Causal estimands for aging-relevant outcomes in the presence of death as a competing or truncating event

UCLA Fielding School of Public Health

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Part I: Time-to-event outcomes with death as a competing event

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Part I: Time-to-event outcomes with death as a competing event

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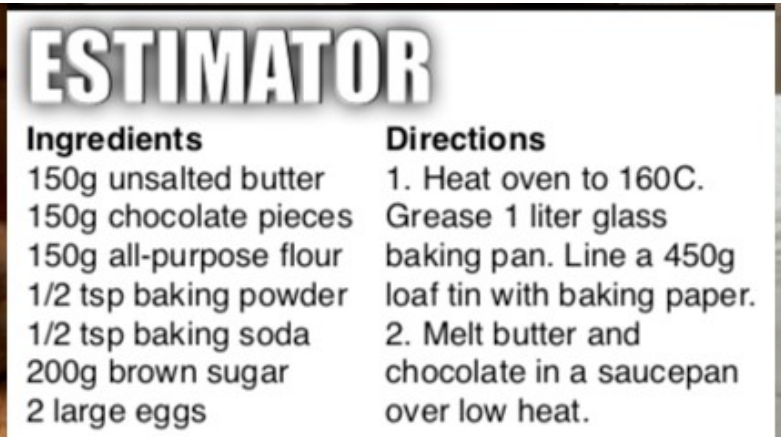
Estimand



Specific quantity that we want to estimate that answers our research question (*parameter of interest*).

Causal estimands have 5 elements

- Target population
- Exposure/Treatment arms
- Outcome: within a time frame
- Summary measure: A population-level measure of frequency that is *interpretable*
- Intercurrent events: Events that will prevent us from observing the exposure or outcome

The estimands framework: a primer on the ICH E9(R1) addendum

Motivating example

1. Target population: Older adults who smoke, with no cardiovascular or lung comorbidities
2. Exposure/Treatment arms (A): Smoking cessation program vs. no intervention
3. Outcome (Y): Dementia diagnosis over 12 years
4. Summary measure:

$$Pr[Y_{12}^{a=1} = 1] - Pr[Y_{12}^{a=0} = 1]$$

5. Intercurrent events: not present

Ideal trial

- Study sample is a random sample from the target population
- Starting point (baseline) is the same for all participants
- Defined observation period at risk
- Perfect randomization and adherence
- Complete follow-up over the observation period
- New (incident) cases only

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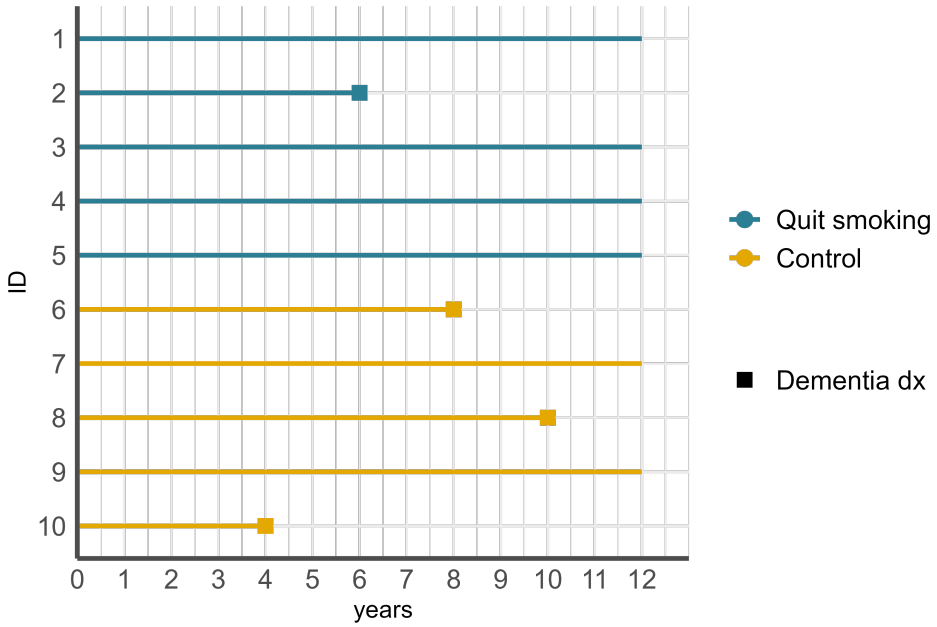


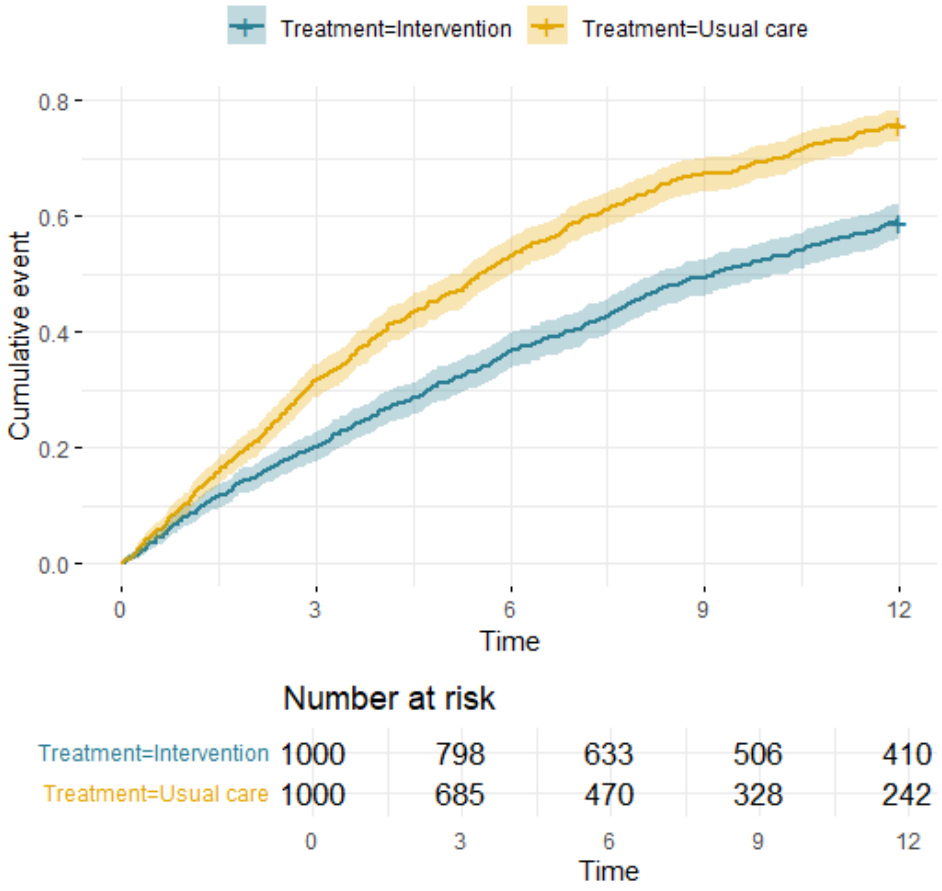
Risk / Incidence proportion

- The probability of having an incident event, Y, in a **fixed period of time** , k
- $Pr[Y_k = 1]$ = N/T, where:
  - N = people experiencing the event
  - T = people free of event at start of follow-up

Treatment	Dementia diagnosis at 12 years
Quit smoking	10%
Continued smoking	30%

Cumulative incidence

- In the ideal scenario (no drop out)
- $Pr[T \leq t]$, where:
  - T = time to event
  - t = specific time point of interest
- At baseline, cumulative incidence is 0, $Pr[T \leq 0] = 0$
- Increases monotonically (or remains constant)



Censoring

- By design, we want to prevent participant's drop out
- But in real-world data, people are loss to follow-up and drop out during the study period
- *A censoring event* makes the event of interest *unknown* at all future time points
- Censoring is the *key* feature of time-to-event analysis

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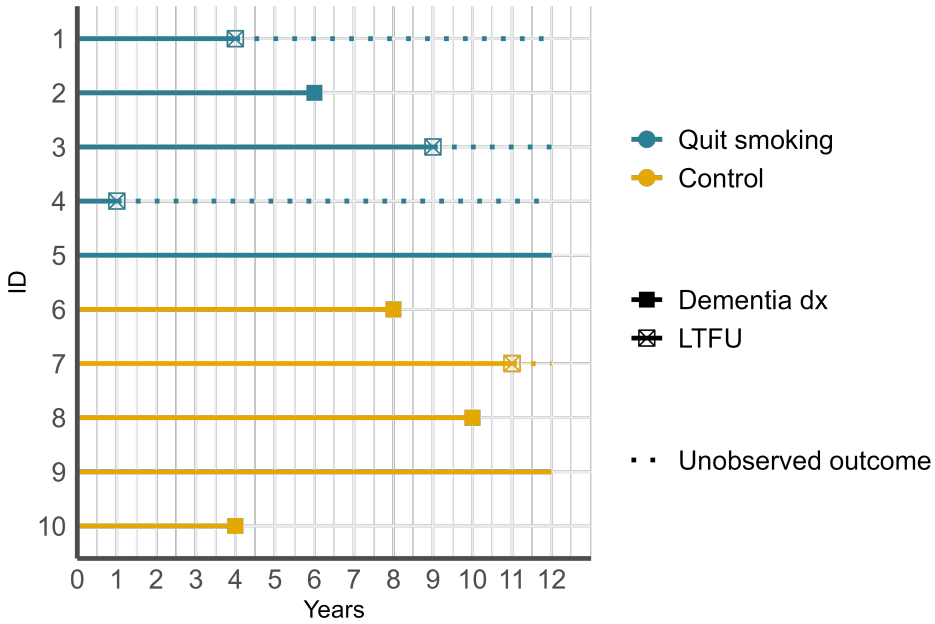

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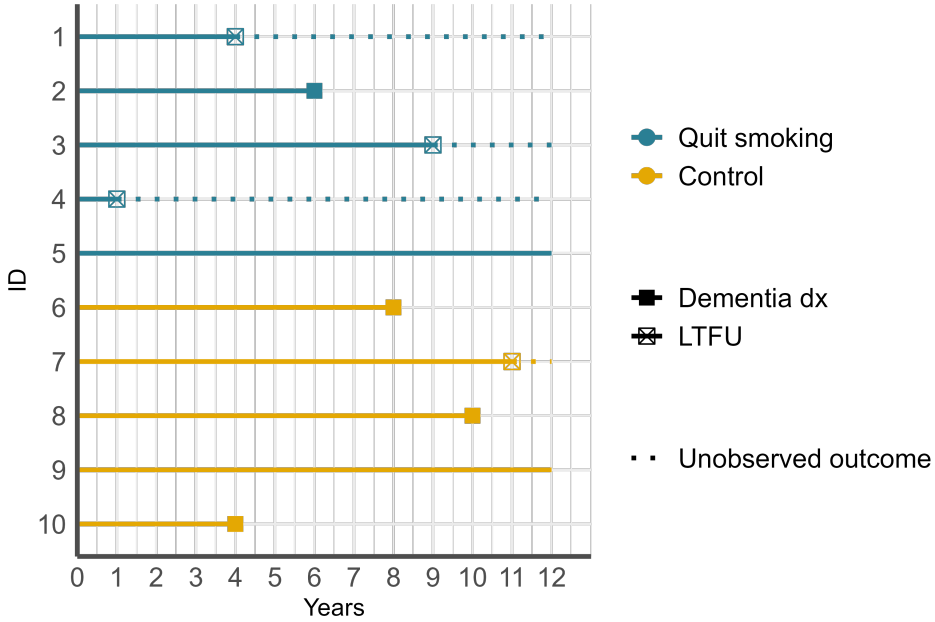
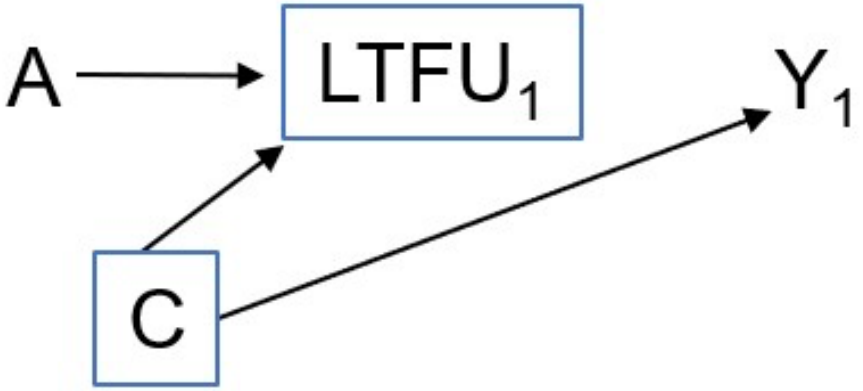


- *Time of end of study* is often defined as *administrative censoring* but I will refrain from using this jargon for now

Implications of censoring

- In statistics, censoring events are:
  - are independent of the outcome
- In causal literature
  - Counterfactual where LTFU was prevented
  - $Pr[Y_{k+1}] = Pr[Y_{k+1}^{\overline{\text{LTFU}}=0}]$
  - $Pr[Y_{k+1}^{a=1,\overline{\text{LTFU}}=0}]$ - $Pr[Y_{k+1}^{a=0,\overline{\text{LTFU}}=0}]$



C: Shared risk factors

Incidence rates

Frequency with which incident events occur within a given amount of follow-up time.
N/PT
where:

- N = Number of incident cases
- PT = "Person-time", total amount of time that all individuals were at risk of the outcome

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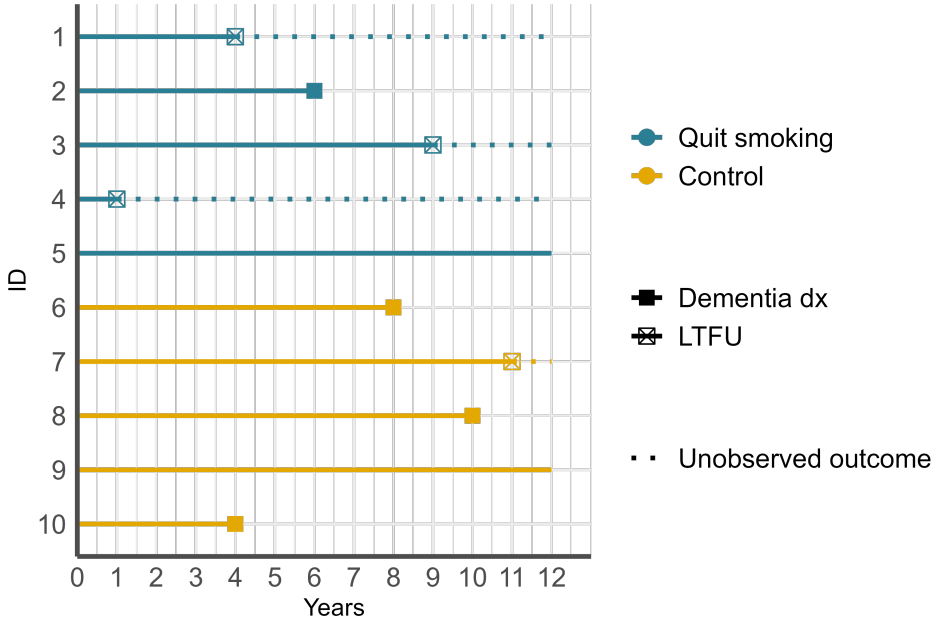

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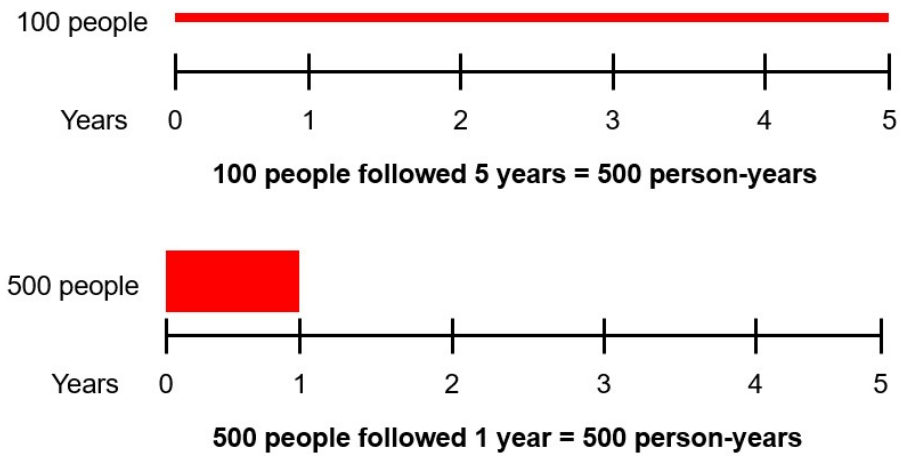
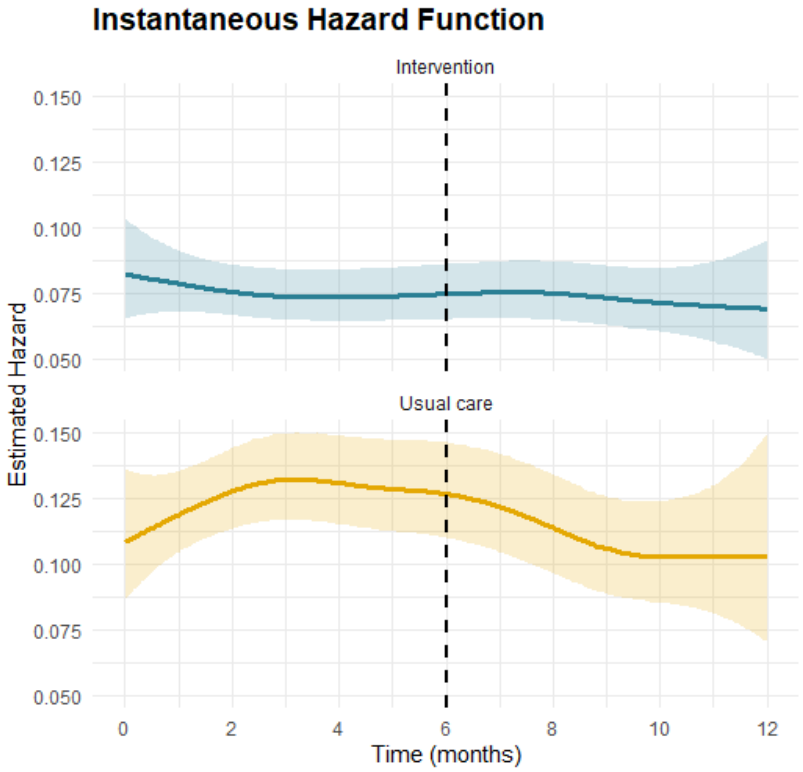
Comparison of incidence rates across groups is tricky



Hazards

- At any given time, the probability of experiencing the event of interest, Y, in the next interval among individuals who had not yet experienced the event by the start of the interval
- **Discrete hazards**
  - $Pr[T = t | T > t - 1]$
  - $Pr[Y_k = 1 | Y_{k-1} = 0]$
- They can rise, fall, or vary non-monotonically across time points



Hazard ratios (HR)

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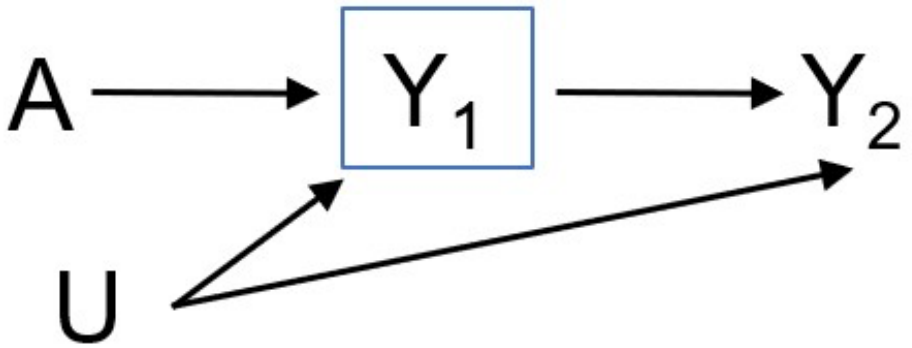
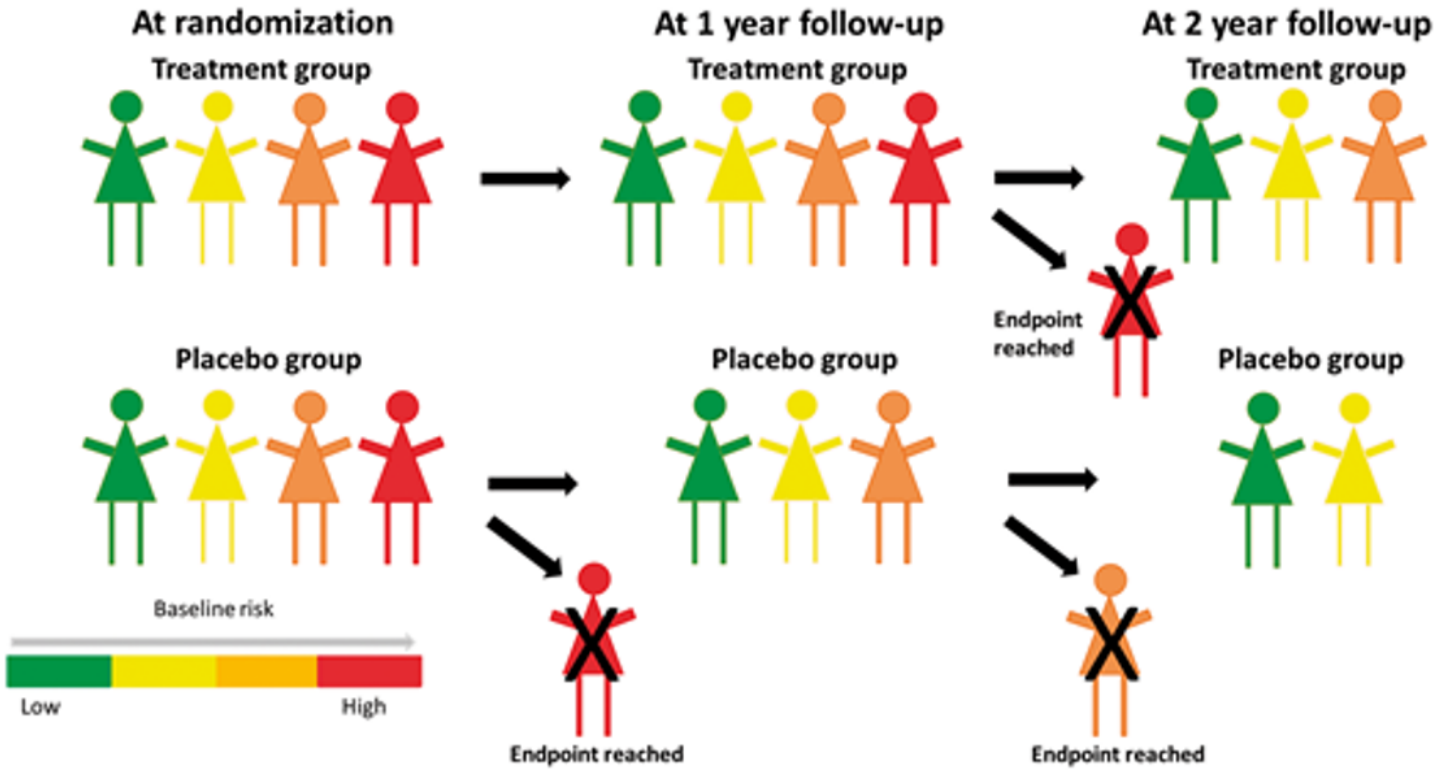
- Hazard ratios have an inherent issue of selection bias
- The proportional hazard assumption is often unrealistic
  - If treatment effects change over time
  - If outcome susceptibility varies between individuals



Dumas E, Stensrud M. EJE. 2025

The hazard of hazard ratios



Stensrud. European Heart Journal. 2019

Causal estimands

- Contrast of (counterfactual) outcome distributions in the **same individuals** but under **different levels of exposure**

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Measure	Numerator	Denominator
Risk	Events over fixed period	Individuals at baseline
Rate	Events over person-time	Total person-time at risk
Hazard	Events in next interval	Individuals at start of interval

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- Risks are the most intuitive causal contrast, and when censoring is present we can use hazards to calculate risks

From hazard to risks

- Hazard models are useful to estimate risks when censoring is present
- In **discrete time**, the risk at time $k+1$ is the conditional probability of dementia in year $k+1$ × cumulative probability of surviving dementia-free up to the previous time point k

$$\Pr[Y_{k+1} = 1] = \left(\prod_{j=1}^{k} (1 - h_j) \right) \cdot h_{k+1}$$

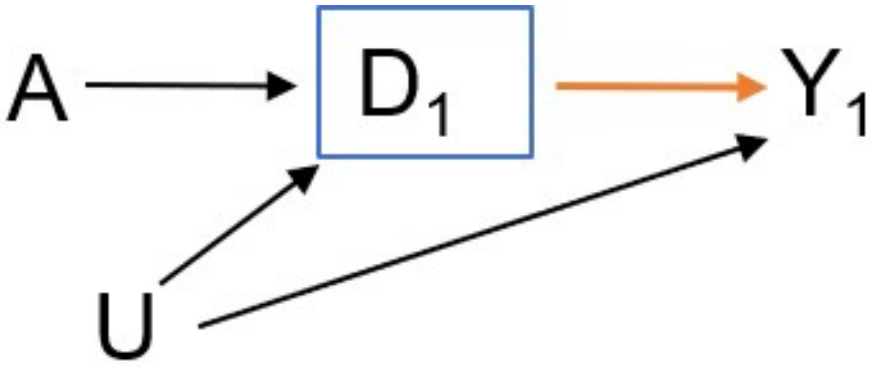
Where

$$h_j = \Pr[Y_j = 1 \mid Y_{j-1} = 0]$$

Competing events

- Events that *preclude** the outcome of interest.

  *to prevent the existence, or occurrence of; make impossible



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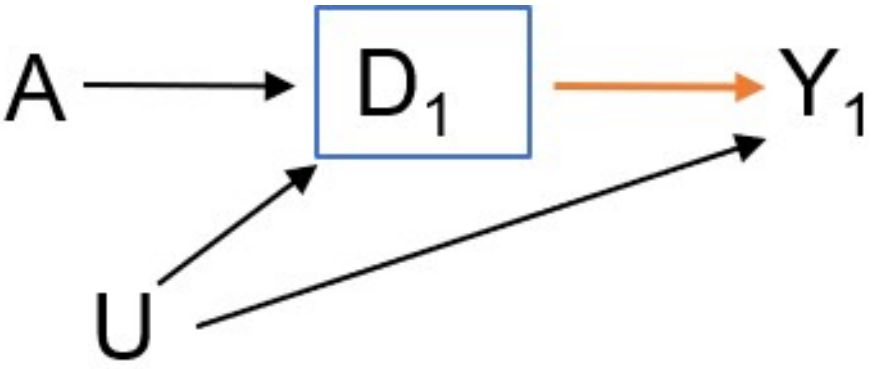
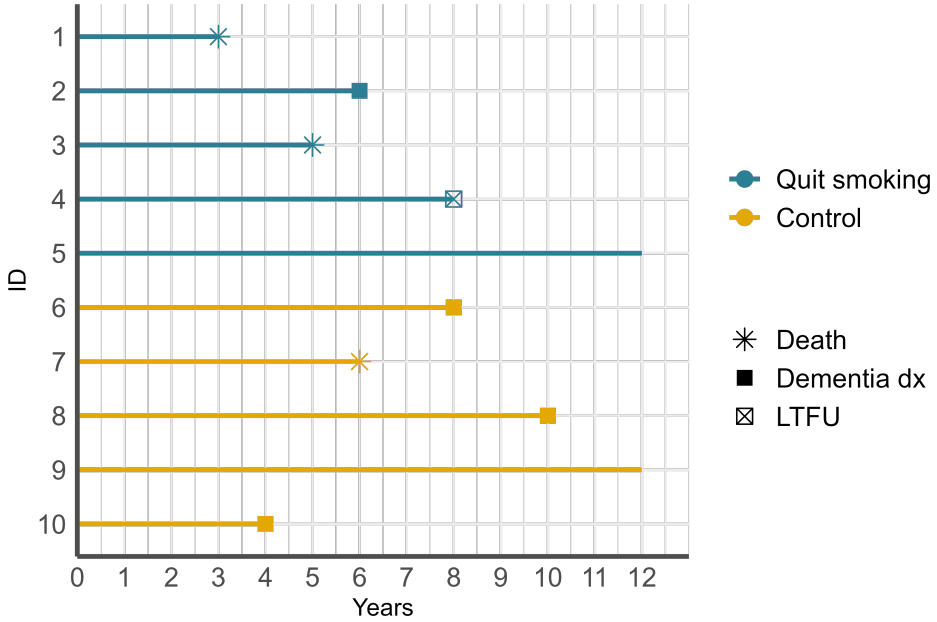
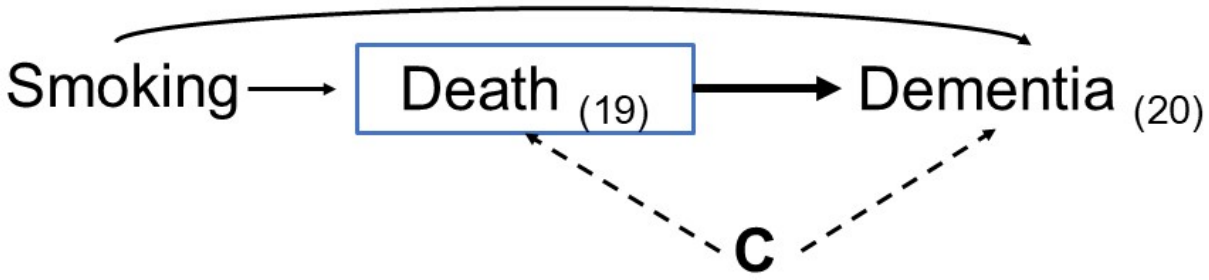




Quitting smoking and 20-year dementia risk



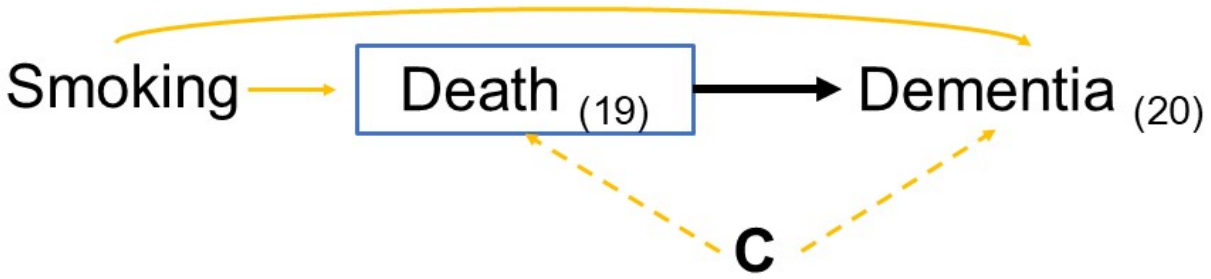
C: Shared risk factors

Rojas-Saunero. AJE. 2023

Total effect

What is the risk** of dementia at 20 years of follow-up had all individuals stopped smoking, compared to had all individuals continued smoking?

$$Pr[Y_{20}^{a=1} = 1] - Pr[Y_{20}^{a=0} = 1]$$

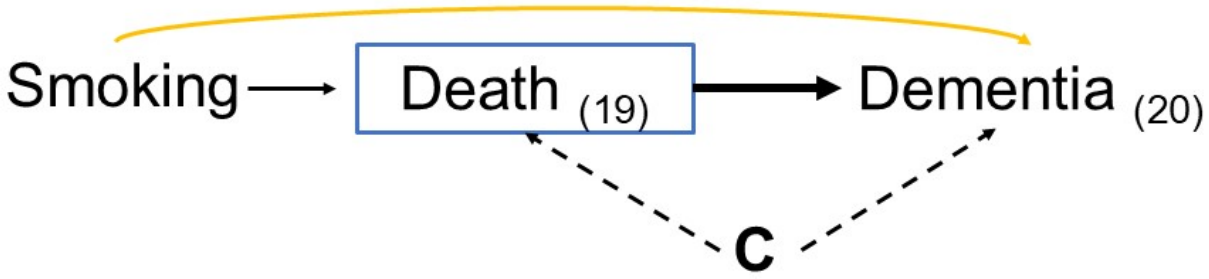


** *Cause-specific cumulative incidence* or *crude* risk

Controlled direct effect

What is the risk** of dementia at 20 years of follow-up had all individuals stopped smoking *and not died* during the study period, compared to had all individuals continued smoking *and not died* ?

$$Pr[Y_{20}^{a=1,d_{19}=0} = 1] - Pr[Y_{20}^{a=0,d_{19}=0} = 1]$$



** *Marginal* or *net* risk

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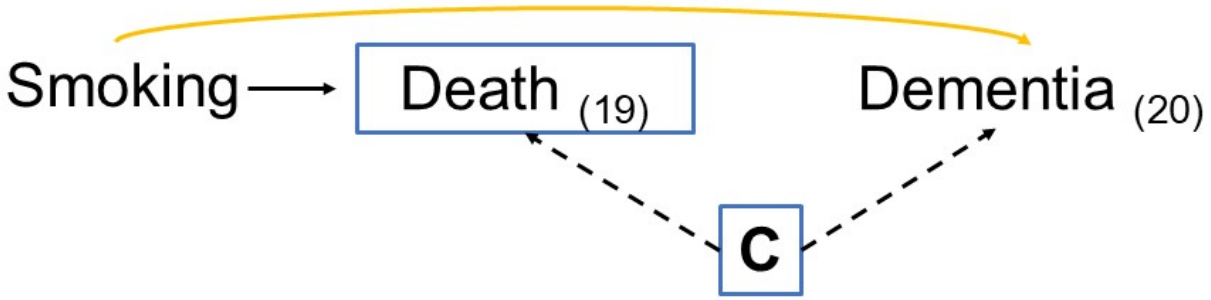
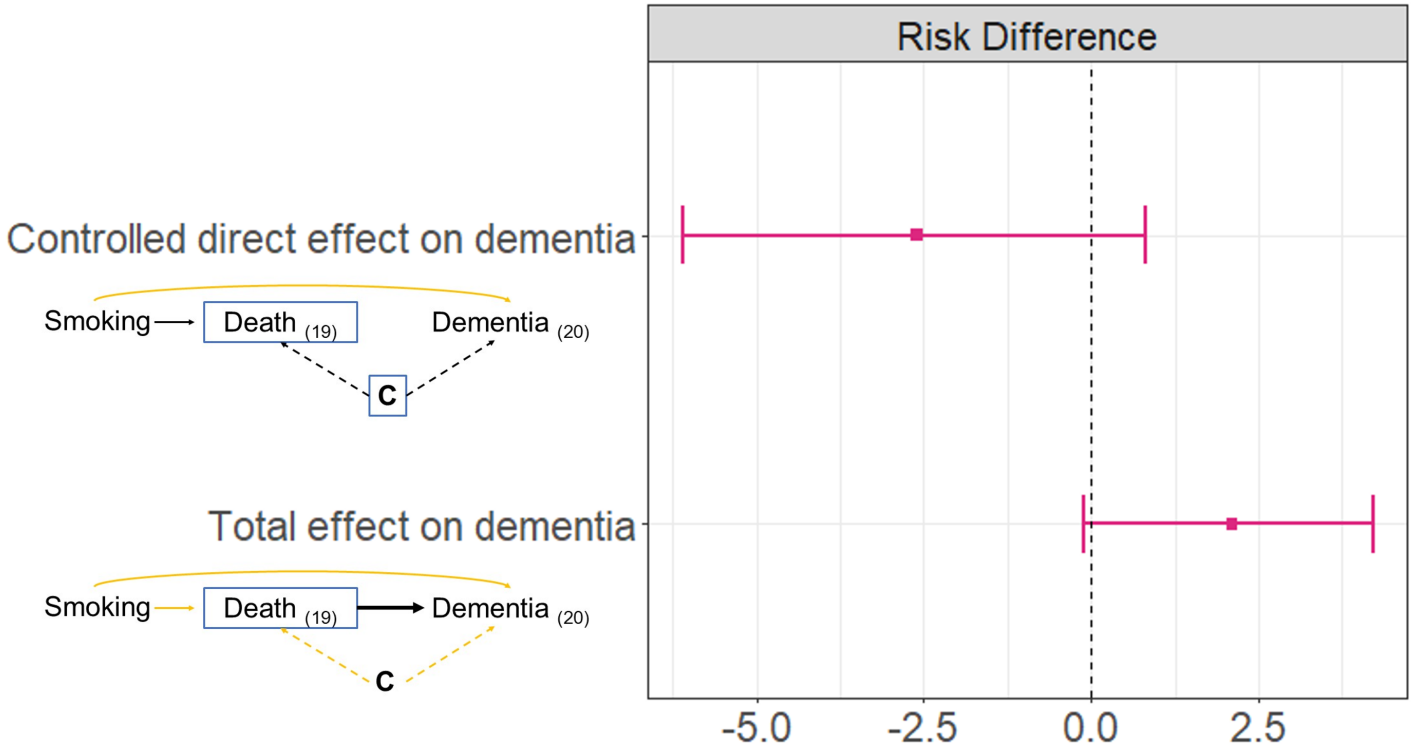


** *Marginal* or *net* risk

Quitting smoking on dementia risk at 20 years



Rojas-Saunero. AJE. 2023

Identifiability assumptions for death

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Assumption	Total Effect	Controlled direct effect
Exchangeability	Not needed	Death is independent of future outcomes had everyone followed A = a and death was eliminated, conditional on covariates

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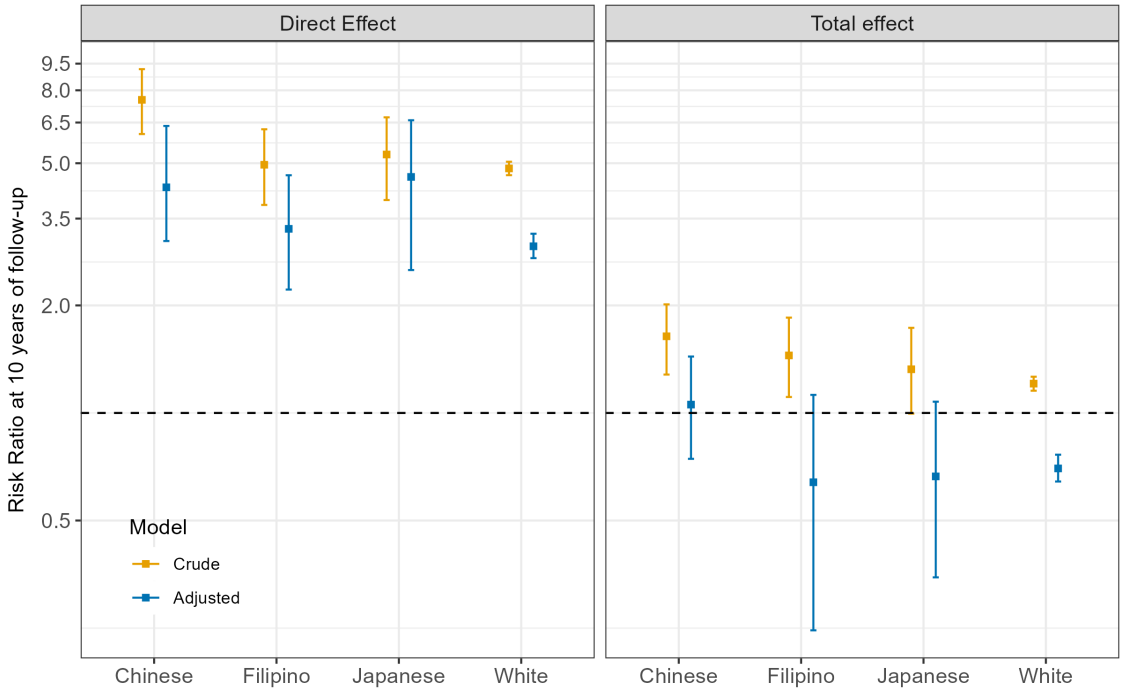
Positivity	Not needed	At every follow-up time, there are individuals with any possibly observed level A = a and covariate history who remain alive and free of dementia diagnosis.
Consistency	Not needed	An intervention that “eliminates death” is well-defined.

Estimators

Feature	Total Effect	Controlled Direct Effect
Estimator	Aalen–Johansen	Kaplan–Meier
Death handling	Competing event	Censoring event
Hazards needed	Dementia + death	Dementia only
Risks	Risk of dementia = conditional risk of dementia in year t × cumulative probability of surviving dementia-free and death-free up to t–1	Risk of dementia = conditional risk of dementia in year t × cumulative probability of surviving dementia-free up to t–1

Young et al. Statistics in Medicine. 2020

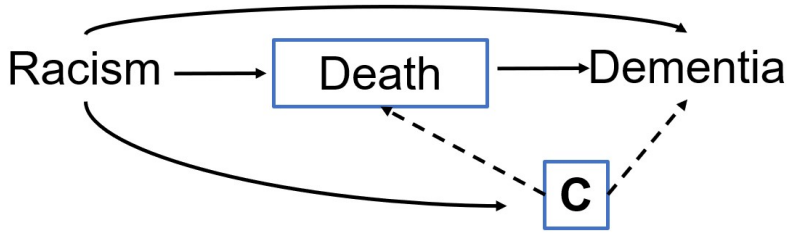
Incident stroke on dementia risk in Asian American and White population in California



Rojas-Saunero et al. Neurology. 2025

Why this matters in health disparities research

- Mortality rates are often higher for marginalized populations
- Disparity estimands for dementia risk will be impacted by differential mortality
- We can either allow the disparity effect measure to be impacted by the effect of death or we can try to imagine an scenario were death does



Rojas-Saunero et al. Current Epidemiology Reports. 2024

Other possible estimands

- **Composite outcome**

$$Pr[Y_t^{a=1} = 1 \text{ or } D_t^{a=1} = 1] - Pr[Y_t^{a=0} = 1 \text{ or } D_t^{a=1} = 1]$$

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- **Survivors average causal effect:**

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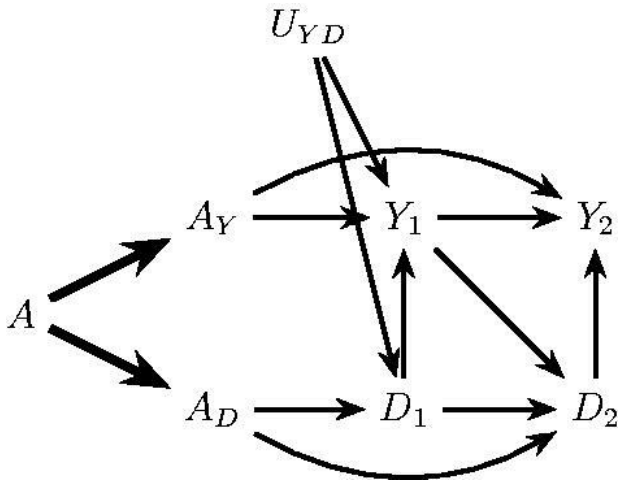
- **Natural direct effects**:

$$Pr[Y_t^{a=1,\bar{D}_t^{a=0}} = 1] - Pr[Y_t^{a=0,\bar{D}_t^{a=0}} = 1]$$

Separable effects

Physical decomposition of the exposure assumed to operate on Y and D through separate pathways. (*Stensrud et al. JASA. 2020*)



Take away points

- When competing events are present there is more than one way to consider them as part of the primary research question

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Take away points

- When competing events are present there is more than one way to consider them as part of the primary research question
- Let the question guide the most appropriate methods and estimators
- We need to communicate that all these questions are possible with their trade-offs, rather than continuing a narrative that "One size fits all"

Recomended readings

- How hazard ratios can mislead and why it matters in practice
- Transplant as a competing risk in the analysis of dialysis patients
- A comparison of different methods to adjust survival curves for confounders
- Considering Questions Before Methods in Dementia Research With Competing Events and Causal Goals
- A causal framework for classical statistical estimands in failure-time settings with competing events

Thank you! Gracias!

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Supplementary slides

Competing events & estimands, *Young 2020*

Definition	Description	Statistical Literat
$\Pr[Y_{k+1}^{\bar{d}=\bar{0}} = 1]$	Risk under elimination of competing events	Marginal cumulative inc
$\Pr[Y_{k+1} = 1]$	Risk without elimination of competing events	Subdistribution functio cumulative incidence, c
$\Pr[Y_{k+1}^{\bar{d}=\bar{0}} = 1 \mid Y_k^{\bar{d}=\bar{0}} = 0]$	Hazard under elimination of competing events	Marginal hazard
$\Pr[Y_{k+1} = 1 \mid Y_k = 0]$	Hazard without elimination of competing events	Subdistribution hazard
$\Pr[Y_{k+1} = 1 \mid D_{k+1} = Y_k = 0]$	Hazard conditioned on competing events	Cause-specific hazard

Bounds for the controlled direct effect

Bounds for the controlled direct effect

- Lower bound: All those who died would not have had dementia
  - Cause-specific cumulative risk contrast
- Upper bound: Everyone who died would have had dementia around the same time of death
  - Risk for the composite outcome for dementia and death contrast

Peterson. *PNAS*. 1976; van Geloven. *Statistics in Medicine*. 2014