Statistical Analyses Addressing Competing Risks in Alzheimer Disease Research

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Outline

- Background
  - Survival analysis and competing risks
  - Competing risks in Alzheimer Diseases (AD) research
- A case study: estimating the effect of smoking on MCI or dementia (CDR $\geq$ 0.5)
- Conclusions

Background
survival analysis

- Failure time: the time between the start of follow up and the occurrence of an event.
- Goals:
  - Identify factors associated with the occurrence of AD.
  - Estimate the probability of the occurrence of AD during the follow-up period.

Background

quantities of interest in survival analysis

- Survival function $S(t)$ describes the probability of an event beyond time t.
- Hazard function $h(t)$ describes the instantaneous risk for an event in the interval $[t, t + dt)$ provided survival up to time t.
- One-to-one relationship between survival and cumulative hazard

$$S(t) = exp\{-H(t)\} = exp\left\{-\int_0^t h(u)du\right\}$$

Background

censoring

- Right censoring: the event time of interest is only known to occur after a certain time point.
- Noninformative censoring: the reason for withdrawing from the study is unrelated to the prognosis.
- Informative censoring: the reason for withdrawing from the study is related to the expected failure time.

Background
models for survival data

- The Kaplan-Meier method (or the product-limit method) is used to estimate a population survival function $S(t)$ from a sample.

Background

models for survival data

- Cox proportional hazards (PH) model

$$h_i(t; Z) = h_0 \exp\{\beta^T Z_i\}$$

where $h_0(t)$ is baseline hazards for $Z_i = 0$

- We are interested in estimating hazard ratio, exp(β).
- "Individuals who were APOE*4 carriers had 2 fold increased risk of developing AD compared to those who were not APOE*4 carriers."

Background

competing risks

- The event of interest (e.g., AD) is the main event; others are competing risks.
- A competing event prevents the occurrence of the main event; not just prevents the observation of the main event.
- Note: for censoring, the main event might occur at a later time but it cannot be observed.

Background

competing risks - complications

- The relationship between survival and cumulative hazard is no longer one-to-one.
    - The Kaplan-Meier estimate is biased.
    - The way in which covariates are associated with the cause-specific hazards may not coincide with the way these covariates are associated with the cumulative incidence.

Background

competing risks regression model

- Cumulative incidence function (CIF) $F_j(t)$ is defined as the probability of an event of type j has occurred by time t
- CIF describes the probability that nothing happens the first 5 years, but when something does happen, it is AD, not death.
- Fine and Gray regression model models the hazard corresponding to the CIF

Background

competing risks in AD research

- Elderly are subject to certain risks, including dementia and death of various causes (e.g., cancer, heart failure). Death is a major competing risk for AD in elder population
- Subjects have lived long enough to enter the age of risk for developing AD.
- When examining the effect of risk factors, e.g. smoking, cholesterol, blood pressure, and body mass index (BMI) on incident AD, fail to take deaths into consideration may lead to biased results.

Competing risks in AD research

effect of smoking on AD

- Challenges in Statistical Modelling: the usual survival regression model assumes that an individual being "censored" due to death is unrelated to the probability of developing AD.
- What if individuals who die before developing AD are younger and include a higher percentage of smokers?
- Smokers have higher mortality rate than nonsmokers and only "healthier" smokers survived beyond certain age.

A case study
objectives

- Comparing the estimated effect of smoking on MCI or dementia ("the main event") between treating mortality/death as
  - noninformative censoring
  - competing risks

A case study
study population

- A completed population-based cohort, Monongahela Valley Independent Elders Survey (MoVIES), followed biennially between 1987- 2002.
  - The analytic sample contains 1242 participants at baseline.
  - Aged 65 years or older
  - The majority were women (≈ 61%) and white (≈97%)

A case study
statistical models

- Outcome variables:
  - MCI or dementia: a CDR value of ≥ 0.5
  - Mortality
- Predictor variables:
  - Main variable of interest: lifetime smokers (or ever having smoked regularly) versus nonsmoker
  - Demographic variables: age, sex, and education
  - Potential confounders: depression, APOE*4 carrier status, etc.
- Analyses were stratified by age groups: 65 to 74 years (n=751) and 75 years or above (n=491).

A case study
statistical models

Models not adjusting for competing risks

- Regular Cox proportional hazard model
- Mortality was treated as "censored"

Models adjusting for competing risks

- Fine and Gray (FG) proportional subdistribution hazard model

A case study
statistical models

Models not adjusting for competing risks

- Regular Cox proportional hazard model
- Mortality was treated as "censored"

Models adjusting for competing risks

- Fine and Gray (FG) proportional subdistribution hazard model
- Assume that those who died without developing MCI or dementia would never experience the event had they lived the follow-up period

A case study
statistical models

Models not adjusting for competing risks

- Regular Cox proportional hazard model
- Mortality was treated as "censored"

Models adjusting for competing risks

- **Modified** Fine and Gray (FG) proportional subdistribution hazard model
- Incorporate the probability of experiencing the event among those who died had they survived the entire follow-up period using **propensity models.**

A case study

construction of the propensity model

- Fitting a logistic model with potential risk factors (smoking, age, sex, and education) as covariates
  - "event outcome": developed MCI or dementia during the follow-up period
  - "nonevent outcome": remained alive and free of MCI or dementia until the end of the study
- Each individual was then assigned a propensity score by calculating his/her estimated probability.

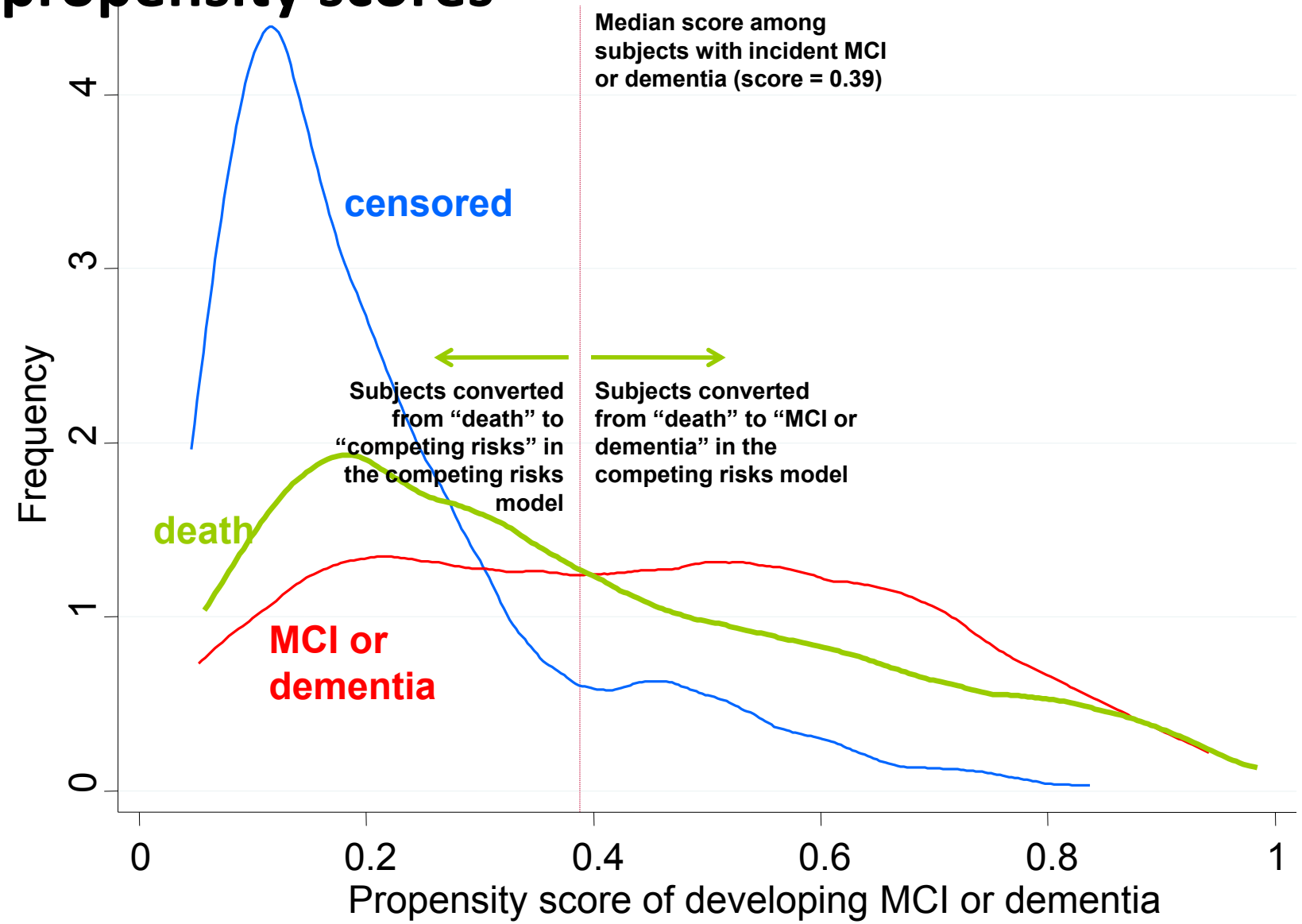
A case study

construction of the propensity model

Subjects died without developing MCI or dementia were then reclassified into two groups based on their propensity scores:

- The main events: death with high probability of having MCI or dementia
- The competing events: death with low probability of having MCI or dementia

A case study: propensity scores



A case study
survival models

For both Cox and modified FG regression, three different models were fit by sequentially adding more covariates:

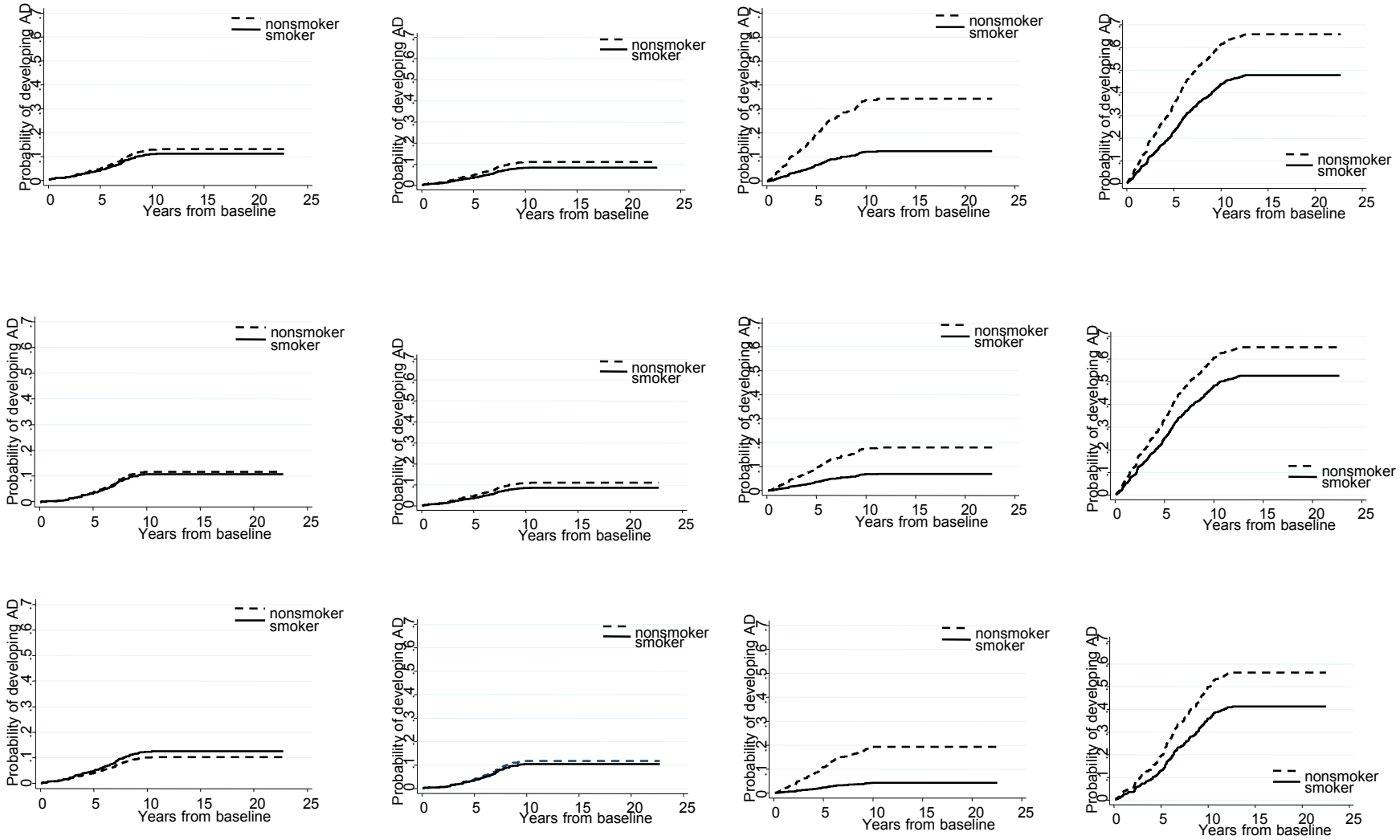
- **Model 1:** smoking and MCI or dementia;
- **Model 2:** smoking and MCI or dementia adjusting for baseline and demographic covariates;
- **Model 3:** smoking and MCI or dementia adjusting for baseline and demographic covariates, APOE*4 allele, and vascular risk factors.

A case study
estimated effect

Model	Age Stratum	Cox Model HR (95% CONFI INT)	Competing Risks Model SHR (95% CONFI INT)
1. smoking status only	65-74	0.79 (0.39-1.58)	0.75 (0.37-1.49)
	≥ 75	0.32 (0.10-0.99)	0.48 (0.26-0.86)
2. smoking status + other baseline covariates	65-74	0.82 (0.41-1.68)	0.75 (0.37-1.53)
	≥ 75	0.37 (0.17-1.17)	0.53 (0.29-0.97)
3. smoking status + other baseline covariates + vascular risk factors	65-74	0.88 (0.39-2.00)	0.87 (0.38-1.99)
	≥ 75	0.20 (0.03-1.45)	0.34 (0.11-1.05)

CONFI INT indicates confidence interval; HR, hazard ratio; SHR, subdistribution hazard ratio

A case study
estimated cumulative incidence probability



Conclusions

- Lifetime smoking was associated with a lower hazard of developing MCI or dementia. The association was consistent across statistical models and both age groups.
- The results of the adjusted and unadjusted models were very similar in subjects aged 65 to 74 years but quite different in those aged 75 years or older.
- Identifying and addressing competing risks can help eliminate or reduce bias in the risk analysis.
- Competing risks in sociology and behavioral science.

References

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