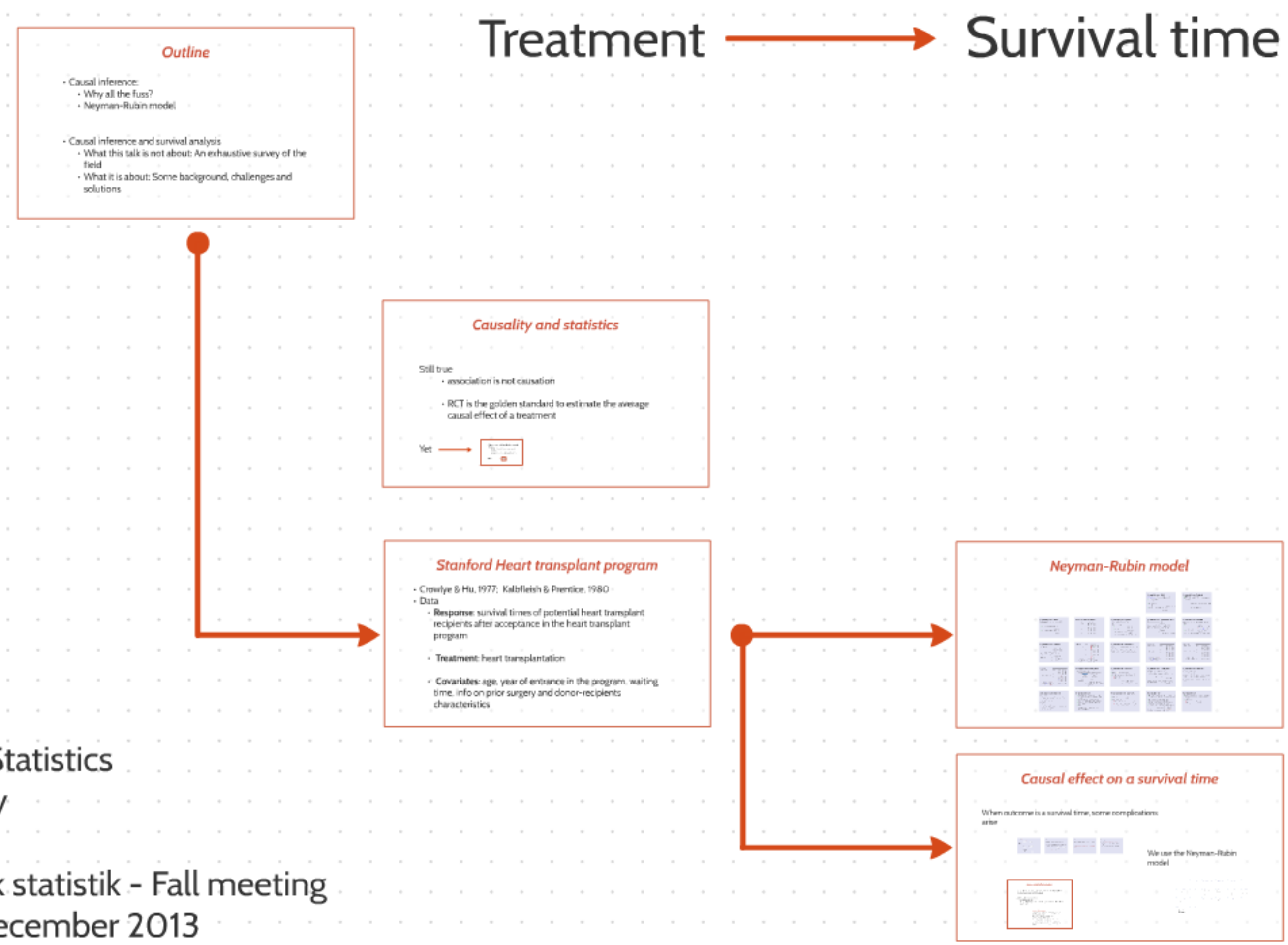
Causal inference and survival analysis



Xavier de Luna, Dept of Statistics
USBE @ Umeå University

Föreningen för medicinsk statistik - Fall meeting
AstraZeneca, Mölndal, December 2013

Causal inference and survival analysis

Treatment → Survival time

Outline

- Causal inference:
  - Why all the fuss?
  - Neyman-Rubin model
- Causal inference and survival analysis
  - What this talk is not about: An exhaustive survey of the field
  - What it is about: Some background, challenges and solutions

Causality and statistics

Still true
- association is not causation
- RCT is the golden standard to estimate the average causal effect of a treatment

Yet →

Stanford Heart transplant program

- Crowlye & Hu, 1977; Kalbfleish & Prentice, 1980
- Data
  - **Response**: survival times of potential heart transplant recipients after acceptance in the heart transplant program
  - **Treatment**: heart transplantation
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Neyman-Rubin model

Causal effect on a survival time

When outcome is a survival time, some complications arise

We use the Neyman-Rubin model

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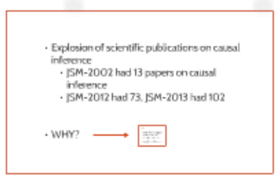
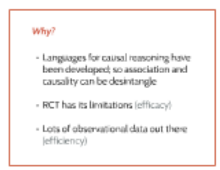


- Explosion of scientific publications on causal inference
  - JSM-2002 had 13 papers on causal inference
  - JSM-2012 had 73, JSM-2013 had 102
- WHY? →



Why?

- Languages for causal reasoning have been developed; so association and causality can be desintangle
- RCT has its limitations (efficacy)
- Lots of observational data out there (efficiency)

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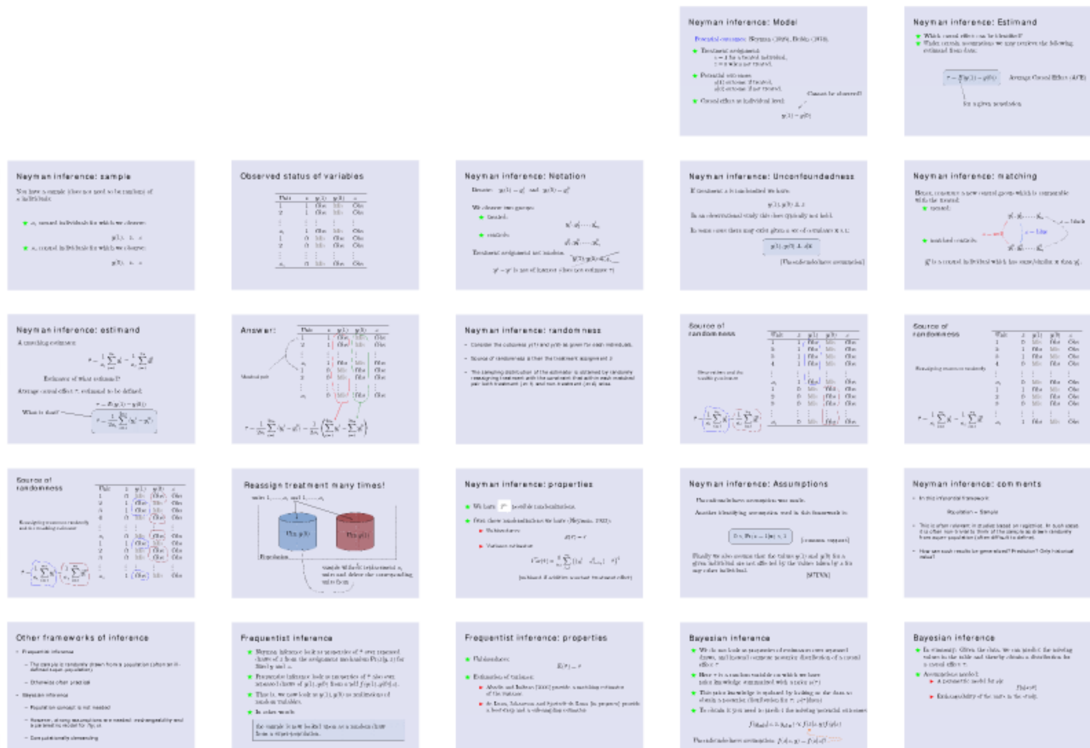
Neyman-Rubin model



Neyman inference: Model

Potential outcomes: Neyman (1923), Rubin (1974).

★ Treatment assignment:

$z = 1$ for a treated individual,

$z = 0$ when not treated.

★ Potential outcomes:

$y(1)$ outcome if treated,

$y(0)$ outcome if not treated.

★ Causal effect at individual level:

Cannot be observed!

$$y(1) - y(0)$$

Neyman inference: Estimand

- Which causal effect can be identified?
- Under certain assumptions we may retrieve the following estimand from data:

$$\tau = E(y(1) - y(0))$$

Average Causal Effect (ACE)

for a given population

Neyman inference: sample

You have a sample (does not need to be random) of n individuals:

- n_t treated individuals for which we observe:

$$y(1), \quad z, \quad x$$

- n_c control individuals for which we observe:

$$y(0), \quad z, \quad x$$

Observed status of variables

Unit	z	$y(1)$	$y(0)$	x
1	1	Obs	Mis	Obs
2	1	Obs	Mis	Obs
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
n_t	1	Obs	Mis	Obs
1	0	Mis	Obs	Obs
2	0	Mis	Obs	Obs
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
n_c	0	Mis	Obs	Obs

Neyman inference: Notation

Denote: $y_i(1) = y_i^1$ and $y_i(0) = y_i^0$

We observe two groups:

- treated:

$$y_1^1, y_2^1 \ldots, y_{n_t}^1$$

- controls:

$$y_1^0, y_2^0, \ldots, y_{n_c}^0$$

Treatment assignment not random.

$$\cancel{y(1), y(0) \perp\!\!\!\perp z}$$

$\bar{y}^t - \bar{y}^c$ is not of interest (does not estimate τ)

Neyman inference: Unconfoundedness

If treatment z is randomized we have:

$$y(1), y(0) \perp\!\!\!\perp z$$

In an observational study this does typically not hold.

In some cases there may exist given a set of covariates $\mathbf{x}$ s.t.:

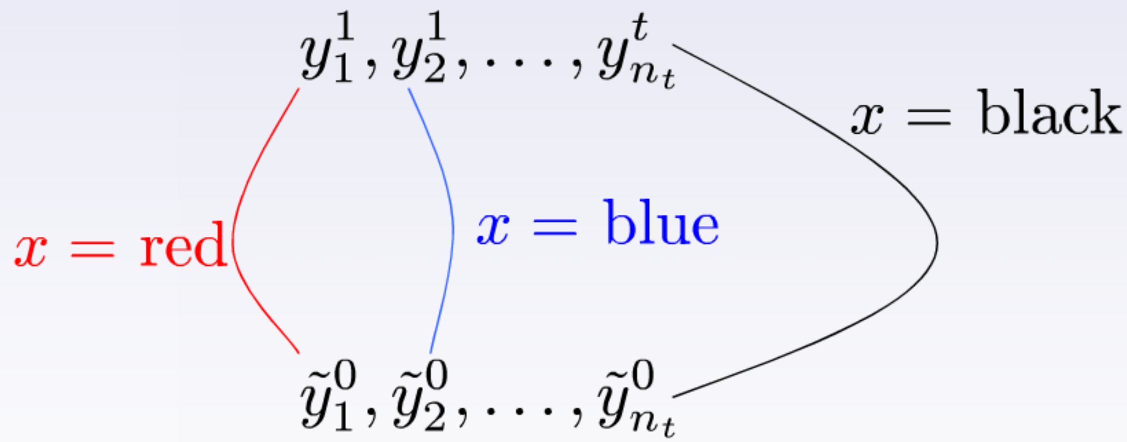
$$y(1), y(0) \perp\!\!\!\perp z | \mathbf{x}$$

[Unconfoundedness assumption]

Neyman inference: matching

Hence, construct a new control group which is comparable with the treated:

- treated:
- matched controls:



$\tilde{y}_j^0$ is a control individual which has same/similar $\mathbf{x}$ than y_j^1.

Neyman inference: estimand

A matching estimator:

$$\hat{\tau} = \frac{1}{n_t}\sum_{i=1}^{n_t} y_i^1 - \frac{1}{n_t}\sum_{i=1}^{n_t} \tilde{y}_i^0$$

Estimator of what estimand?

Average causal effect τ, estimand to be defined:

$$\tau = E(y(1) - y(0))$$

What is that? →

$$\tau = \frac{1}{2n_t}\sum_{i=1}^{2n_t} \left(y_i^1 - y_i^0\right)$$

Answer:

Unit	z	$y(1)$	$y(0)$	x
1	1	Obs	Mis	Obs
2	1	Obs	Mis	Obs
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
n_t	1	Obs	Mis	Obs
1	0	Mis	Obs	Obs
2	0	Mis	Obs	Obs
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
n_t	0	Mis	Obs	Obs

Matched pair

$$\tau = \frac{1}{2n_t}\sum_{i=1}^{2n_t}\left(y_i^1 - y_i^0\right) = \frac{1}{2n_t}\left(\sum_{i=1}^{2n_t} y_i^1 - \sum_{i=1}^{2n_t} y_i^0\right)$$

Neyman inference: randomness

- Consider the outcomes *y(1)* and *y(0)* as given for each individuals.
- Source of randomness is then the treatment assignment *z*
- The sampling distribution of the estimator is obtained by randomly reassigning treatment with the constraint that within each matched pair both treatment ($z=1$) and non-treatment ($z=0$) arise.

Source of randomness

Observations and the resulting estimator

$$\hat{\tau} = \frac{1}{n_t}\sum_{i=1}^{n_t} y_i^1 - \frac{1}{n_t}\sum_{i=1}^{n_t} \tilde{y}_i^0$$

Unit	z	$y(1)$	$y(0)$	x
1	1	Obs	Mis	Obs
2	1	Obs	Mis	Obs
3	1	Obs	Mis	Obs
4	1	Obs	Mis	Obs
⋮	⋮	⋮	⋮	⋮
n_t	1	Obs	Mis	Obs
1	0	Mis	Obs	Obs
2	0	Mis	Obs	Obs
3	0	Mis	Obs	Obs
⋮	⋮	⋮	⋮	⋮
n_t	0	Mis	Obs	Obs

Source of randomness

Reassigning treatment randomly

$$\hat{\tau} = \frac{1}{n_t}\sum_{i=1}^{n_t} y_i^1 - \frac{1}{n_t}\sum_{i=1}^{n_t} \tilde{y}_i^0$$

Unit	z	$y(1)$	$y(0)$	x
1	0	Mis	Obs	Obs
2	1	Obs	Mis	Obs
3	1	Obs	Mis	Obs
4	0	Mis	Obs	Obs
⋮	⋮	⋮	⋮	⋮
n_t	0	Mis	Obs	Obs
1	1	Obs	Mis	Obs
2	0	Mis	Obs	Obs
3	0	Mis	Obs	Obs
⋮	⋮	⋮	⋮	⋮
n_t	1	Obs	Mis	Obs

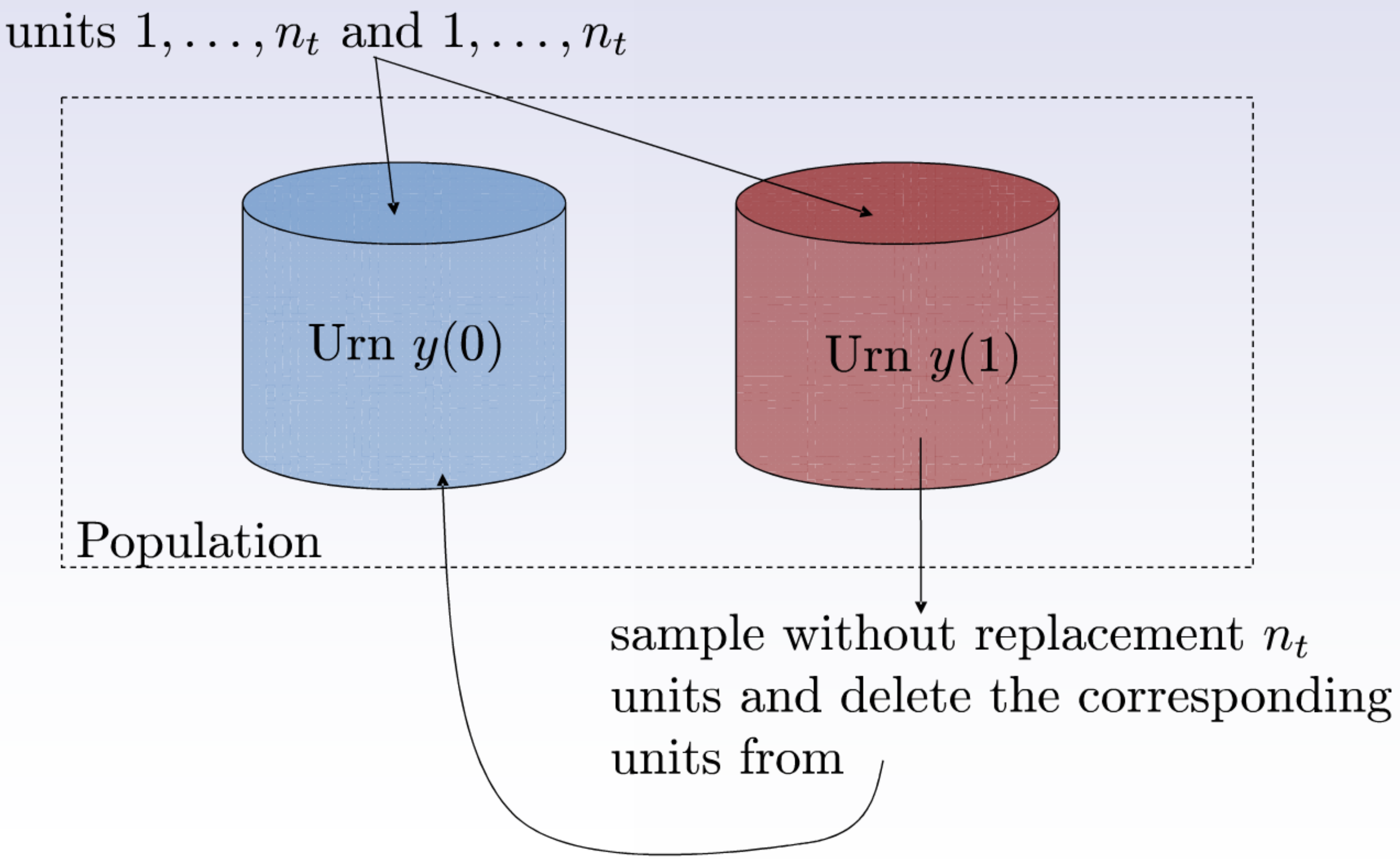
Source of randomness

Reassigning treatment randomly and the resulting estimator

$$\hat{\tau} = \frac{1}{n_t}\sum_{i=1}^{n_t} y_i^1 - \frac{1}{n_t}\sum_{i=1}^{n_t} \tilde{y}_i^0$$

Unit	z	$y(1)$	$y(0)$	x
1	0	Mis	Obs	Obs
2	1	Obs	Mis	Obs
3	1	Obs	Mis	Obs
4	0	Mis	Obs	Obs
⋮	⋮	⋮	⋮	⋮
n_t	0	Mis	Obs	Obs
1	1	Obs	Mis	Obs
2	0	Mis	Obs	Obs
3	0	Mis	Obs	Obs
⋮	⋮	⋮	⋮	⋮
n_c	1	Obs	Mis	Obs

Reassign treatment many times!



Neyman inference: properties

- We have 2^{n_t} possible randomizations.
- Over these randomizations we have (Neyman, 1923):
  - Unbiasedness:

$$E(\hat{\tau}) = \tau$$

  - Variance estimator:

$$\widehat{Var}(\hat{\tau}) = \frac{1}{n_t} \sum_{i=1}^{n_t} \left\{ (y_i^1 - y_{i+n_t}^0) - \hat{\tau} \right\}^2$$

(unbiased if additive constant treatment effect)

Neyman inference: Assumptions

Unconfoundedness assumption was made.

Another identifying assumption used in this framework is:

$$0 < \Pr(z = 1|\mathbf{x}) < 1$$

[common support]

Finally we also assume that the values $y(1)$ and $y(0)$ for a given individual are not affected by the values taken by z for any other individual.

[SUTVA]

Neyman inference: comments

- In this inferential framework:

  Population = Sample

- This is often relevant in studies based on registries. In such cases it is often non-trivial to think of the sample as drawn randomly from super-population (often difficult to define).

- How can such results be generalized? Prediction? Only historical value?

Other frameworks of inference

- Frequentist inference
  - The sample is randomly drawn from a population (often an ill-defined super-population)
  - Otherwise often practical
- Bayesian inference
  - Population concept is not needed
  - However, strong assumptions are needed: exchangeability and a parametric model for $f(y|x)$.
  - Computationally demanding

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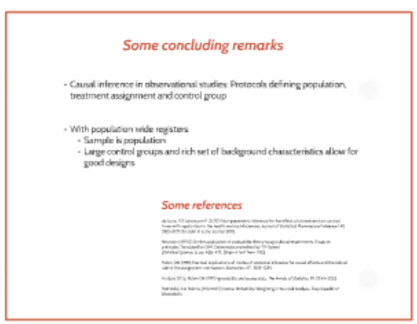
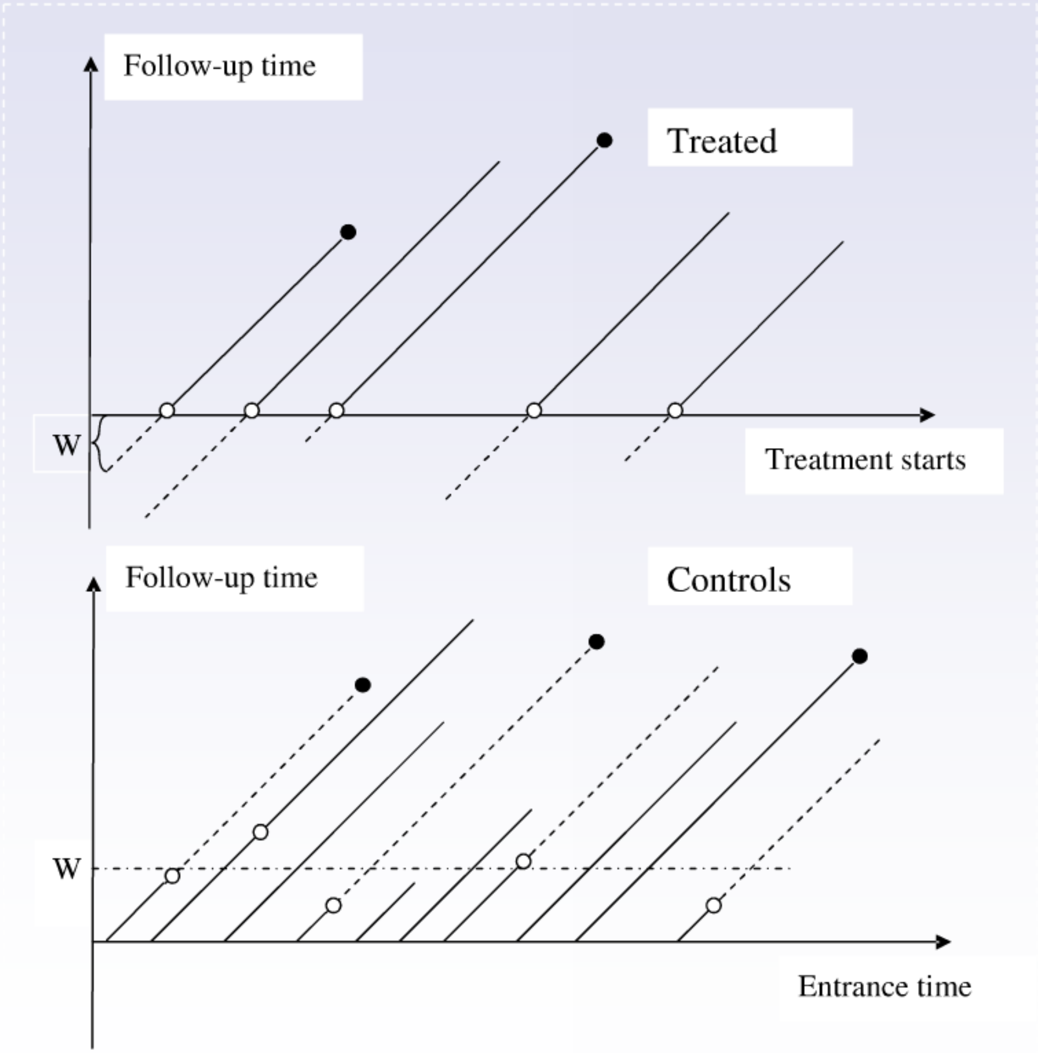


Note 1: Control group must include treated

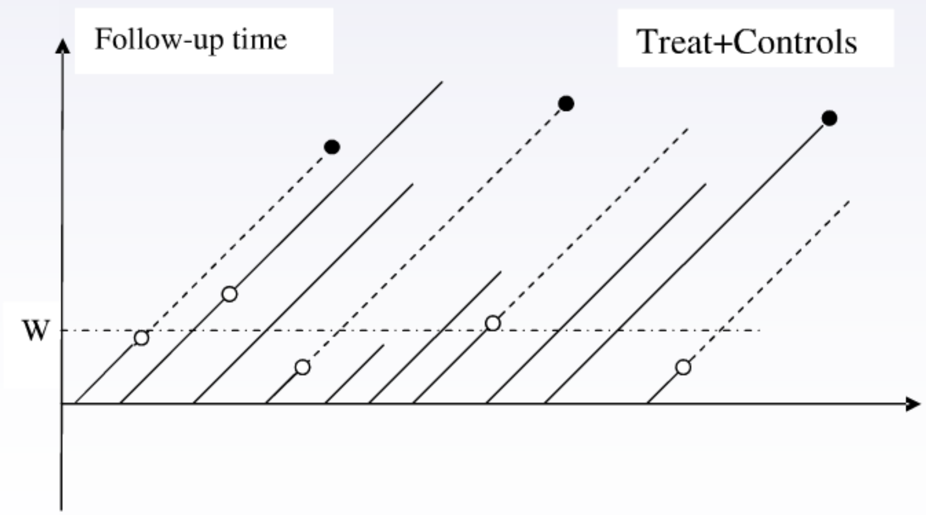
Lexis diagrams



Case of randomized treatment

- Assume each time a heart is available, a patient is randomly chosen.
- In contrast with usual studies, treated and controls cannot be directly compared: on average, survival time of a treated after transplantation is shorter than survival time of a control

Note 2: Inference must be conditioned on waiting time.



Observed treatment

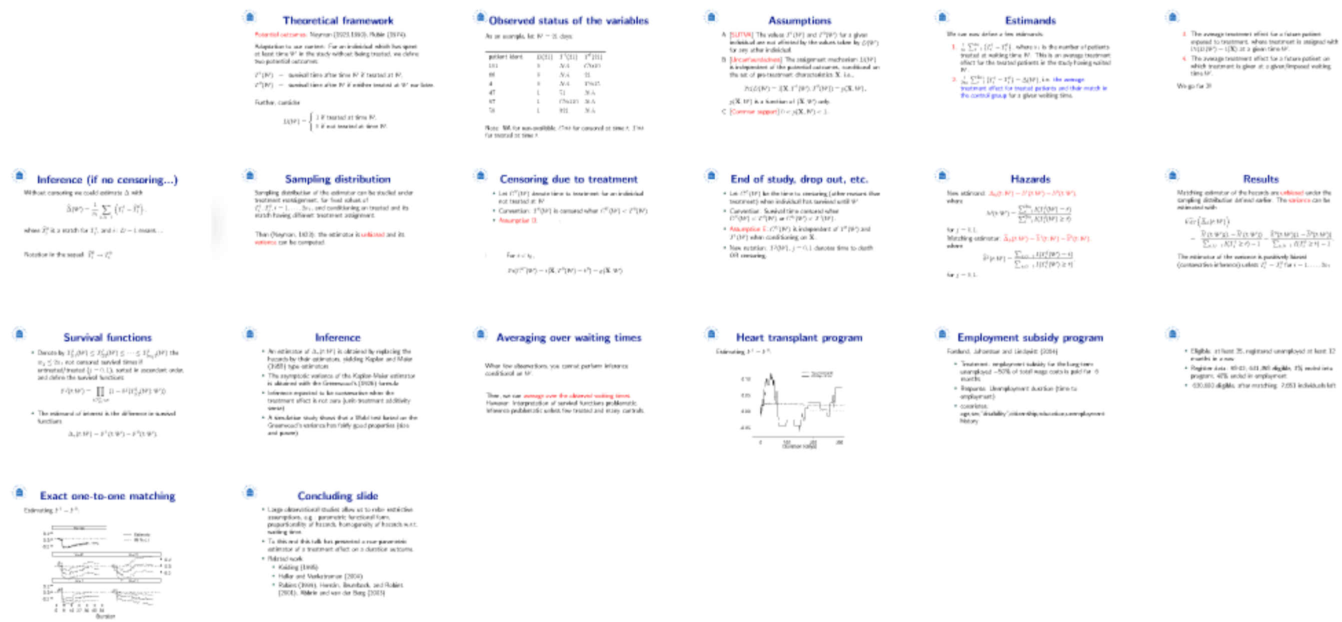
- Among those having a given waiting time, match for covariates affecting response and treatment.

Note 3: For a given waiting time, conditional on the covariates, the treatment can be considered as randomized. (unconfoundedness assumption)

Censoring

- Note 4: Patient's survival is censored in two ways:
  - end of study, drop out, etc. ; independent mechanism (assumption)
  - controls may receive treatment (need of an extra assumption)

We use the Neyman-Rubin model



Theoretical framework

Potential outcomes: Neyman (1923,1990), Rubin (1974).

Adaptation to our context: For an individual which has spent at least time W in the study without being treated, we define two potential outcomes:

$$\begin{aligned} T^1(W) &= \text{survival time after time } W \text{ if treated at } W, \\ T^0(W) &= \text{survival time after } W \text{ if neither treated at } W \text{ nor later.} \end{aligned}$$

Further, consider

$$D(W) = \begin{cases} 1 \text{ if treated at time } W, \\ 0 \text{ if not treated at time } W. \end{cases}$$

Observed status of the variables

As an example, let $W = 21$ days:

patient ident.	$D(21)$	$T^1(21)$	$T^0(21)$
101	0	NA	C@10
66	0	NA	21
4	0	NA	T@15
47	1	51	NA
97	1	C@110	NA
58	1	321	NA

Note: NA for non-available; C@t for censored at time t; T@t for treated at time t.

Censoring due to treatment

- Let $C^T(W)$ denote time to treatment for an individual not treated at W
- Convention: $T^0(W)$ is censored when $C^T(W) < T^0(W)$
- Assumption D:

For $i < t_0$,

$$\Pr(C^T(W) = i | \mathbf{X}, T^0(W) = t^0) = g(\mathbf{X}, W)$$

End of study, drop out, etc.

- Let $C^E(W)$ be the time to censoring (other reasons than treatment) when individual has survived until W
- Convention: Survival time censored when $C^E(W) < T^0(W)$ or $C^E(W) < T^1(W)$.
- Assumption E: $C^E(W)$ is independent of $T^0(W)$ and $T^1(W)$ when conditioning on $\mathbf{X}$.
- New notation: $T^j(W)$, $j = 0, 1$ denotes time to death OR censoring.

Hazards

New estimand: $\Delta_h(t; W) = h^1(t; W) - h^0(t; W)$,
where

$$h^j(t; W) = \frac{\sum_{i=1}^{2n_1} I(T_i^j(W) = t)}{\sum_{i=1}^{2n_1} I(T_i^j(W) \geq t)}$$

for $j = 0, 1$.

Matching estimator: $\widehat{\Delta}_h(t; W) = \widehat{h}^1(t; W) - \widehat{h}^0(t; W)$,
where

$$\widehat{h}^j(t; W) = \frac{\sum_{i:D=1} I(T_i^j(W) = t)}{\sum_{i:D=1} I(T_i^j(W) \geq t)},$$

for $j = 0, 1$.

Results

Matching estimator of the hazards are unbiased under the sampling distribution defined earlier. The variance can be estimated with

$$\widehat{Var}\left(\widehat{\Delta}_h(t;W)\right)$$
$$= \frac{\widehat{h}^1(t;W)(1-\widehat{h}^1(t;W))}{\sum_{i:D=1} I(T_i^1 \geq t) - 1} + \frac{\widehat{h}^0(t;W)(1-\widehat{h}^0(t;W))}{\sum_{i:D=1} I(T_i^0 \geq t) - 1}.$$

The estimator of the variance is positively biased (conservative inference) unless $T_i^1 = T_i^0$ for $i = 1, \ldots, 2n_1$

Survival functions

- Denote by $T^j_{(1)}(W) \le T^j_{(2)}(W) \le \cdots \le T^j_{(m_j)}(W)$ the $m_j \le 2n_1$ not censored survival times if untreated/treated ($j = 0, 1$), sorted in ascendant order, and define the survival functions:

$$F^j(t; W) = \prod_{i: T^1_{(i)} < t} (1 - h^j(T^j_{(i)}(W); W))$$

- The estimand of interest is the difference in survival functions

$$\Delta_s(t; W) = F^1(t; W) - F^0(t; W).$$

Inference

- An estimator of $\Delta_s(t;W)$ is obtained by replacing the hazards by their estimators, yielding Kaplan and Meier (1958) type estimators
- The asymptotic variance of the Kaplan-Meier estimator is obtained with the Greenwood's (1926) formula
- Inference expected to be conservative when the treatment effect is not zero (unit-treatment additivity sense)
- A simulation study shows that a Wald test based on the Greenwood's variance has fairly good properties (size and power)

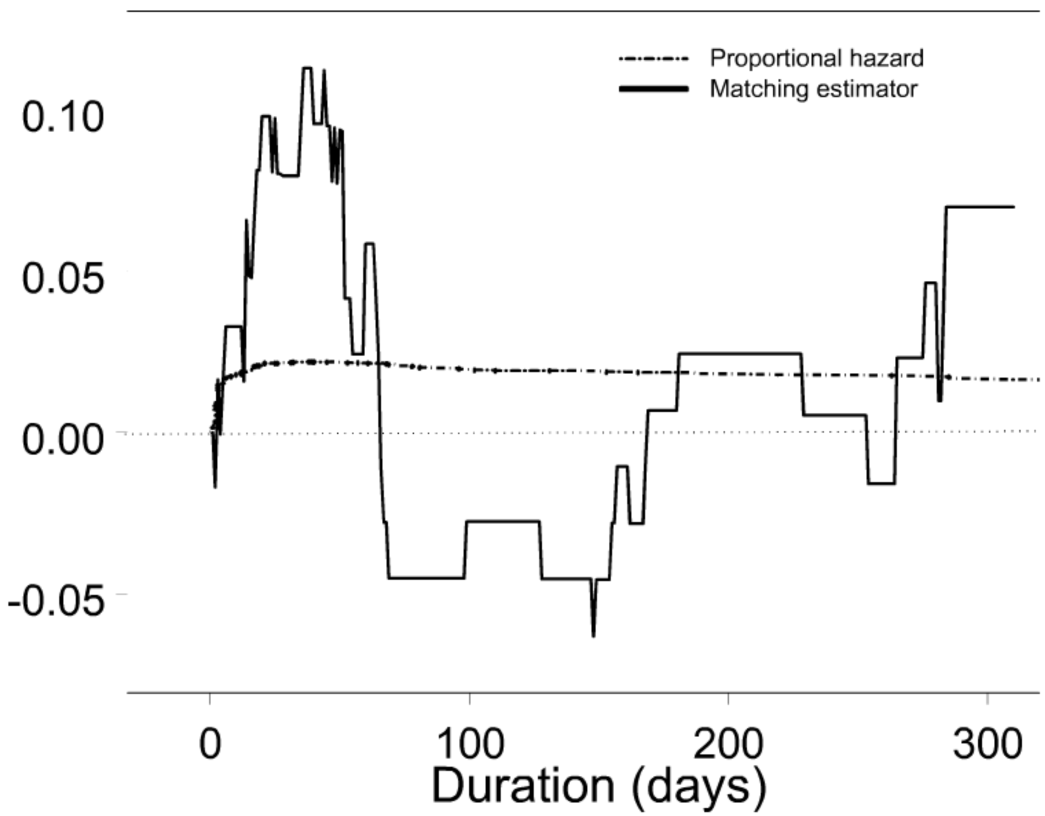
Averaging over waiting times

When few observations, you cannot perform inference conditional on W.

Then, we can average over the observed waiting times.
However: Interpretation of survival functions problematic.
Inference problematic unless few treated and many controls.

Heart transplant program

Estimating $F^1 - F^0$:



Employment subsidy program

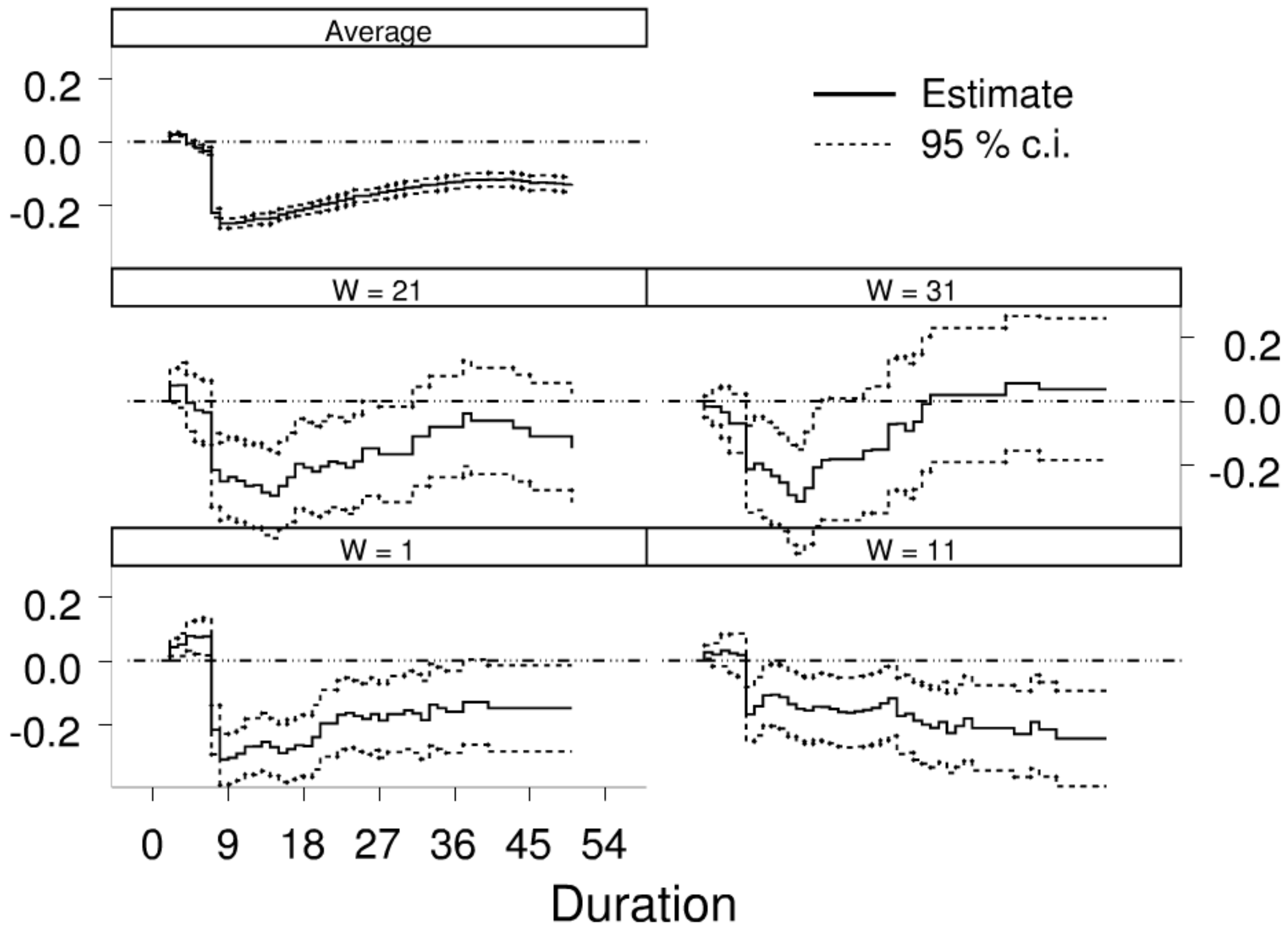
Forslund, Johansson and Lindqvist (2004)

- Treatment: employment subsidy for the long-term unemployed –50% of total wage costs is paid for 6 months
- Response: Unemployment duration (time to employment)
- covariates: age,sex,"disability",citizenship,education,unemployment history

- Eligible: at least 25, registered unemployed at least 12 months in a row
- Register data: 98-02; 631,358 eligible, 3% ended into program; 40% ended in employment
- 630,000 eligible; after matching: 7,651 individuals left

Exact one-to-one matching

Estimating $F^1 - F^0$:



Some concluding remarks

- Causal inference in observational studies: Protocols defining population, treatment assignment and control group

- With population wide registers:
  - Sample is population
  - Large control groups and rich set of background characteristics allow for good designs

Some references

de Luna, X & Johansson P (2010) Non-parametric inference for the effect of a treatment on survival times with application in the health and social sciences, *Journal of Statistical Planning and Inference* 140, 2122-2137. Erratum in same journal 2012.

Neyman J (1990) On the application of probability theory to agricultural experiments. Essay on principles Translated by D.M. Dabrowska and edited by T.P. Speed *Statistical Science*, 5, pp. 465–472. Original text from 1923.

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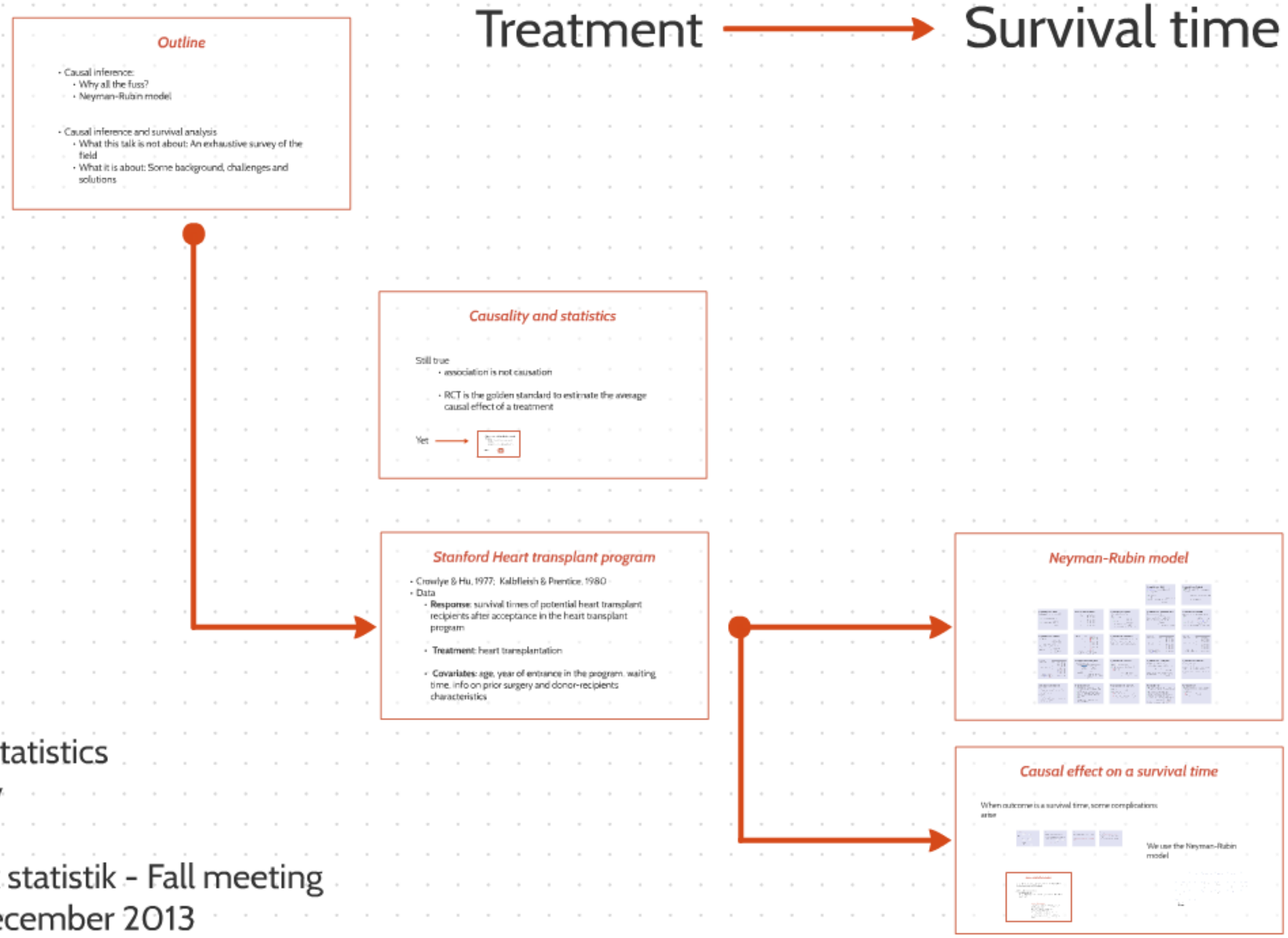

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