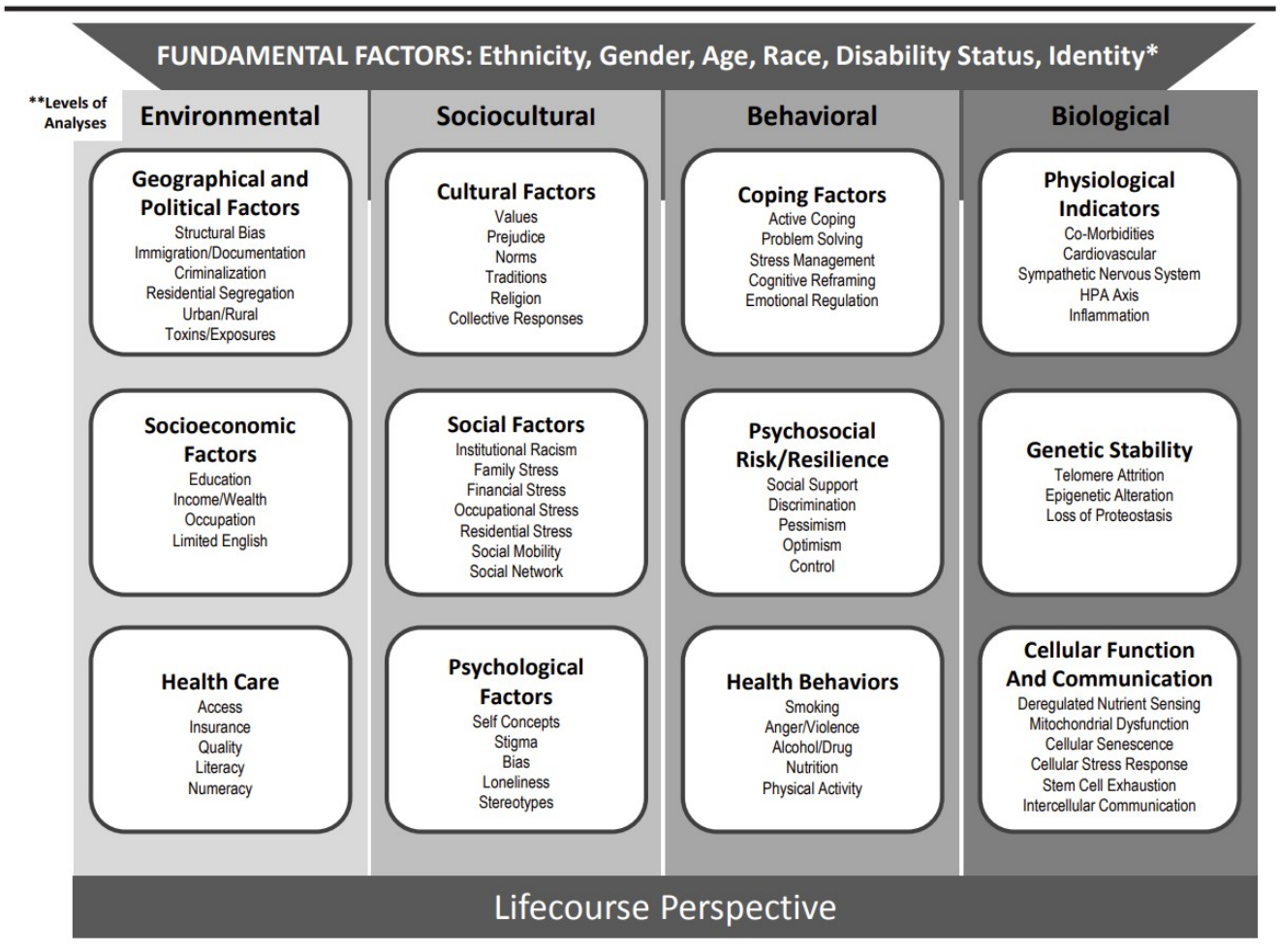
Considering questions before methods in dementia research with competing events and causal goals

L. Paloma Rojas-Saunero MD, PhD
Postdoctoral scholar
Mayeda Research Group, Department of Epidemiology

UCLA Fielding School of Public Health



Hill et al. *Ethnicity and disease*. 2015

Why smoking may prevent dementia, according to researchers

NICOTINE has been found to protect the brain as it ages so smoking could help prevent dementia, researchers claimed.

By JOHN FITZPATRICK

PUBLISHED: 16:25, Sun, Oct 2, 2016 | UPDATED: 18:09, Sun, Oct 2, 2016

SHARE TWEET 0

www.express.co.uk, 2016

Medscape Tuesday, December 3, 2019

NEWS & PERSPECTIVE DRUGS & DISEASES CME & EDUCATION ACADEMY

News > Medscape Medical News > Neurology News

No Link Between Smoking and Increased Dementia Risk?

Batya Swift Yasgur, MA, LSW

March 26, 2019

2 Read Comments

There appears to be no causal link between smoking and dementia, new research suggests.

Investigators followed over 500 senior adults for an average of 11 years, analyzing the potential association between smoking and dementia and adjusting for the competing risk of death without dementia.

Medscape, 2019

Cause-specific vs. subdistribution HR

Table 3. Recommendations for Analyzing Competing Risk Survival Data

- Cumulative incidence functions (CIFs) should be used to estimate the incidence of each of the different types of competing risks. Do not use the Kaplan-Meier estimate of the survival function for this purpose.
- Researchers need to decide whether the research objective is on addressing etiologic questions or on estimating incidence or predicting prognosis.
- Use the Fine-Gray subdistribution hazard model when the focus is on estimating incidence or predicting prognosis in the presence of competing risks.
- Use the cause-specific hazard model when the focus is on addressing etiologic questions.
- In some settings, both types of regression models should be estimated for each of the competing risks to permit a full understanding of the effect of covariates on the incidence and the rate of occurrence of each outcome.

Austin et al. *Circulation*.2016

Systematic review

Searching criteria

- Original research published between Jan/2018 to Dec/2019
- Dementia/AD & longitudinal/cohort & hazard/risk
- Alzheimer’s and Dementia, Annals of Neurology, BMJ, Neurology, JAMA, Jama Neurology, Lancet, Lancet Neurology

Systematic review

Searching criteria

- Original research published between Jan/2018 to Dec/2019
- Dementia/AD & longitudinal/cohort & hazard/risk
- Alzheimer's and Dementia, Annals of Neurology, BMJ, Neurology, JAMA, Jama Neurology, Lancet, Lancet Neurology

Eligibility criteria

- Time-to-dementia/AD as primary or co-primary outcome
- With a clear exposure/intervention, and uses methods to handle confounding
- Not a descriptive or predictive aim

Results

Out of **57/209** papers included:

Results

Out of **57/209** papers included:

- **56%** report death numbers, **18%** death by exposure level

Results

Out of **57/209** papers included:

- **56%** report death numbers, **18%** death by exposure level
- **47%** do not include any description about death in the methods section, **26%** consider it a sensitivity example, **14%** only mention it was treated as a censoring event

Results

Out of **57/209** papers included:

- **56%** report death numbers, **18%** death by exposure level
- **47%** do not include any description about death in the methods section, **26%** consider it a sensitivity example, **14%** only mention it was treated as a censoring event
- **87%** use Cox PH models, **93%** present hazard ratios

Results

Out of **57/209** papers included:

- **56%** report death numbers, **18%** death by exposure level
- **47%** do not include any description about death in the methods section, **26%** consider it a sensitivity example, **14%** only mention it was treated as a censoring event
- **87%** use Cox PH models, **93%** present hazard ratios
- **86%** innacurate interpretations (e.g. "*risks*")

Methods development

Applications

Interpretation

Science communication

RESEARCH ARTICLE

A causal framework for classical statistical estimands in failure-time settings with competing events

Jessica G. Young, Mats J. Stensrud, Eric J. Tchetgen Tchetgen, Miguel A. Hernán

First published: 27 January 2020 | https://doi.org/10.1002/sim.8471 | Citations: 97

Funding information NIH, R37 AI102634; Norges Forskningsråd, NFR239956/F20

American Journal of EPIDEMIOLOGY

Society for Epidemiologic Research

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

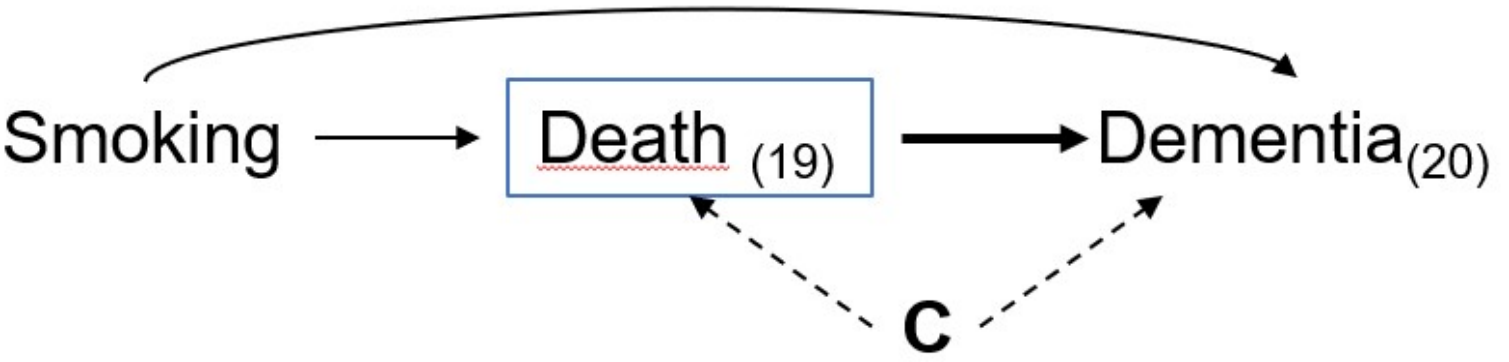
JOURNAL ARTICLE

Considering Questions Before Methods in Dementia Research With Competing Events and Causal Goals

L Paloma Rojas-Saunero ✉, Jessica G Young, Vanessa Didelez, M Arfan Ikram, Sonja A Swanson

American Journal of Epidemiology, Volume 192, Issue 8, August 2023, Pages 1415–1423, https://doi.org/10.1093/aje/kwad090

Published: 03 May 2023 **Article history** ▾


Smoking
Death (19)
Dementia(20)
C

Total effect

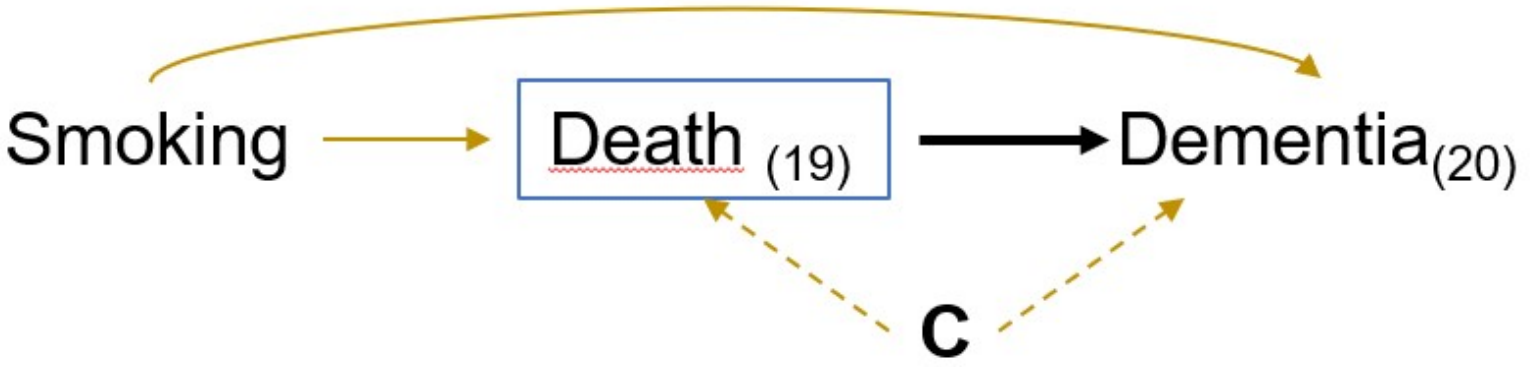
What is the risk of dementia at 20 years of follow-up had all individuals initiated smoking in adulthood, compared to had all individuals not initiated smoking?

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

Total effect

What is the risk of dementia at 20 years of follow-up had all individuals initiated smoking in adulthood, compared to had all individuals not initiated smoking?

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



Controlled direct effect

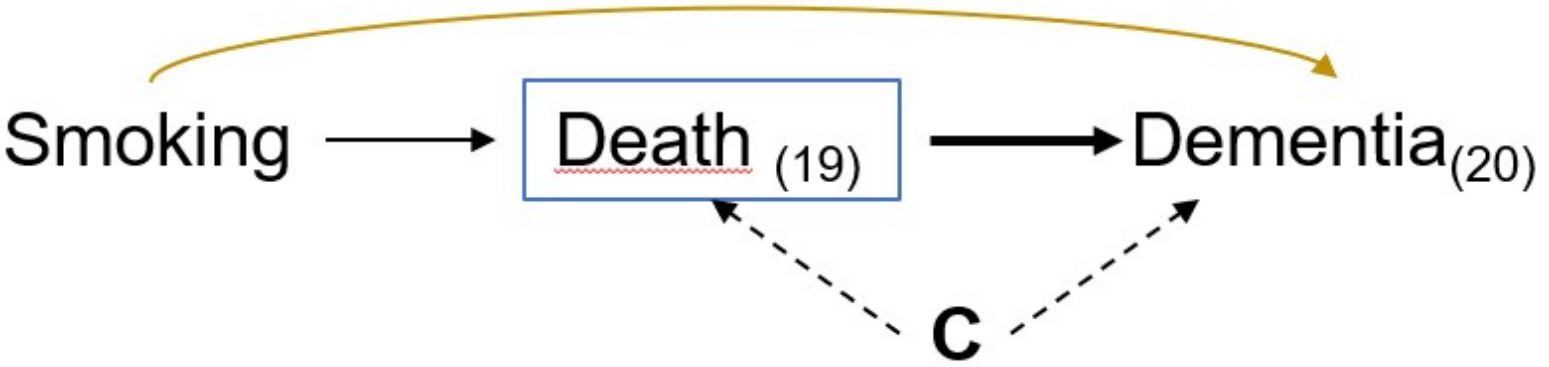
What is the risk of dementia at 20 years of follow-up had all individuals initiated smoking in adulthood and not died throughout the study period, compared to had all individuals not initiated smoking in adulthood and not died throughout the study period?

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

Controlled direct effect

What is the risk of dementia at 20 years of follow-up had all individuals initiated smoking in adulthood and not died throughout the study period, compared to had all individuals not initiated smoking in adulthood and not died throughout the study period?

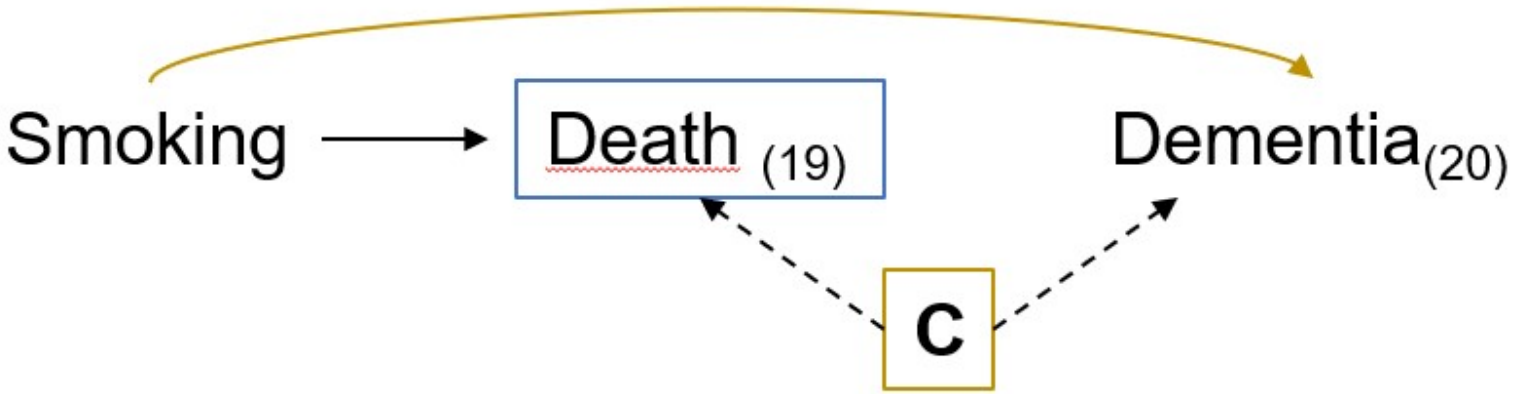
$$Pr[Y_{20}^{a=1,d_{19}=0}] - Pr[Y_{20}^{a=0,d_{19}=0}]$$



Controlled direct effect

What is the risk of dementia at 20 years of follow-up had all individuals initiated smoking in adulthood and not died throughout the study period, compared to had all individuals not initiated smoking in adulthood and not died throughout the study period?

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



Identifiability assumptions

Assumption	Total Effect	Controlled direct effect
Exchangeability assumption needed for death (competing events)?	Not needed	At each k + 1, conditional on the measured past, death is independent of future counterfactual outcomes had everyone followed and death was eliminated.

Identifiability assumptions

Assumption	Total Effect	Controlled direct effect
Exchangeability assumption needed for death (competing events)?	Not needed	At each k + 1, conditional on the measured past, death is independent of future counterfactual outcomes had everyone followed and death was eliminated.
Positivity assumption needed for death (competing events)?	Not needed	For any possibly observed level of exposure and covariate history amongst those remaining uncensored (alive) and free of dementia diagnosis through k, some individuals continue to remain alive through _k + 1_.

Identifiability assumptions

Assumption	Total Effect	Controlled direct effect
Exchangeability assumption needed for death (competing events)?	Not needed	At each k + 1, conditional on the measured past, death is independent of future counterfactual outcomes had everyone followed and death was eliminated.
Positivity assumption needed for death (competing events)?	Not needed	For any possibly observed level of exposure and covariate history amongst those remaining uncensored (alive) and free of dementia diagnosis through k, some individuals continue to remain alive through _k + 1_.
Consistency assumption needed for death (competing events)	Not needed	An intervention that “eliminates death (competing events)” is well-defined.

Application

- Participants from Rotterdam Study I, recruited between 1990-1993 and followed during 1993-1995, 1997-1999 and 2002-2005
  - Current and former smokers
  - No prior history of dementia diagnosis
  - Complete information at baseline
- Final sample size of 4179 participants
- Mean age at baseline of 62 years
- 368 developed dementia and 1318 died

Analysis plan

- **For confounding:** Inverse probability weighting for treatment (IPTW)

Analysis plan

- **For confounding:** Inverse probability weighting for treatment (IPTW)
- **Total effect:** Cause-specific cumulative incidence / Aalen-Johansen estimator + IPTW

Analysis plan

- **For confounding:** Inverse probability weighting for treatment (IPTW)
- **Total effect:** Cause-specific cumulative incidence / Aalen-Johansen estimator + IPTW
- **Controlled direct effect:** Kaplan-Meier + Inverse probability censoring weights + IPTW

Analysis plan

- **For confounding:** Inverse probability weighting for treatment (IPTW)
- **Total effect:** Cause-specific cumulative incidence / Aalen-Johansen estimator + IPTW
- **Controlled direct effect:** Kaplan-Meier + Inverse probability censoring weights + IPTW
- Bootstrapping for confidence intervals

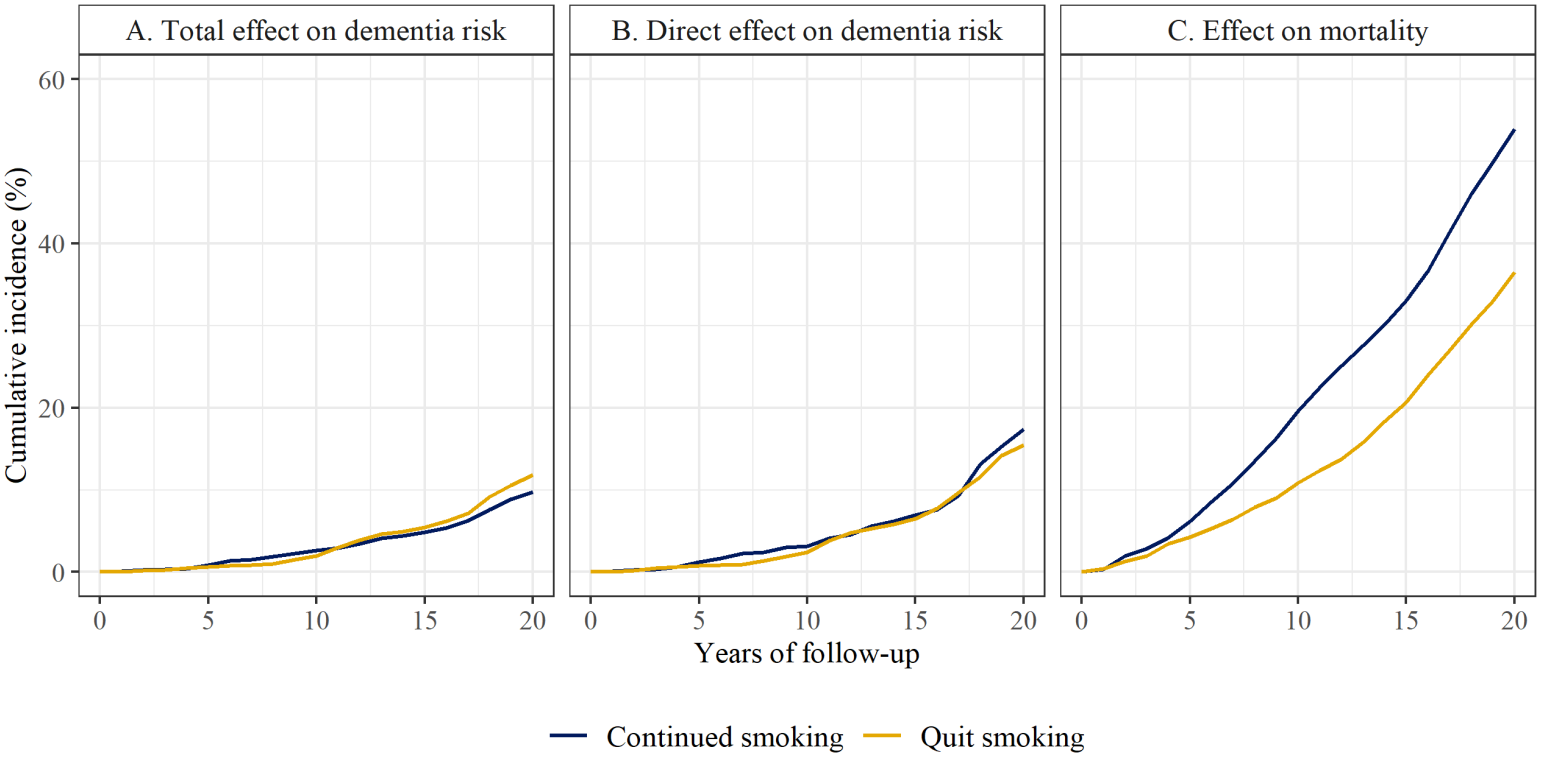
Semi-parametric or parametric alternatives are also possible

Results

Causal effect	Risk Difference (95%CI)	Risk Ratio (95%CI)
Total effect on dementia	2.1 (-0.1, 4.2)	1.21 (0.99, 1.50)
Controlled direct effect on dementia (with IPCW for death)	-2.6 (-6.1, 0.8)	0.86 (0.72, 1.05)
Total effect on mortality	-17.4 (-20.5, -14.2)	0.68, (0.63, 0.72)

Results

Assumption	Risk Difference (95%CI)	Risk Ratio (95%CI)
Evoking unconditional exchangeability assumption for censoring	-0.7 (-3.3, 2.2)	0.96 (0.82, 1.16)
Evoking conditional exchangeability assumption on baseline covariates for censoring	-1.5 (-4.6, 1.8)	0.92 (0.78, 1.12)
Evoking conditional exchangeability assumption on baseline and time-varying covariates for censoring	-2.7 (-6.1, 0.8)	0.86 (0.7, 1.1)


A. Total effect on dementia risk
B. Direct effect on dementia risk
C. Effect on mortality
Cumulative incidence (%)
60
40
20
0
0
5
10
15
20
Years of follow-up
Continued smoking
Quit smoking

Other possible estimands

- **Survivors average causal effect:** The risk of dementia on a subgroup of individuals who would never experience the competing event.

Other possible estimands

- **Survivors average causal effect:** The risk of dementia on a subgroup of individuals who would never experience the competing event.
- **Separable effects:** Effects of modified treatments motivated by the physical decomposition of the exposure assumed to operate on dementia and death through separate pathways.

Other possible estimands

- **Survivors average causal effect:** The risk of dementia on a subgroup of individuals who would never experience the competing event.
- **Separable effects:** Effects of modified treatments motivated by the physical decomposition of the exposure assumed to operate on dementia and death through separate pathways.
- **Composite outcome of dementia and death**

Conclusion

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

Conclusion

- 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 appropiate methods and estimators.

Conclusion

- 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 appropiate methods and estimators.
- For various reasons, risks and survival curves should be preferred over hazards.

Conclusion

- 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 appropiate methods and estimators.
- For various reasons, risks and survival curves should be preferred over hazards.
- Collaborative work between clinical researchers, epidemiologists and statisticians should narrow the gap between methods development and applied research.

Thank you! Gracias!

lp.rojassaunero@ucla.edu

@palolili23

@palolili23