

Session 2.2

Clone-censor-weighting approach

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Returning to simple example of immortal time bias

Comparing mortality between:

- long-term users of a medication (2+ years)
- short-term users of a medication (<1 year)
- non-users



The randomized trial solution

In randomized trials with full adherence:

- People classified by **assigned** treatment duration
- Not by **observed** treatment duration
 - People might not achieve the full treatment duration because they die! (Or because they have health problems that puts them more at risk for whatever you're looking at, which is also a problem)
- Dead people don't deviate from assigned strategy

Hernán (2018) example: randomized trial

12 people randomly assigned to:

- $\text{durA} = 0$: no aspirin
- $\text{durA} = 1$: one year of aspirin
- $\text{durA} = 2$: two years of aspirin

Because this is a randomized trial, we have the assignment labels

Person	durA	Aspirin year 1	Dead end year 1	Aspirin year 2	Dead end year 2
1	0	No	No	No	No
2	0	No	No	No	Yes
3	0	No	No	No	Yes
4	0	No	Yes	-	Yes
5	1	Yes	No	No	No
6	1	Yes	No	No	Yes
7	1	Yes	No	No	Yes
8	1	Yes	Yes	-	Yes
9	2	Yes	No	Yes	No
10	2	Yes	No	Yes	Yes
11	2	Yes	No	Yes	Yes
12	2	Yes	Yes	-	Yes

By assigned treatment

Two-year mortality by assigned treatment duration:

Assigned duration	N	Deaths at 2 years	Mortality risk
0	4	3	0.75
1	4	3	0.75
2	4	3	0.75

No effects (again operating under the null!)

Moving to observational data

In observational data, we don't observe `durA` (assigned treatment duration)

We only see:

- what treatment people actually received
- when they received it
- when they died

By achieved treatment

Compare those who **actually** took aspirin for 2 years:

Person	durA	Aspirin year 1	Dead end year 1	Aspirin year 2	Dead end year 2
9	2	Yes	No	Yes	No
10	2	Yes	No	Yes	Yes
11	2	Yes	No	Yes	Yes

Risk of death after 2 years = $2/3$

By achieved treatment

To those who **actually** took it for 1 year:

Person	durA	Aspirin year 1	Dead end year 1	Aspirin year 2	Dead end year 2
5	1	Yes	No	No	No
6	1	Yes	No	No	Yes
7	1	Yes	No	No	Yes
8	1	Yes	Yes	-	Yes
12	2	Yes	Yes	-	Yes

Risk of death after 2 years = 4/5

By achieved treatment

To those who took it for 0 years:

Person	durA	Aspirin year 1	Dead end year 1	Aspirin year 2	Dead end year 2
1	0	No	No	No	No
2	0	No	No	No	Yes
3	0	No	No	No	Yes
4	0	No	Yes	-	Yes

Risk of death after 2 years = $3/4$

Why the bias occurs

People who achieved 2 years of treatment:

- had to survive the first year (immortal time)
- are a selected subset of those assigned to 2 years

The naive analysis treats survival to 2 years as if it were irrelevant to the outcome **when it is in fact the outcome**

The three-step solution

- **Step 1: cloning** - assign people to treatment strategies at time zero (when they meet eligibility criteria)
- **Step 2: censoring** - censor clones when they deviate from assigned strategy (in this case, they stop taking aspirin while still alive but before they were supposed to)
- **Step 3: weighting** - adjust for selection bias from censoring

Step 1: cloning

For each person, create clones for all treatment strategies compatible with their observed data at time zero

scenario	person	durA	aspirin_year1
Observed	5	?	Yes
Assigned to 1 year	5a	1	Yes
Assigned to 2 years	5b	2	Yes

Person 5 received treatment at time zero → gets cloned to both $\text{durA} = 1$ and $\text{durA} = 2$

Cloning all participants

Clone	durA	Aspirin year 1	Dead end year 1	Aspirin year 2	Dead end year 2
1	0	No	No	No	No
2	0	No	No	No	Yes
3	0	No	No	No	Yes
4	0	No	Yes	-	Yes
5a	1	Yes	No	No	No
6a	1	Yes	No	No	Yes
7a	1	Yes	No	No	Yes
8a	1	Yes	Yes	-	Yes
9a	1	Yes	No	Yes	No
10a	1	Yes	No	Yes	Yes
11a	1	Yes	No	Yes	Yes

Clone	durA	Aspirin year 1	Dead end year 1	Aspirin year 2	Dead end year 2
12a	1	Yes	Yes	-	Yes
5b	2	Yes	No	No	No
6b	2	Yes	No	No	Yes
7b	2	Yes	No	No	Yes
8b	2	Yes	Yes	-	Yes
9b	2	Yes	No	Yes	No
10b	2	Yes	No	Yes	Yes
11b	2	Yes	No	Yes	Yes
12b	2	Yes	Yes	-	Yes

Step 2: censoring

Censor clones when their observed data becomes incompatible with assigned strategy:

- $\text{durA} = 1$ clones censored if they take aspirin in year 2
- $\text{durA} = 2$ clones censored if they *don't* take aspirin in year 2



Note that we could have cloned ids 5-12 to $\text{durA} = 0$ and “censored” them immediately, and cloned ids 1-4 to $\text{durA} = 1$ and $\text{durA} = 2$ and “censored” them immediately.

Censoring

Clone	durA	Aspirin year 2 (observed)	Aspirin year 2 (required)	Censored?
9a	1	Yes	No	Yes
10a	1	Yes	No	Yes
11a	1	Yes	No	Yes
9b	2	Yes	Yes	No
10b	2	Yes	Yes	No
11b	2	Yes	Yes	No

Clones 9a, 10a, 11a are censored because they didn't adhere to their assigned strategy



In this example, no one started aspirin after not taking it in year 1, but that would be another reason for censoring

After censoring

Clone	durA	Aspirin year 1	Dead end year 1	Aspirin year 2	Dead end year 2
1	0	No	No	No	No
2	0	No	No	No	Yes
3	0	No	No	No	Yes
4	0	No	Yes	-	Yes
5a	1	Yes	No	No	No
6a	1	Yes	No	No	Yes
7a	1	Yes	No	No	Yes
8a	1	Yes	Yes	-	Yes
12a	1	Yes	Yes	-	Yes
8b	2	Yes	Yes	-	Yes
9b	2	Yes	No	Yes	No

Clone	durA	Aspirin year 1	Dead end year 1	Aspirin year 2	Dead end year 2
10b	2	Yes	No	Yes	Yes
11b	2	Yes	No	Yes	Yes
12b	2	Yes	Yes	-	Yes

Step 3: weighting

Selection bias introduced by censoring must be corrected

Use **inverse probability weighting**:

Calculating weights

For $\text{durA} = 0$ strategy:

- No one was censored $\rightarrow$ everyone has weight = 1

Calculating weights

For $\text{durA} = 1$ strategy:

- Persons 8 and 12 died before they had the “opportunity” to be censored $\rightarrow$ weight = 1
 - We’re really only calculating weights for year 2
- In year 2, persons 9, 10, and 11 were censored and persons 5, 6, and 7 were uncensored
 - Probability of being uncensored = $3/6 = 0.5 \rightarrow$ weight = 2 for persons 5, 6, and 7

Calculating weights

For $\text{durA} = 2$ strategy:

- Persons 8 and 12 died before they had the “opportunity” to be censored $\rightarrow$ weight = 1
- In year 2, persons 5, 6, and 7 were censored and persons 9, 10, and 11 were uncensored
 - Probability of being uncensored = $3/6 = 0.5 \rightarrow$ weight = 2 for persons 9, 10, and 11

Weighted data

Clone	durA	Aspirin year 1	Dead end year 1	Aspirin year 2	Dead end year 2	Weight
1	0	No	No	No	No	1
2	0	No	No	No	Yes	1
3	0	No	No	No	Yes	1
4	0	No	Yes	-	Yes	1
5a	1	Yes	No	No	No	2
6a	1	Yes	No	No	Yes	2
7a	1	Yes	No	No	Yes	2
8a	1	Yes	Yes	-	Yes	1
12a	1	Yes	Yes	-	Yes	1
8b	2	Yes	Yes	-	Yes	1
9b	2	Yes	No	Yes	No	2

Clone	durA	Aspirin year 1	Dead end year 1	Aspirin year 2	Dead end year 2	Weight
10b	2	Yes	No	Yes	Yes	2
11b	2	Yes	No	Yes	Yes	2
12b	2	Yes	Yes	-	Yes	1

Weighted analysis

Treatment duration	Weighted N	Weighted deaths	Mortality risk
0	4	3	0.75
1	8	6	0.75
2	8	6	0.75

Yay!

Why it works

The three steps:

1. **Cloning** eliminates immortal time bias by assigning strategies at time zero
2. **Censoring** ensures clones follow their assigned strategy
3. **Weighting** corrects for selection bias introduced by censoring

Extensions

This approach can handle:

- multiple time points
- time-varying confounding
- loss to follow-up
- complex sustained treatment strategies

Additional inverse probability weighting may be needed for baseline confounding adjustment

When to use clone-censor-weighting

Use when studying:

- treatment duration effects
- sustained treatment strategies that evolve over time
- any strategy where assignment isn't identifiable at time zero

Alternative: g-formula

Key assumptions

Validity requires:

- No unmeasured confounding (of baseline treatment and treatment continuation/discontinuation/changes)
- Correct specification of treatment/censoring models
- Positivity (some probability of continuing the treatment strategy – being uncensored – at each time)

Hernán, Miguel A. 2018. “How to Estimate the Effect of Treatment Duration on Survival Outcomes Using Observational Data.” *BMJ* 360 (February): k182.
<https://doi.org/10.1136/bmj.k182>.