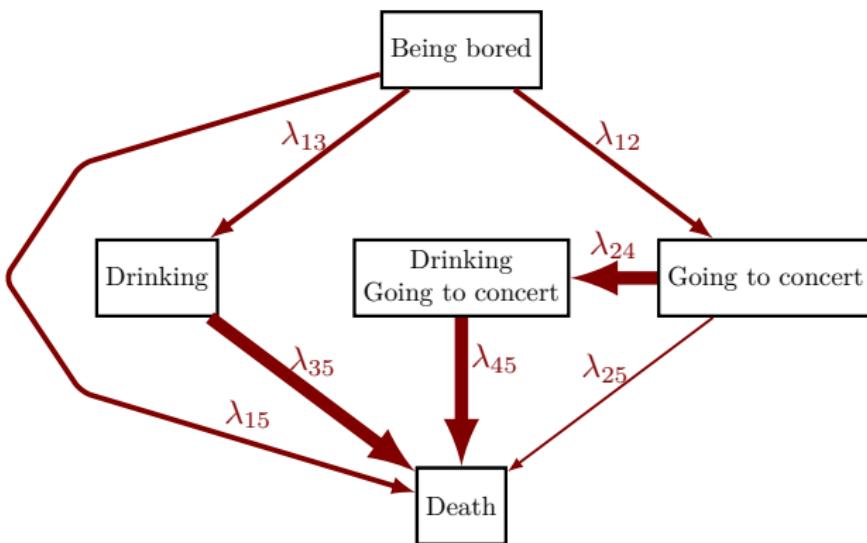
Going to concert vs. staying bored:



What can go wrong?

Going to concert vs. staying bored:

- lower *instantaneous* risk ($\frac{\lambda_{25}}{\lambda_{15}} < 1$)
 - higher *long-term* risk (as one is likely to start drinking)



Parameter of interest

Typically the risk or risk ratio under different exposures:

- starting with , possibly switching at some point to vs. staying under

$$RR_1(t) = \frac{\mathbb{P}[T \leq t | E = \text{blue capsule} \xrightarrow{?} \text{red syringe}]}{\mathbb{P}[T \leq t | E = \text{blue capsule}]}$$

- being under vs. staying under

$$RR_2(t|s) = \frac{\mathbb{P}[T \leq t | E = \text{red syringe}, T > s]}{\mathbb{P}[T \leq t | E = \text{blue capsule}, T > s]}$$

Parameter of interest

Typically the risk or risk ratio under different exposures:

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$$RR_1(t) = \frac{\mathbb{P}[T \leq t | E = \text{blue capsule} \xrightarrow{?} \text{red syringe}]}{\mathbb{P}[T \leq t | E = \text{blue capsule}]}$$

- being under vs. staying under

$$RR_2(t|s) = \frac{\mathbb{P}[T \leq t | E = \text{red syringe}, T > s]}{\mathbb{P}[T \leq t | E = \text{blue capsule}, T > s]}$$

$$RR_2(t|s=0) \approx \frac{1 - \exp\left(-\int_0^t \lambda_0(s) \exp(\beta) ds\right)}{1 - \exp\left(-\int_0^t \lambda_0(s) ds\right)}$$

: $\beta = 0 \iff RR_2 = 1$
 $\beta > 0 \iff RR_2 > 1$
 $\beta < 0 \iff RR_2 < 1$

Parameter of interest

Typically the risk or risk ratio under different exposures:

- starting with , possibly switching at some point to vs. staying under

$$RR_1(t) = \frac{\mathbb{P}[T \leq t | E = \text{blue capsule} \xrightarrow{?} \text{red syringe}]}{\mathbb{P}[T \leq t | E = \text{blue capsule}]}$$

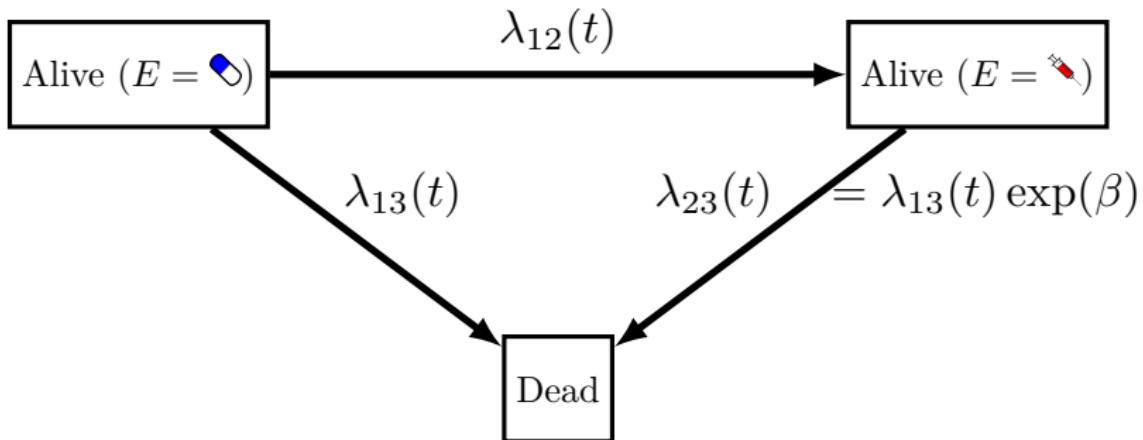
- being under vs. staying under

$$RR_2(t|s) = \frac{\mathbb{P}[T \leq t | E = \text{red syringe}, T > s]}{\mathbb{P}[T \leq t | E = \text{blue capsule}, T > s]}$$

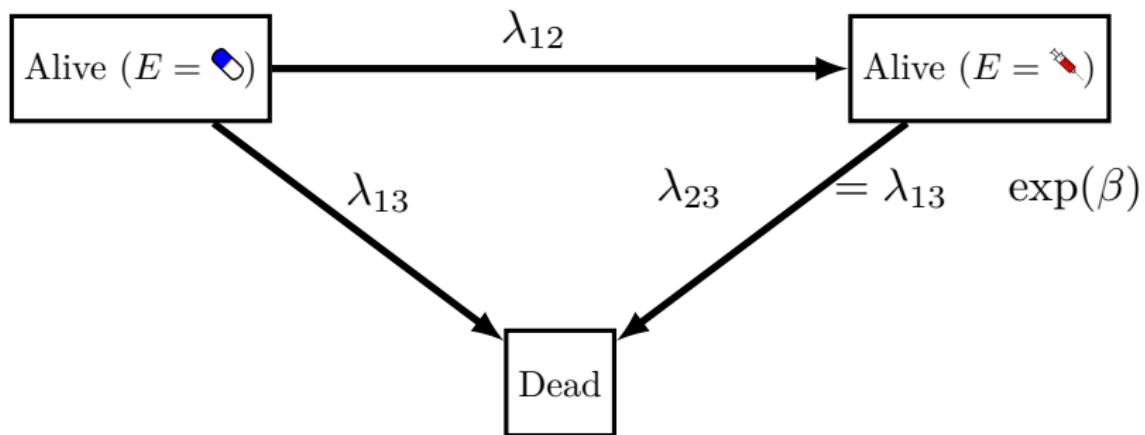
$$\beta = 0 \iff RR_1 = 1, \beta > 0 \iff RR_1 > 1, \beta < 0 \iff RR_1 < 1$$

- is true with a single, binary, monotone, time-varying exposure
- but not necessarily true otherwise! (Blanche et al., 2022)

Single binary exposure



Single binary exposure



Assuming constant rates and denoting $\theta = \exp(\beta)$:

$$\mathbb{P}(T \leq t | E = \text{blue}) = 1 - e^{-\lambda_{13}t}$$

$$\mathbb{P}(T \leq t | E = \text{blue} \rightarrow \text{red}) = 1 - \frac{\lambda_{12}e^{-\theta\lambda_{13}t} + \lambda_{13}(1-\theta)e^{-(\lambda_{12}+\lambda_{13})t}}{\lambda_{12} + \lambda_{13}(1-\theta)}$$

Summary - Cox model

- ✓ handles time-varying exposure
- ✓ implemented in statistical softwares
numerically fast
- ⚠ Assumes transitions are outcome independent
(possibly conditionally on covariates)
- ⚠ Interpretation of the coefficients is not straightforward
 - intuitive with single exposure
 - can be counter-intuitive with multiple exposures

Helpful multistate representation of time-varying exposures suggested by **Cortese and Andersen (2010)**.

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Inverse probably weighting (IPW)

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The elephant in the room

A major assumption of the previous solutions is:

- transitions are outcome independent

The elephant in the room

A major assumption of the previous solutions is:

- transitions are outcome independent

This is rarely met in practice:

- patient switch treatment for a reason:
lack of effectiveness, side effects, ...
- doctors will adjust dosage depending on patient's health status

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The elephant in the room

A major assumption of the previous solutions is:

- transitions are outcome independent

This is rarely met in practice:

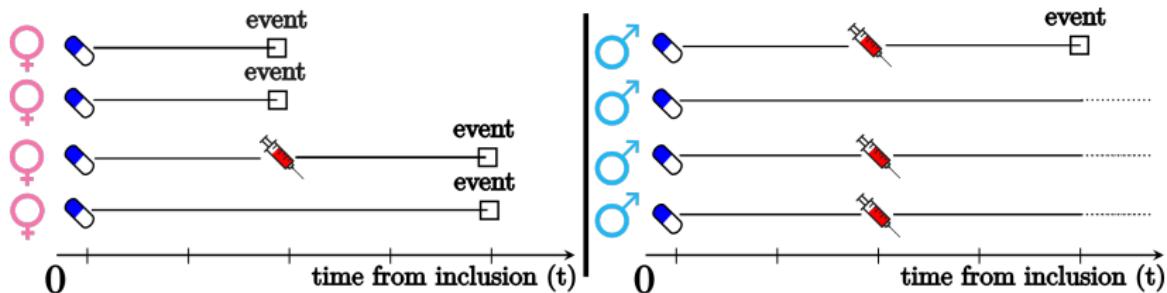
- patient switch treatment for a reason:
lack of effectiveness, side effects, ...
- doctors will adjust dosage depending on patient's health status

A typical example is HIV treatment

- very low CD4 counts is associated high risk of death
 - CD4 counts is used to monitor HIV treatment
- confounding by indication

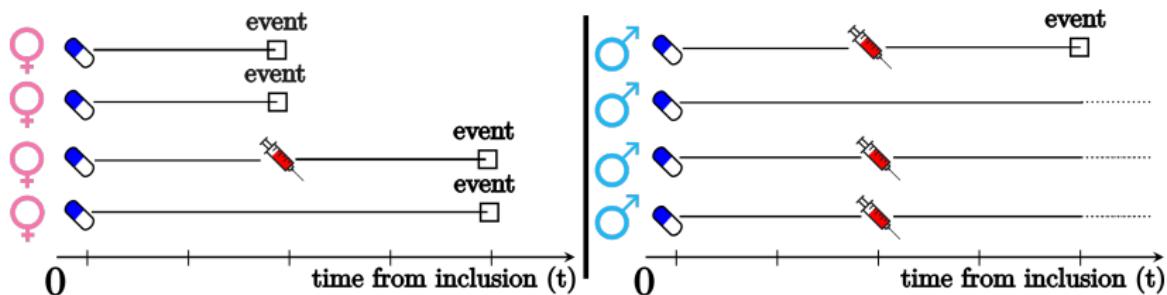
A simpler situation

- the treatment is time-varying
- the covariate (gender) is constant over time
- no unobserved confounder



A simpler situation

- the treatment is time-varying
- the covariate (gender) is constant over time
- no unobserved confounder



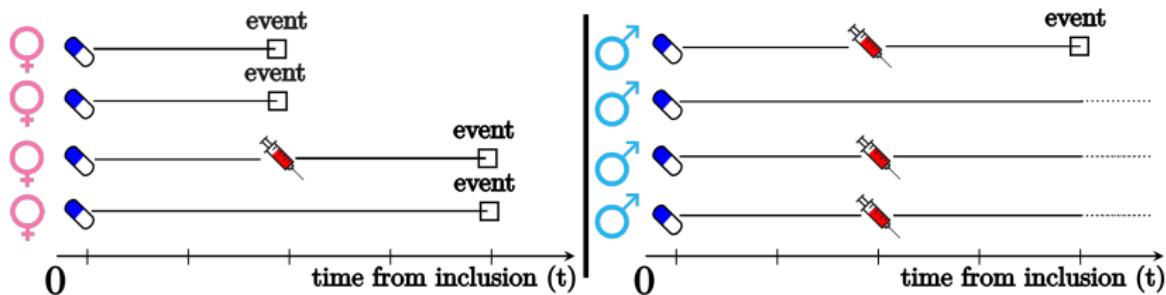
At time 2:

- more males than females among the →
 - incident is higher among females
- 💡 can we re-weight the data to remove unbalance?

Intuition behind IPW

- learning treatment allocation based on data

$$\mathbb{P}[\text{♂} \rightarrow \text{♀}(t) | T > t] = \begin{cases} 0 & \text{if } t \neq 2 \\ \text{♀}/2 + 3\text{♂}/4 & \text{at } t = 2 \end{cases}$$
$$\mathbb{P}[T > t] = \begin{cases} \dots & \text{if } t \neq 2 \\ \text{♀}/2 + \text{♂} & \text{at } t = 2 \end{cases}$$

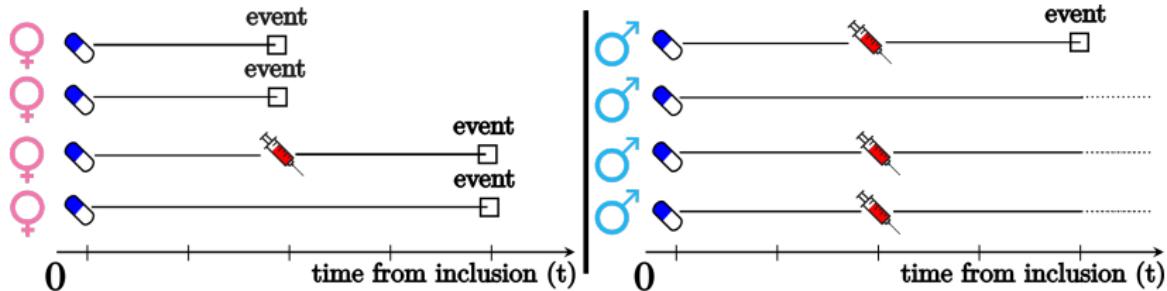


Intuition behind IPW

- learning treatment allocation based on data
- use probability calculus ...

$$\begin{aligned}\mathbb{P}[\text{blue capsule} \rightarrow \text{red capsule}(2)] &= \mathbb{P}[\text{blue capsule} \rightarrow \text{red capsule}(t) | T > t] \mathbb{P}[T > t] \\ &= \text{♀}/4 + 3\text{♂}/4\end{aligned}$$

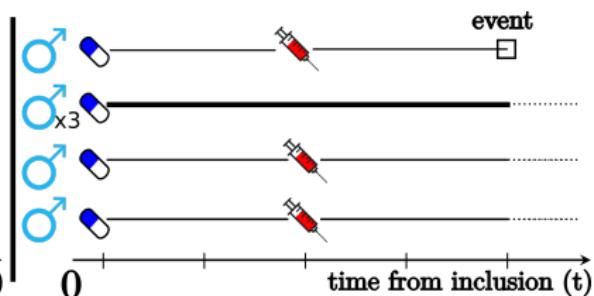
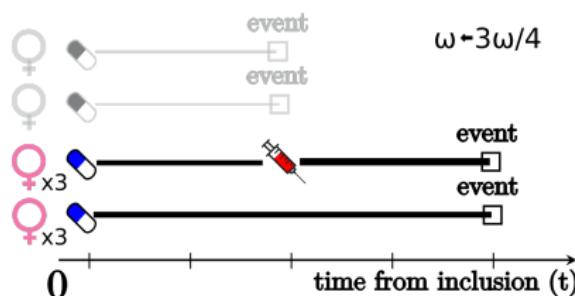
$$\mathbb{P}[\text{blue capsule}(2)] = (1 - \mathbb{P}[\text{blue capsule} \rightarrow \text{red capsule}(t) | T > t]) \mathbb{P}[T > t] = 1/4$$



Intuition behind IPW

- learning treatment allocation based on data
- use probability calculus ...
- ... to mimic a randomized trial by re-weighting the data

$$\omega = \begin{cases} \frac{1}{\mathbb{P}[\text{♂}(2)]} = 4 & \text{if } \text{♂}(2) \\ \frac{1}{\mathbb{P}[\text{♂} \rightarrow \text{♀}(2)]} = 4\text{♀} + 4\text{♂}/3 & \text{if } \text{♂} \rightarrow \text{♀}(2) \end{cases}$$



manual IPW (single timepoint)

id	sex	weight	event	switch
1	1	0	TRUE	FALSE
2	1	0	TRUE	FALSE
3	1	3	TRUE	TRUE
4	1	3	TRUE	FALSE

id	sex	weight	event	switch
5	0	1	TRUE	TRUE
6	0	3	FALSE	FALSE
7	0	1	FALSE	TRUE
8	0	1	FALSE	TRUE

```
e.IPW <- glm(event ~ switch, weights = df.IPW$weight,  
               data = df.IPW, family = binomial(link = "log"))  
  
exp(coef(e.IPW))
```

```
(Intercept)  switchTRUE  
0.500000    1.333333
```

manual IPW (single timepoint)

id	sex	weight	event	switch	id	sex	weight	event	switch
1	1	0	TRUE	FALSE	5	0	1	TRUE	TRUE
2	1	0	TRUE	FALSE	6	0	3	FALSE	FALSE
3	1	3	TRUE	TRUE	7	0	1	FALSE	TRUE
4	1	3	TRUE	FALSE	8	0	1	FALSE	TRUE

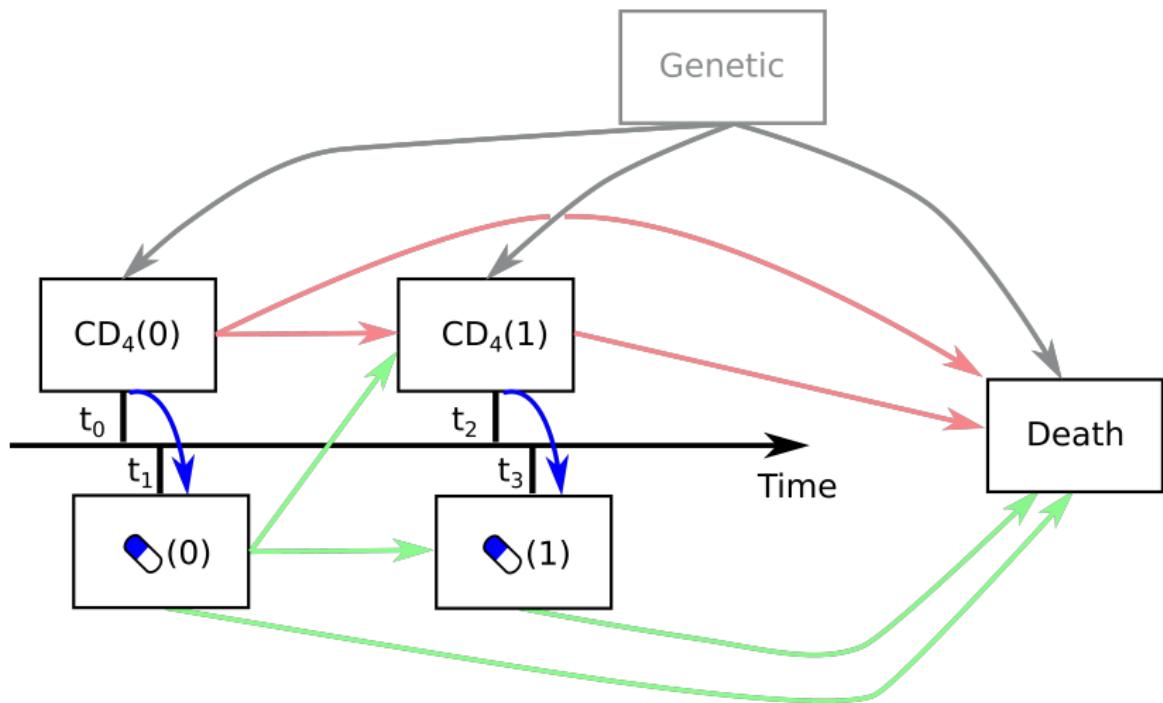
```
e.IPW <- glm(event ~ switch, weights = df.IPW$weight,  
               data = df.IPW, family = binomial(link = "log"))  
  
exp(coef(e.IPW))
```

```
(Intercept)  switchTRUE  
0.500000    1.333333
```

⚠ Standard error from `glm` will be incorrect

- uncertainty about the weights can be accounted for via bootstrap

A more realistic case



See [van der Wal and Geskus \(2011\)](#) for detailed examples.

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IPW - notation

Denote:

- $\bar{E} = \bar{E}_2 = (E(0), E(1))$ the exposure or treatment history
- $\bar{L} = \bar{L}_2 (L(0), L(1))$ the covariates history
- Y the outcome
 $Y^{\bar{E}=\bar{e}}$ the counterfactual outcome under $\bar{E} = (\bar{e}_0, \bar{e}_1)$

Say we are interested in $\Psi = \mathbb{E} [Y^{\bar{E}=(0,0)} - Y^{\bar{E}=(0,1)}]$

⚠ Ψ may differ from the empirical mean among those who switch vs. did not switched treatment.

IPW - definition

The IP weights are defined as:

$$\begin{aligned}\omega(\bar{E}) &= \frac{1}{\mathbb{P}[E(0)|L(0)]} \frac{1}{\mathbb{P}[E(1)|L(0), L(1), E(0)]} \\ &= \prod_{t=0}^1 \frac{1}{\mathbb{P}[E(t)|\bar{L}(t), \bar{E}(t-1)]}\end{aligned}$$

- denominator: individual probability of receiving the treatment history actually received given covariate and treatment history

IPW creates a sub-population:

- with mean identical to the counterfactual mean
- where randomization probabilities at each time are constant (i.e. covariate independent)

IPW - marginal structural model

Then we would use the weighted data set to fit a model relating treatment and outcome, e.g.:

$$\mathbb{E} [Y^{\bar{E}}] = \beta_1 E_0 + \beta_2 E_1$$

- confounding is addressed by the weights so no need for covariates
(unless they interact with treatment)
- coefficients have a causal interpretation ²

² assuming the marginal structural model and the treatment allocation model are correct

Longitudinal IPW - data structure

Long format:

id	sex	start	stop	event	switch	dropout
1	1	0	1	TRUE	FALSE	FALSE
2	1	0	1	TRUE	FALSE	FALSE
3	1	0	1	FALSE	FALSE	FALSE
3	1	1	2	TRUE	TRUE	FALSE
4	1	0	1	FALSE	FALSE	FALSE
4	1	1	2	TRUE	FALSE	FALSE
5	0	0	1	FALSE	FALSE	FALSE
5	0	1	2	TRUE	TRUE	FALSE
6	0	0	1	FALSE	FALSE	FALSE
6	0	1	2	FALSE	FALSE	FALSE
7	0	0	1	FALSE	FALSE	FALSE
7	0	1	2	FALSE	TRUE	FALSE
8	0	0	1	FALSE	FALSE	FALSE
8	0	1	2	FALSE	TRUE	FALSE

Longitudinal IPW - weights

```
library(ipw)

dfL.IPW$IPTW <- ipwtm(exposure = switch,
                         family = "survival", type = "first",
                         denominator = ~sex, id = id,
                         tstart = start, timevar = stop,
                         data = dfL.IPW)$ipw.weights

dfL.IPW$IPCW <- ipwtm(exposure = dropout,
                         family = "survival", type = "first",
                         denominator = ~sex, id = id,
                         tstart = start, timevar = stop,
                         data = dfL.IPW)$ipw.weights

dfL.IPW$weight <- dfL.IPW$IPTW*dfL.IPW$IPCW
```

Longitudinal IPW - updated data structure

```
print(dfL.IPW, row.names = FALSE)
```

id	sex	start	stop	event	switch	dropout	IPTW	IPCW	weight
1	1	0	1	TRUE	FALSE	FALSE	1.000000	1	1.000000
2	1	0	1	TRUE	FALSE	FALSE	1.000000	1	1.000000
3	1	0	1	FALSE	FALSE	FALSE	1.000000	1	1.000000
3	1	1	2	TRUE	TRUE	FALSE	2.101602	1	2.101602
4	1	0	1	FALSE	FALSE	FALSE	1.000000	1	1.000000
4	1	1	2	TRUE	FALSE	FALSE	1.907769	1	1.907769
5	0	0	1	FALSE	FALSE	FALSE	1.000000	1	1.000000
5	0	1	2	TRUE	TRUE	FALSE	1.474049	1	1.474049
6	0	0	1	FALSE	FALSE	FALSE	1.000000	1	1.000000
6	0	1	2	FALSE	FALSE	FALSE	3.109488	1	3.109488
7	0	0	1	FALSE	FALSE	FALSE	1.000000	1	1.000000
7	0	1	2	FALSE	TRUE	FALSE	1.474049	1	1.474049
8	0	0	1	FALSE	FALSE	FALSE	1.000000	1	1.000000
8	0	1	2	FALSE	TRUE	FALSE	1.474049	1	1.474049

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Longitudinal IPW - MSM

```
library(survival)

coxph(Surv(start, stop, event) ~ switch + cluster(id),
      data = dfL.IPW,
      weights = dfL.IPW$weight)
```

Call:

```
coxph(formula = Surv(start, stop, event) ~ switch, data = dfL.IPW,
      weights = dfL.IPW$weight, cluster = id)
```

	coef	exp(coef)	se(coef)	robust se	z	p
switchTRUE	0.4425	1.5566	0.8970	1.1742	0.377	0.706

```
Likelihood ratio test=0.25 on 1 df, p=0.6152
n= 14, number of events= 5
```

IPW - summary

Previous approaches assumed independent transitions

- strong assumption: often clearly violated

IPW can relax this assumption:

- by re-weighting the data at each timepoint
- other, more refined method existing but are omitted here

but this has a cost:

- time need to be discretized
- (a lot of) modeling is necessary

Reference |

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Suissa, S. (2007). Immortal time bias in observational studies of drug effects. *Pharmacoepidemiology and drug safety*, 16(3):241–249.

van der Wal, W. M. and Geskus, R. B. (2011). ipw: an r package for inverse probability weighting. *Journal of Statistical Software*, 43:1–23.

A little bit of math

Recall that:

$$\text{incidence rate } \lambda = \frac{\text{number of events}}{\text{number of person-time}} = \frac{D}{T}$$

A little bit of math

Recall that:

$$\text{incidence rate } \lambda = \frac{\text{number of events}}{\text{number of person-time}} = \frac{D}{T}$$

Model: treatment specific rate assumed constant over time

$$\lambda(E = 0) = \lambda_1 \text{ vs. } \lambda(E = \textcolor{red}{1}) = \lambda_2,$$

A little bit of math

Recall that:

$$\text{incidence rate } \lambda = \frac{\text{number of events}}{\text{number of person-time}} = \frac{D}{T}$$

Model: treatment specific rate assumed constant over time

$$\lambda(E = 0) = \lambda_1 \text{ vs. } \lambda(E = 1) = \lambda_2,$$

Reparametrisation: $\lambda(E = 0) = \exp(\alpha)$ and $\frac{\lambda(E=1)}{\lambda(E=0)} = \exp(\beta)$

$$\log(\lambda(E)) = \log(D(E)) - \log(T(E)) = \alpha + \beta E$$

A little bit of math

Recall that:

$$\text{incidence rate } \lambda = \frac{\text{number of events}}{\text{number of person-time}} = \frac{D}{T}$$

Model: treatment specific rate assumed constant over time

$$\lambda(E = 0) = \lambda_1 \text{ vs. } \lambda(E = 1) = \lambda_2,$$

Reparametrisation: $\lambda(E = 0) = \exp(\alpha)$ and $\frac{\lambda(E=1)}{\lambda(E=0)} = \exp(\beta)$

$$\log(\lambda(E)) = \log(D(E)) - \log(T(E)) = \alpha + \beta E$$

which is equivalent to

$$\log(D(E)) = \log(T(E)) + \alpha + \beta E$$

Solution 0 - with a software

```
coxWrong <- glm(event ~ transplant, data = dfWrong,  
  offset = log(time), family = poisson(link = "log")  
 )  
exp(coef(coxWrong))
```

```
(Intercept) transplantTRUE  
0.2666667 0.6250000
```

```
coxRight <- glm(event ~ transplant, data = dfRight,  
  offset = log(stop-start), family = poisson(link = "log")  
 )  
exp(coef(coxRight))
```

```
(Intercept) transplantTRUE  
0.1176471 6.8000000
```

Cox partial likelihood

$$\mathcal{L}(\beta) = \prod_{i=1}^n \frac{\exp(X_i\beta)}{\sum_{j \in R(t_i)} \exp(X_j\beta)}$$

$$\log(\mathcal{L}(\beta)) = \sum_{i=1}^n \left(X_i\beta - \log \left(\sum_{j \in R(t_i)} \exp(X_j\beta) \right) \right)$$

$$\mathcal{S}(\beta) = \sum_{i=1}^n \left(X_i - \frac{\sum_{j \in R(t_i)} X_j \exp(X_j\beta)}{\log \left(\sum_{j \in R(t_i)} \exp(X_j\beta) \right)} \right)$$

Landmarking

Follow-up starts at the end of the immortal period

"In this method, a fixed time point is first selected as the landmark time. Patients who have experienced the event of interest, or are censored prior to the selected landmark time, are excluded from analysis; **group membership is determined at the specific landmark time**. In this approach, **patients who initiate treatment after the landmark time are included in the no-treatment group**, regardless of any treatment they receive thereafter. The standard Cox proportional hazards model described above was then applied to the landmark data, with the start time for analysis being the landmark time" (Jones and Fowler, 2016)

Introduction

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Examples

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Time-varying Cox

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IP weighting

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Reference

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Approximate illustration of landmarking

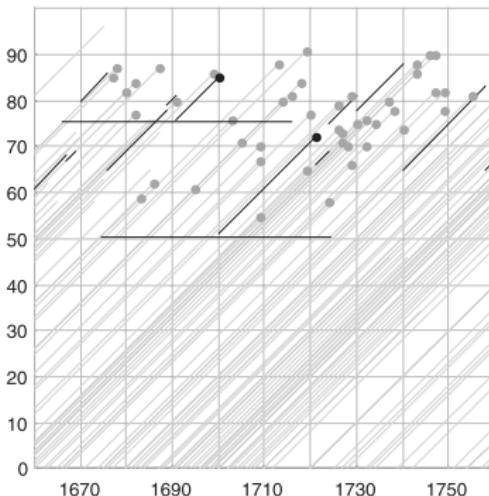


Figure 2 Mini-cohorts based on specific papacies.