Bridging the gap(s): From time-to-event methods to their application in a Framingham Heart study reanalysis

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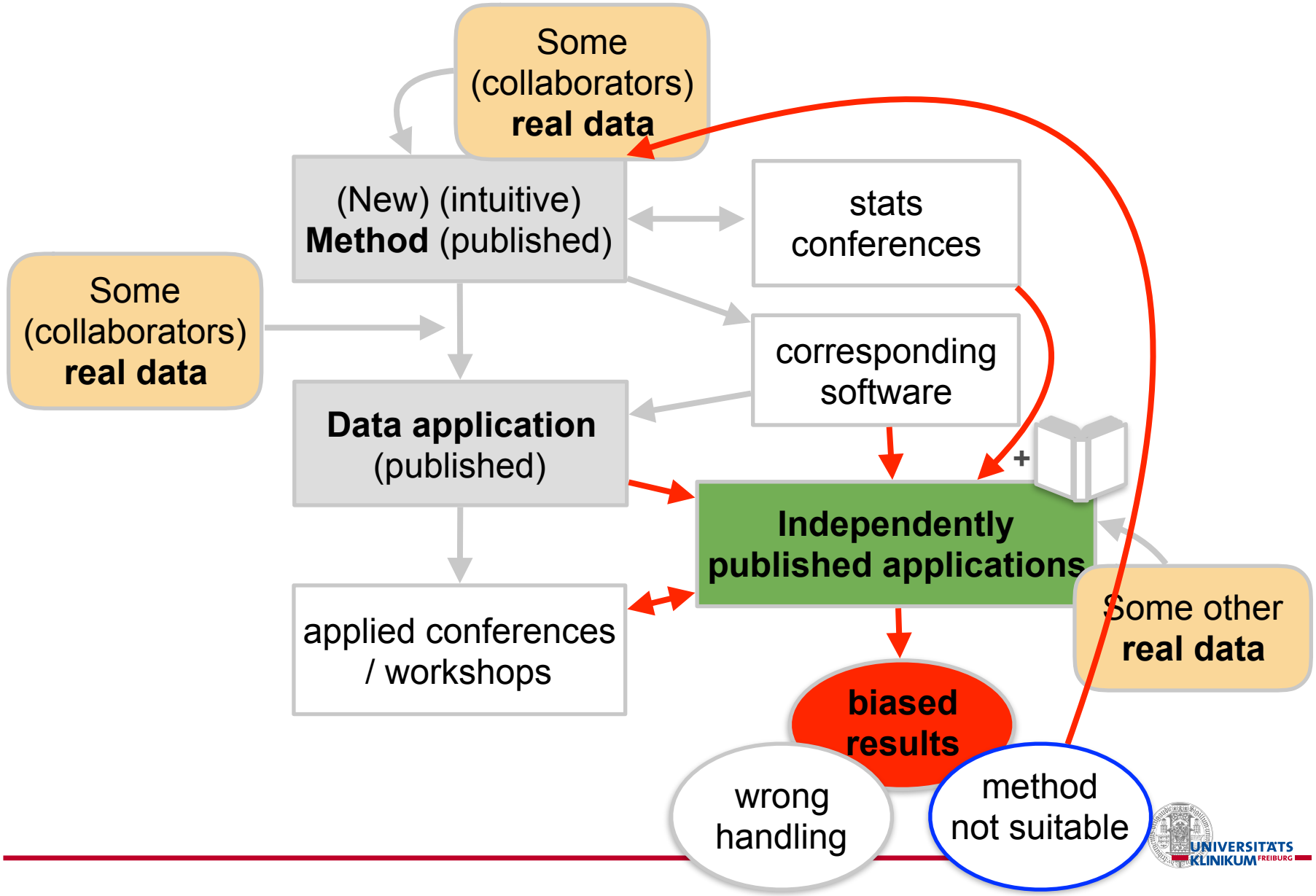
Journey from a (new) method to its (frequent) use



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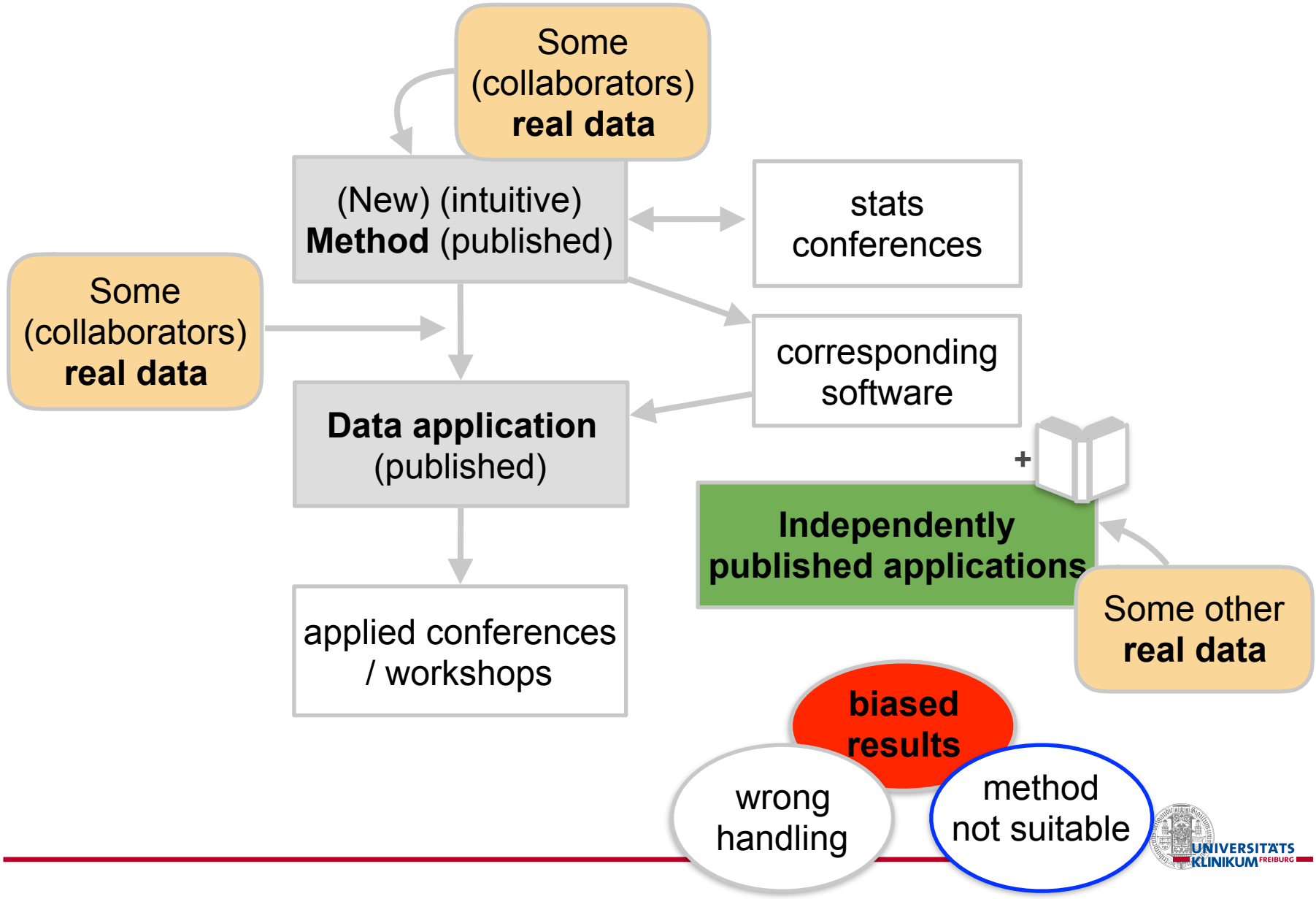

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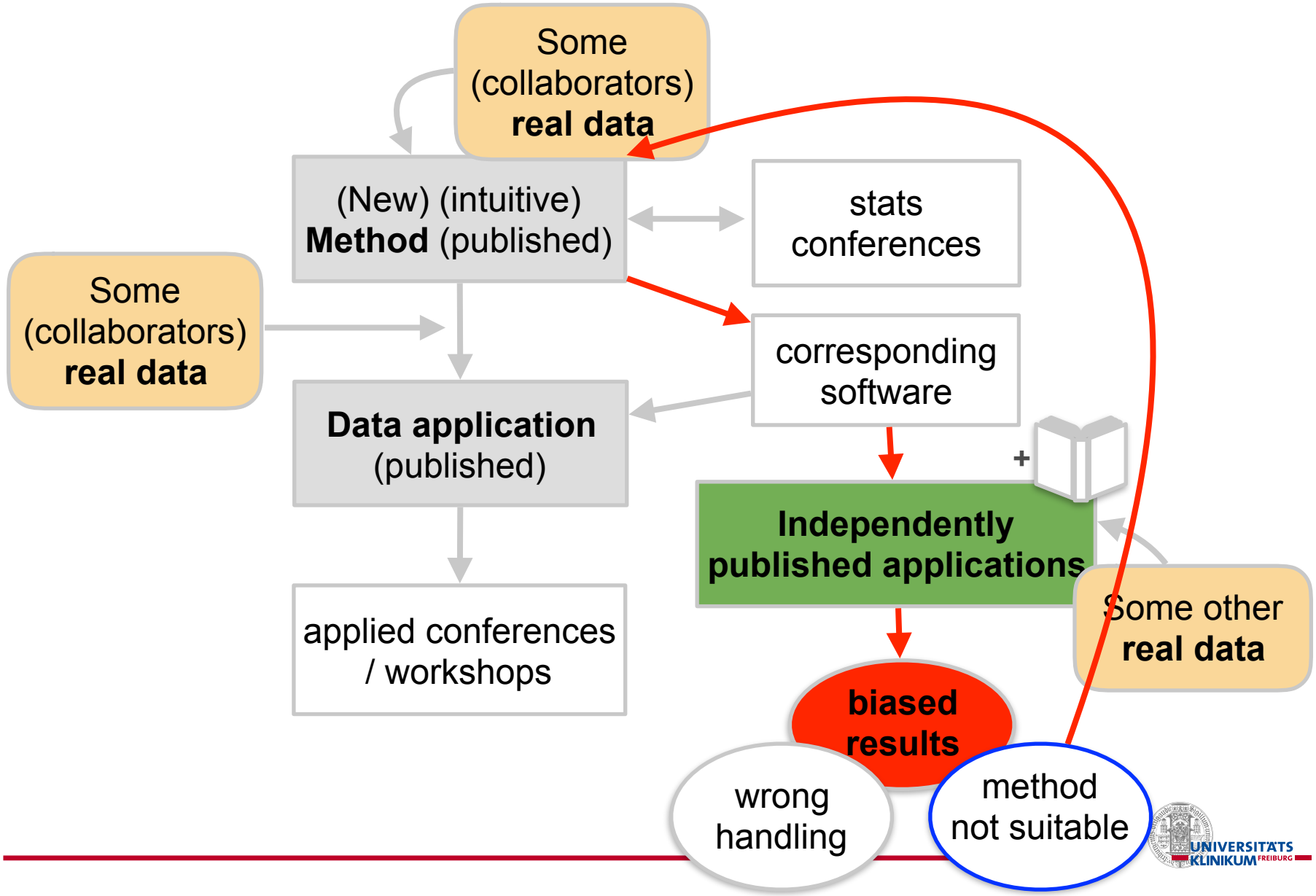
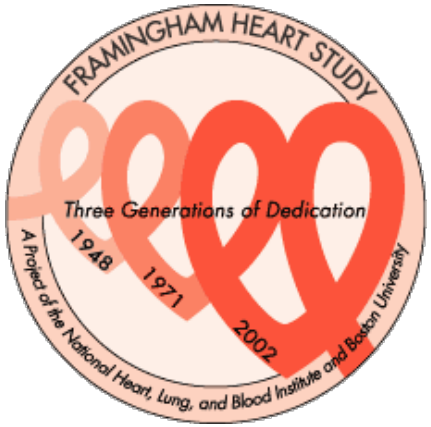


Framingham Heart Study



- First longitudinally-followed large cohort to study **cardiovascular disease epidemiology** in the USA
- Started in **1948**, random sampling, aged 30–59 years, living in Framingham, Massachusetts
- Every **2–6 years in-person examinations**
- Medical history; cardiovascular-focused physical examinations, …
- **Has evolved and expanded** to encompass multiple organ systems, incl. lung, brain, bone and fat depots, among others

The NEW ENGLAND JOURNAL of MEDICINE

This talks' epidemiological example

2016

ORIGINAL ARTICLE

Incidence of Dementia over Three Decades in the Framingham Heart Study

Claudia L. Satizabal, Ph.D., Alexa S. Beiser, Ph.D., Vincent Chouraki, M.D., Ph.D., Geneviève Chêne, M.D., Ph.D., Carole Dufouil, Ph.D., and Sudha Seshadri, M.D.

ABSTRACT

BACKGROUND

The prevalence of dementia is expected to soar as the average life expectancy increases, but recent estimates suggest that the age-specific incidence of dementia is declining in high-income countries. Temporal trends are best derived through continuous monitoring of a population over a long period with the use of consistent diagnostic criteria. We describe temporal trends in the incidence of dementia over three decades among participants in the Framingham Heart Study.

METHODS

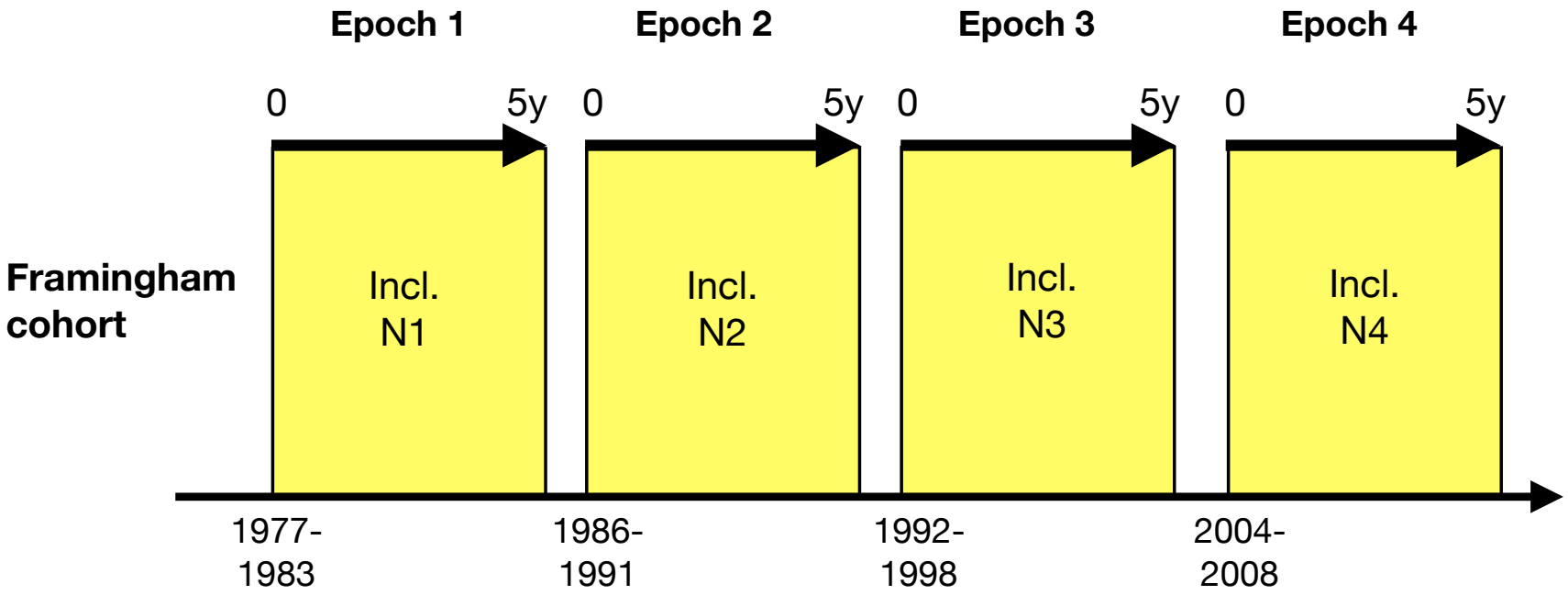
Participants in the Framingham Heart Study have been under surveillance for incident dementia since 1975. In this analysis, which included 5205 persons 60 years of age or older, we used Cox proportional-hazards models adjusted for age and sex to determine the 5-year incidence of dementia during each of four epochs. We also explored the interactions between epoch and age, sex, apolipoprotein E ε4 status, and educational level, and we examined the effects of these interactions, as well as the effects of vascular risk factors and cardiovascular disease, on temporal trends.

From the Boston University Schools of Medicine (C.L.S., A.S.B., V.C., S.S.) and Public Health (A.S.B.), Boston, and the Framingham Heart Study, Framingham (C.L.S., A.S.B., V.C., S.S.) — all in Massachusetts; and Inserm Unité 1219 and CIC 1401-EC (Clinical Epidemiology) and University of Bordeaux, ISPED (Bordeaux School of Public Health) — both in Bordeaux, France (G.C., C.D.). Address reprint requests to Dr. Seshadri at the Boston University School of Medicine, Department of Neurology, 72 E. Concord St., B602, Boston, MA 02118, or at suseshad@bu.edu.

N Engl J Med 2016;374:523-32.
DOI: 10.1056/NEJMoa1504327

UNIVERSITÄTS KLINIKUM FREIBURG

Design Satizabal et al 2016



Incl. = age > 60
+ free of dementia at entry to epoch
+ follow-up

Outcome of interest: time from epoch entry to dementia

Satizabal CL. N Engl J Med. 2016

Results

Table 2. Temporal Trends in the Incidence of Dementia.*

Subtype	No. of Cases	Total No. of Observation Periods	5-Yr Cumulative Hazard Rate (95% CI)†			
			Epoch 1	Epoch 2	Epoch 3	Epoch 4
Overall dementia	371	9015	3.6 (2.9–4.4)	2.8 (2.2–3.5)	2.2 (1.8–2.8)	2.0 (1.5–2.6)

† The 5-year cumulative hazard rates (the cumulative incidence of dementia per 100 persons over a period of 5 years) are adjusted for age and sex.

Outcome of interest:
time from epoch entry
to dementia

5-Yr Hazard Ratio (95% CI)‡		
Epoch 2	Epoch 3	Epoch 4
0.78 (0.59–1.04)	0.62 (0.47–0.83)	0.56 (0.41–0.77)

Abstract continued

RESULTS

The 5-year age- and sex-adjusted cumulative hazard rates for dementia were 3.6 per 100 persons during the first epoch (late 1970s and early 1980s), 2.8 per 100 persons during the second epoch (late 1980s and early 1990s), 2.2 per 100 persons during the third epoch (late 1990s and early 2000s), and 2.0 per 100 persons during the fourth epoch (late 2000s and early 2010s). Relative to the incidence during the first epoch, the incidence declined by 22%, 38%, and 44% during the second, third, and fourth epochs, respectively. This risk reduction was observed only among persons who had at least a high school diploma (hazard ratio, 0.77; 95% confidence interval, 0.67 to 0.88). The prevalence of most vascular risk factors (except obesity and diabetes) and the risk of dementia associated with stroke, atrial fibrillation, or heart failure have decreased over time, but none of these trends completely explain the decrease in the incidence of dementia.

CONCLUSIONS

Among participants in the Framingham Heart Study, the incidence of dementia has declined over the course of three decades. The factors contributing to this decline have not been completely identified. (Funded by the National Institutes of Health.)

A rather simple time-to-event tool…

$$\alpha(t|Z) = \alpha_0(t)\exp(\beta Z)$$

- ✓ arbitrary and unknown function of time
- ✓ **assume** independent censoring

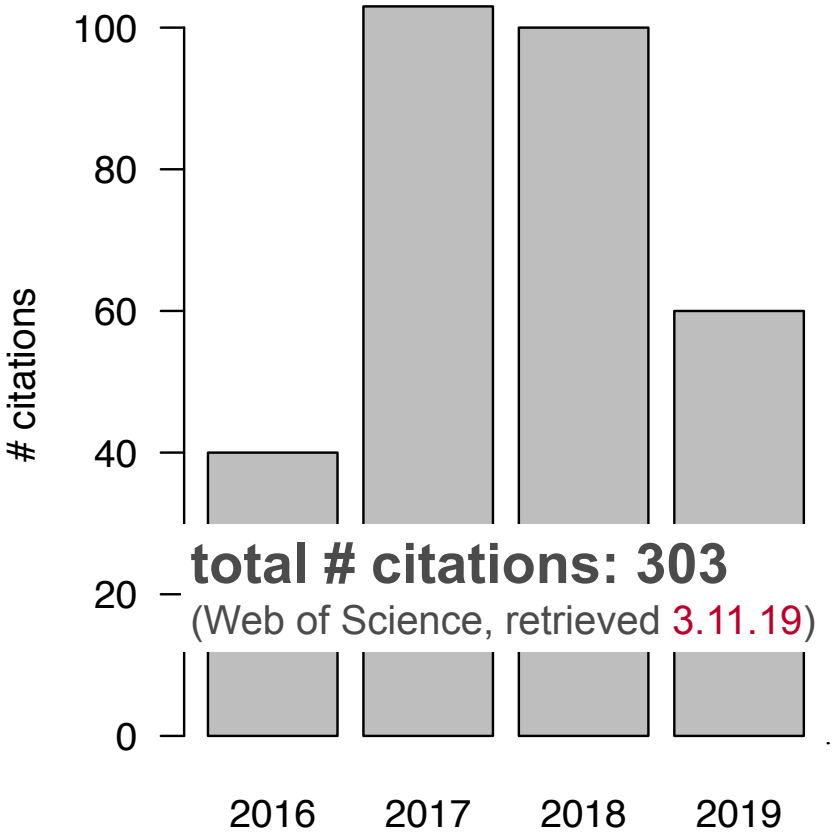
- ✓ explanatory variable(s) Z
- ✓ regression coefficient β
- ✓ **assume** proportionality
- ✓ assume …
- ✓ R, SAS, Stata, …

we don't care so much about it …

Cox, D. **1972** Regression Models and Life-Tables.
Journal of the Royal Statistical Society. Series B (Methodological), 34(2), 187-220.

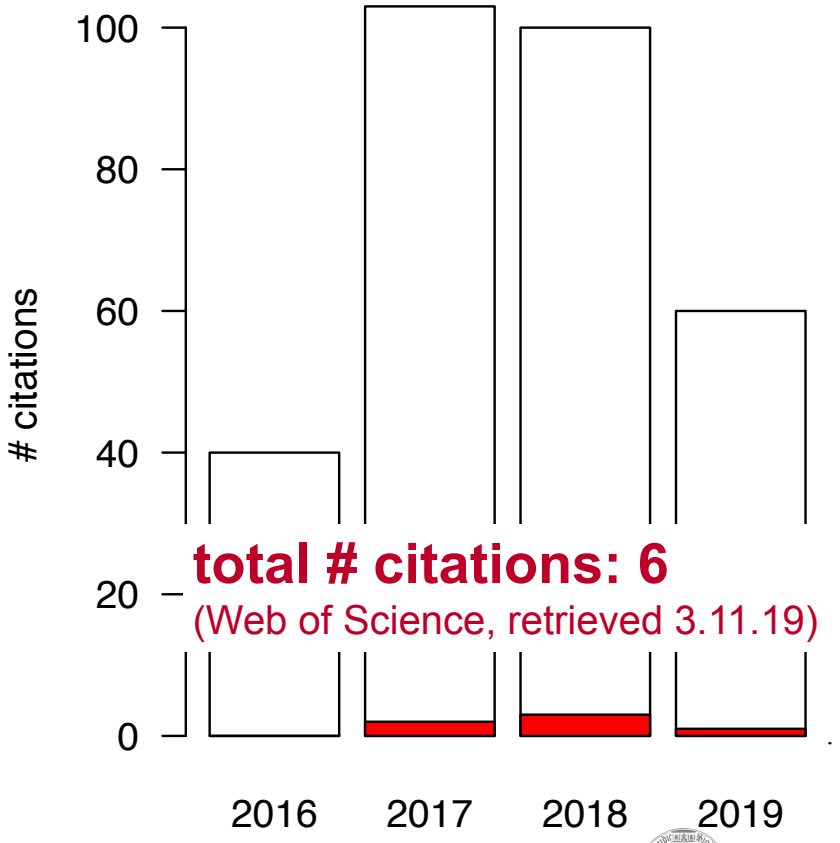
A rather simple time-to-event tool…

Satizabal CL. N Engl J Med. 2016;374(6):523-32



… that potentially ignores more complex structure

Binder N, Schumacher M. **Letter**. N Engl J Med. 2016



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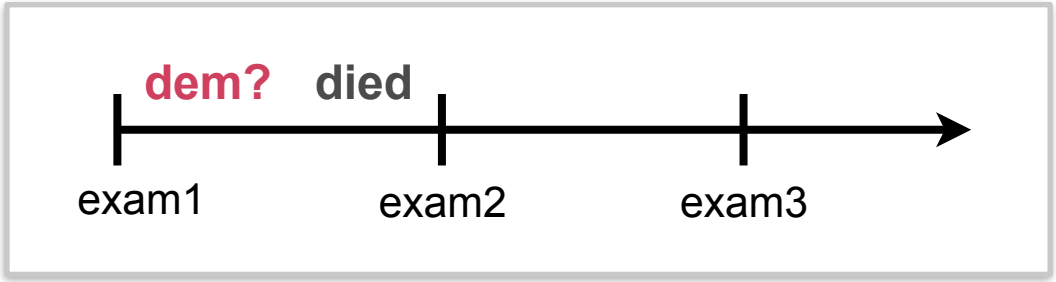
† The 5-year cumulative hazard rates (the cumulative incidence of dementia per 100 persons over a period of 5 years) are adjusted for age and sex.

* participants who died without prior observed dementia were censored at date of death

Missing disease information due to death (MDID)



Satizabal et al. **Response letter**. N Engl J Med. 2016

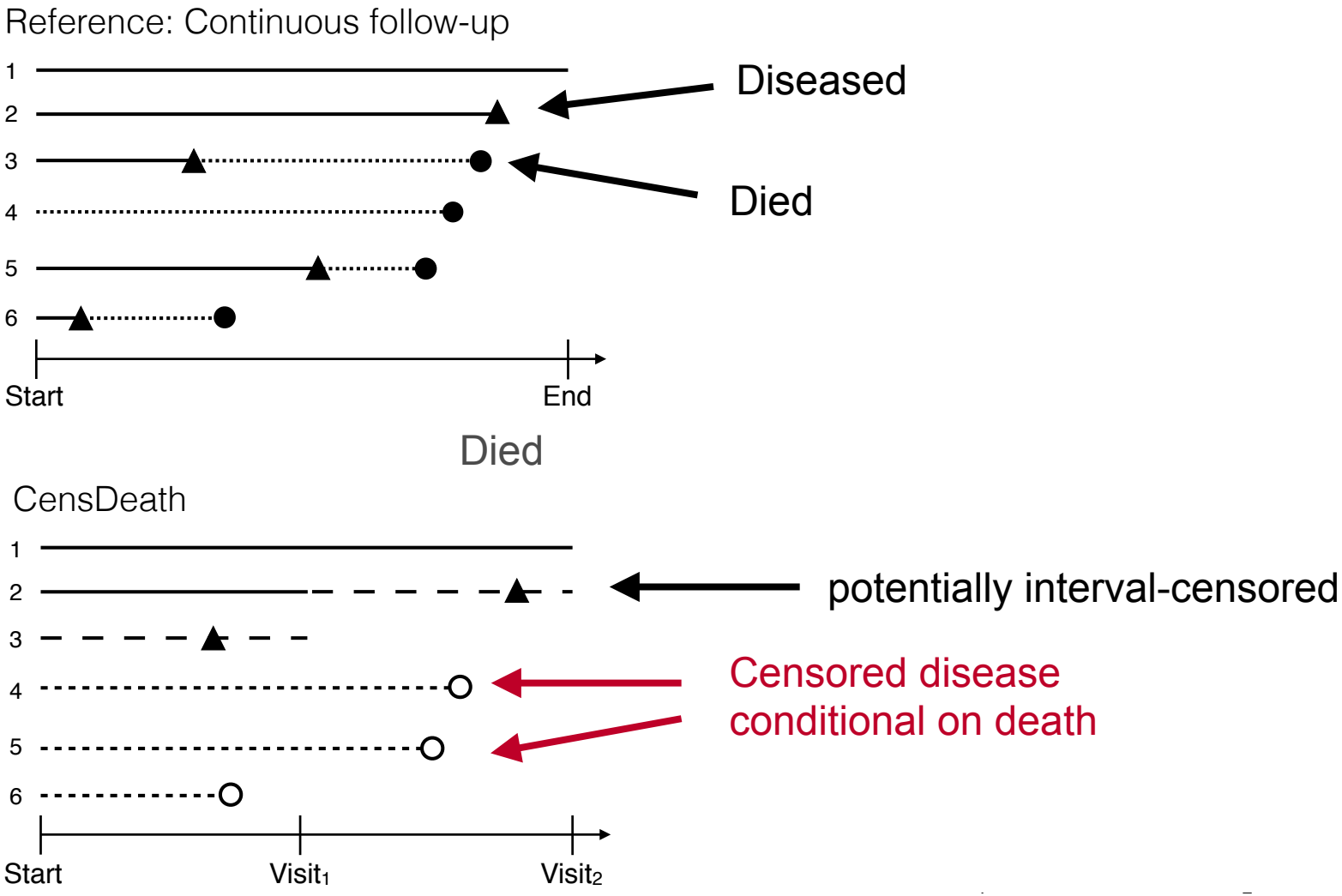
Table 1. Risk of Dementia in the Framingham Heart Study over Time in Two Post Hoc Subgroups.*

Variable	Risk of Dementia			
	Epoch 1	Epoch 2	Epoch 3	Epoch 4
			hazard ratio (95% CI)	
Data censored at death vs. last medical visit				
Censored at death in original study	1.00	0.78 (0.59–1.04)	0.62 (0.47–0.83)	0.56 (0.41–0.77)
Censored at last medical visit in post hoc subgroup analysis	1.00	0.80 (0.60–1.06)	0.63 (0.48–0.84)	0.58 (0.43–0.79)

What’s the problem with the censoring here?

Censoring missing disease info due to death?

MDID



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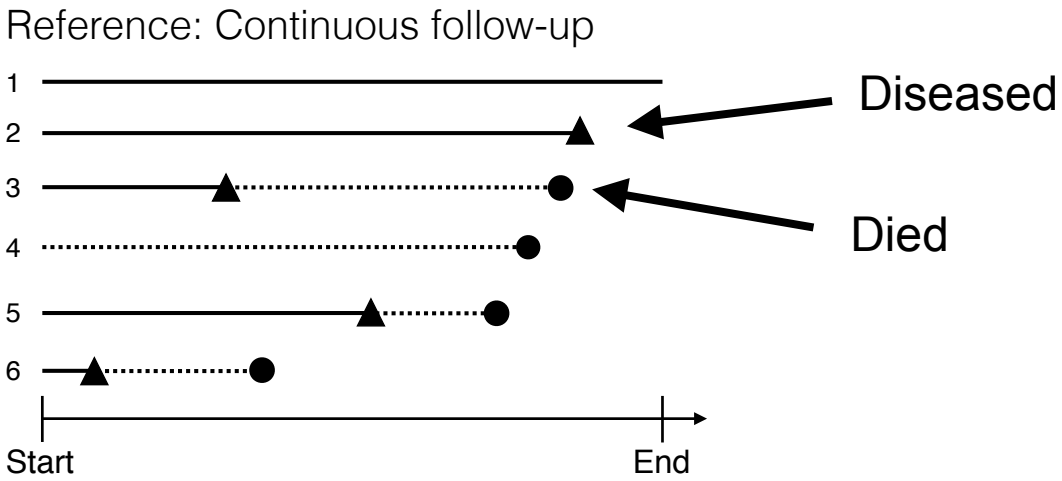
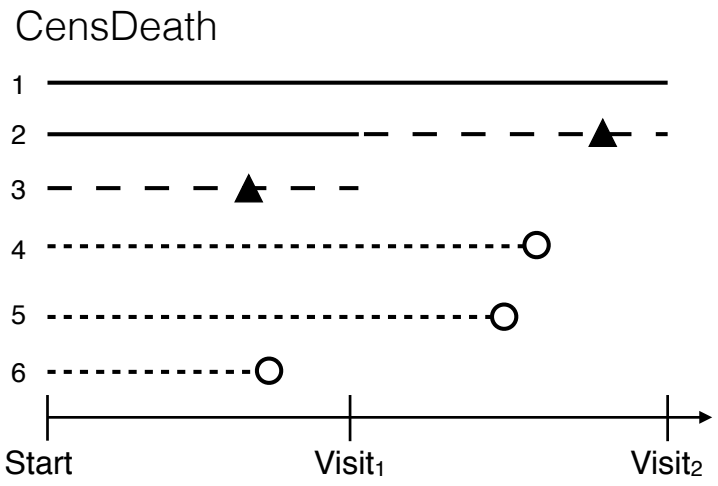
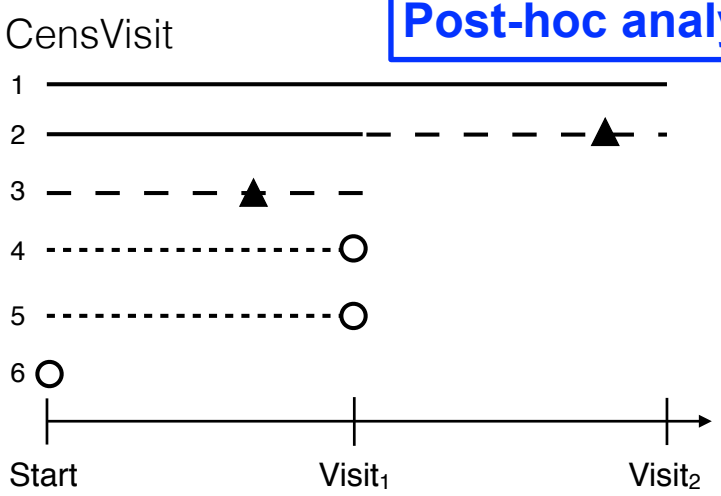


Satizabal et al. reply: Post-hoc analysis





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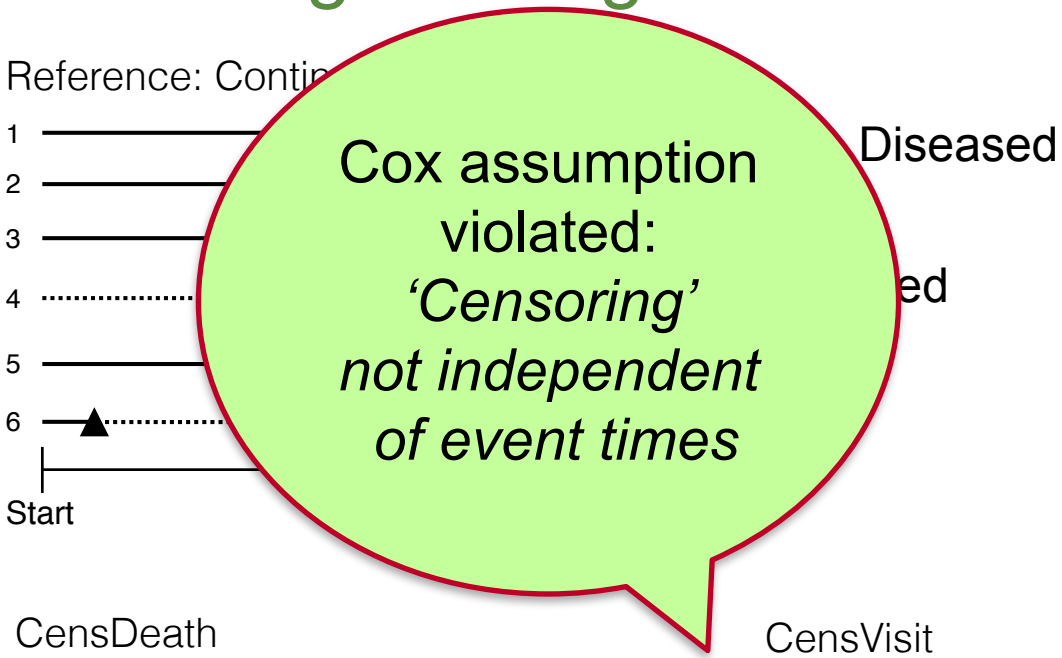

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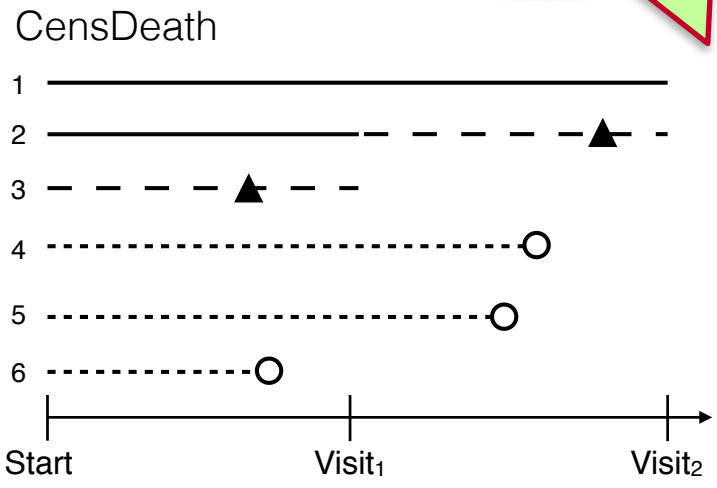
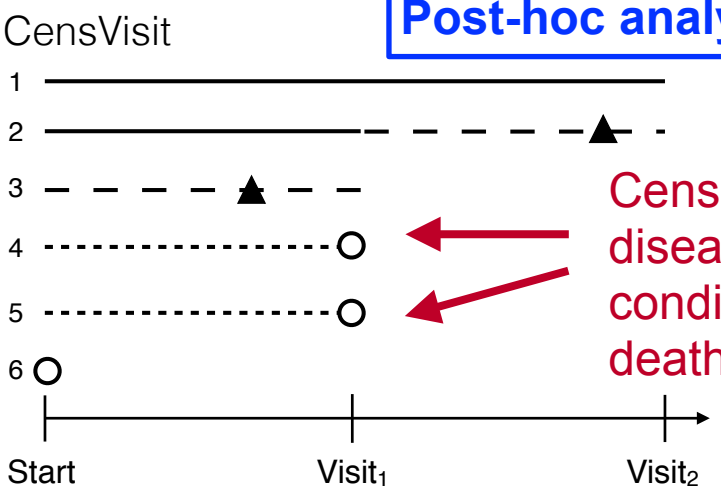
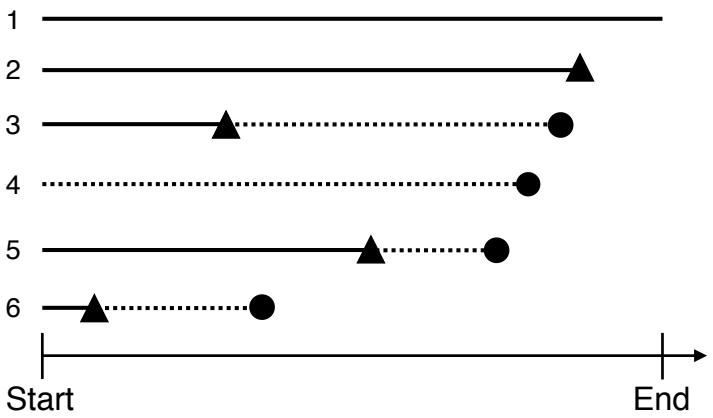




Censoring missing disease info due to death?

MDID

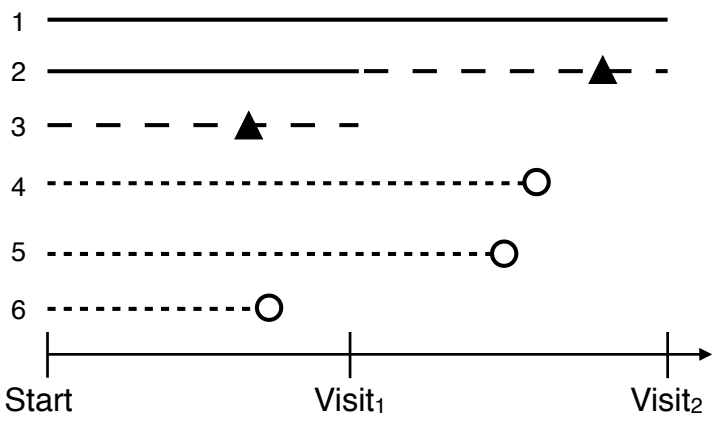
Reference: Continuous follow-up



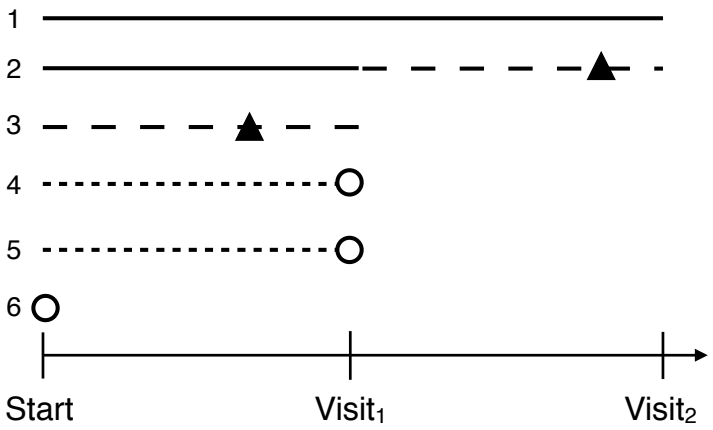
Incidence density =

$$\frac{\#\ \text{diseased}}{\sum\ \text{subject-time at risk}}$$

CensDeath



CensVisit



Binder N et al. *J Clin Epidemiol.* 2019;105:68-79.

MDID

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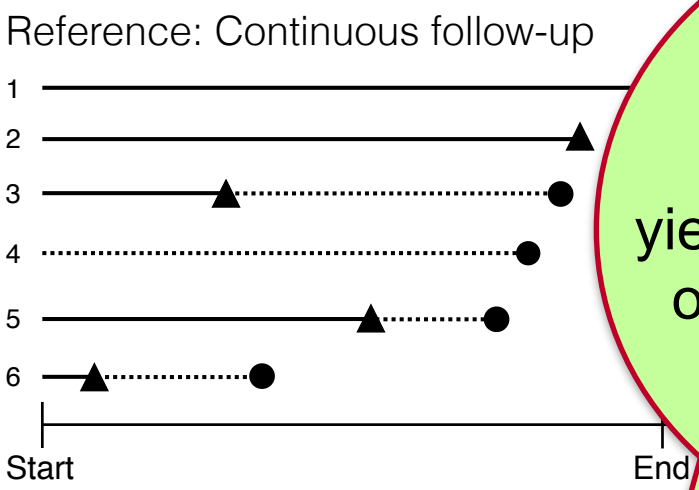
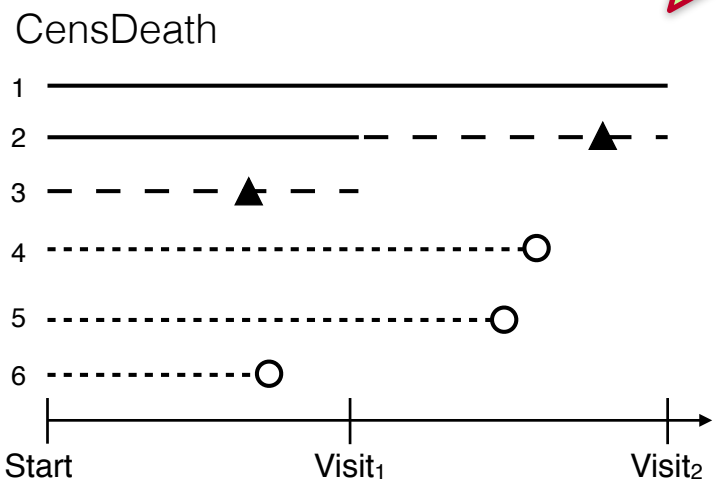
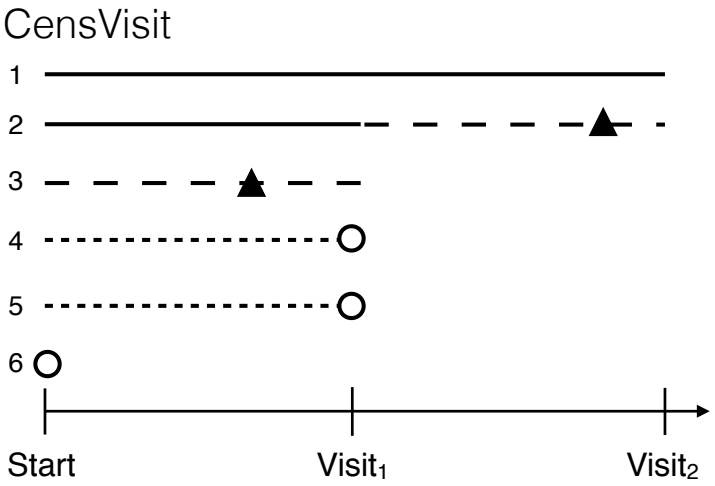


‘Censoring’
yields biased estimates
of disease incidence

ed

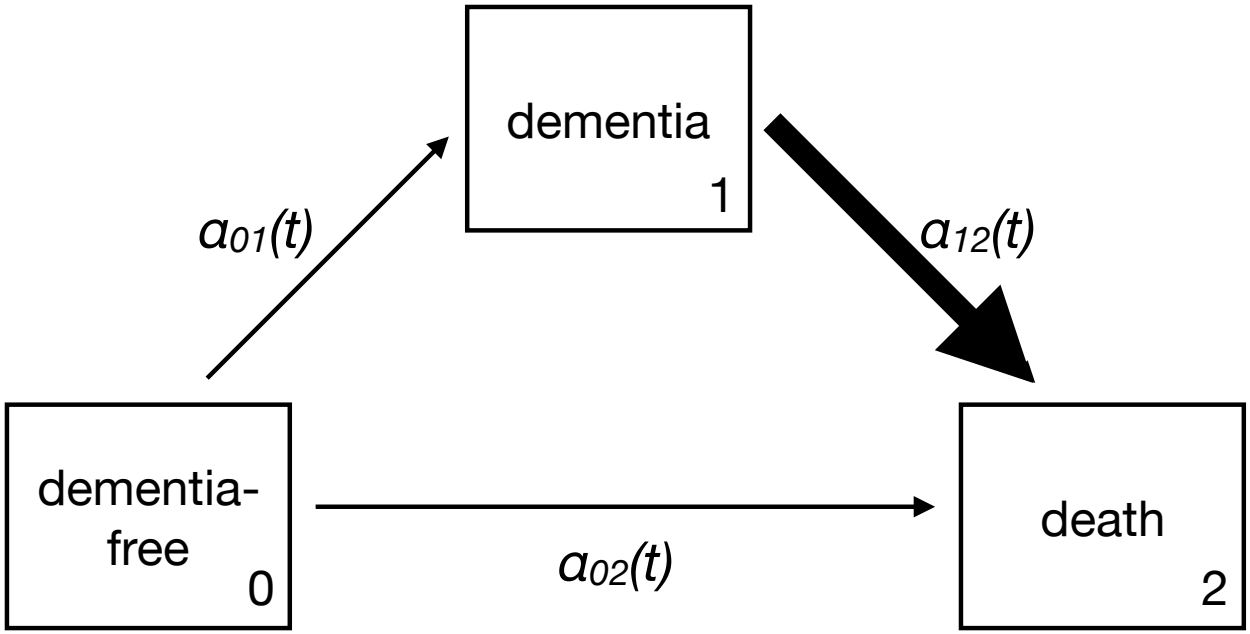
ne at risk





Underlying model for the data

Illness-death multistate model



If $\alpha_{02}(t) \neq \alpha_{12}(t)$, the CensVisit disease incidence estimate is biased. (Joly et al, 2002)

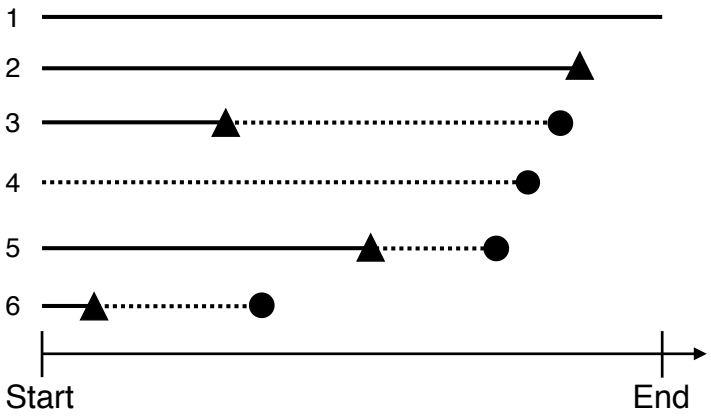
‘Censorings’ yield biased incidence estimates

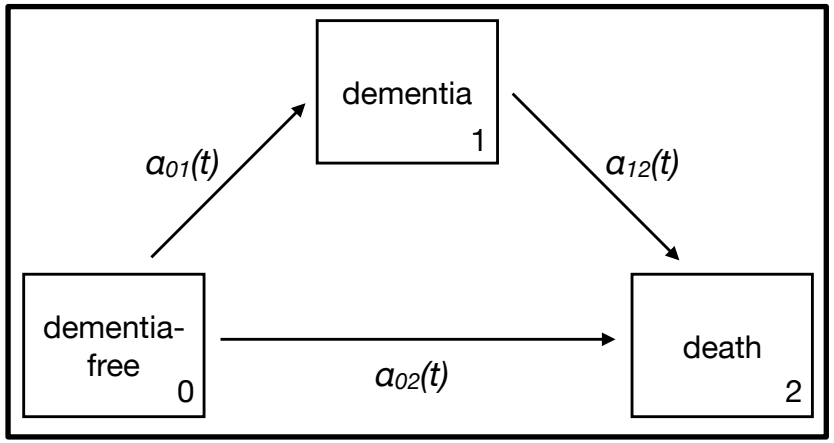
Small simulation study mimicking the Framingham setup

Simulate complete illness-death data

$$(Epoch1) \quad \alpha_{01}(t) = 0.1, \alpha_{02}(t) = 0.1, \alpha_{12}(t) = 0.3$$
$$(Epoch2) \quad \alpha_{01}(t) = 0.1, \alpha_{02}(t) = 0.2, \alpha_{12}(t) = 0.45$$
$$(Epoch3) \quad \alpha_{01}(t) = 0.1, \alpha_{02}(t) = 0.3, \alpha_{12}(t) = 0.6$$

Reference: Continuous follow-up





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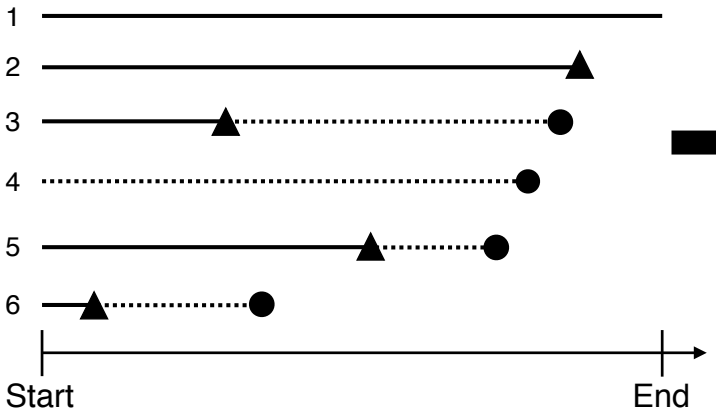

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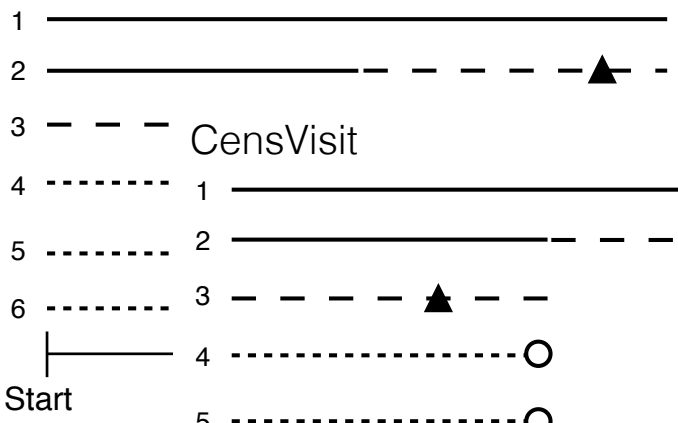
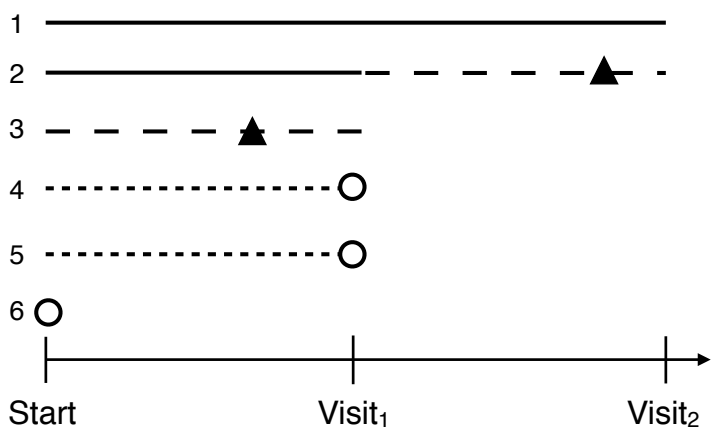


CensVisit



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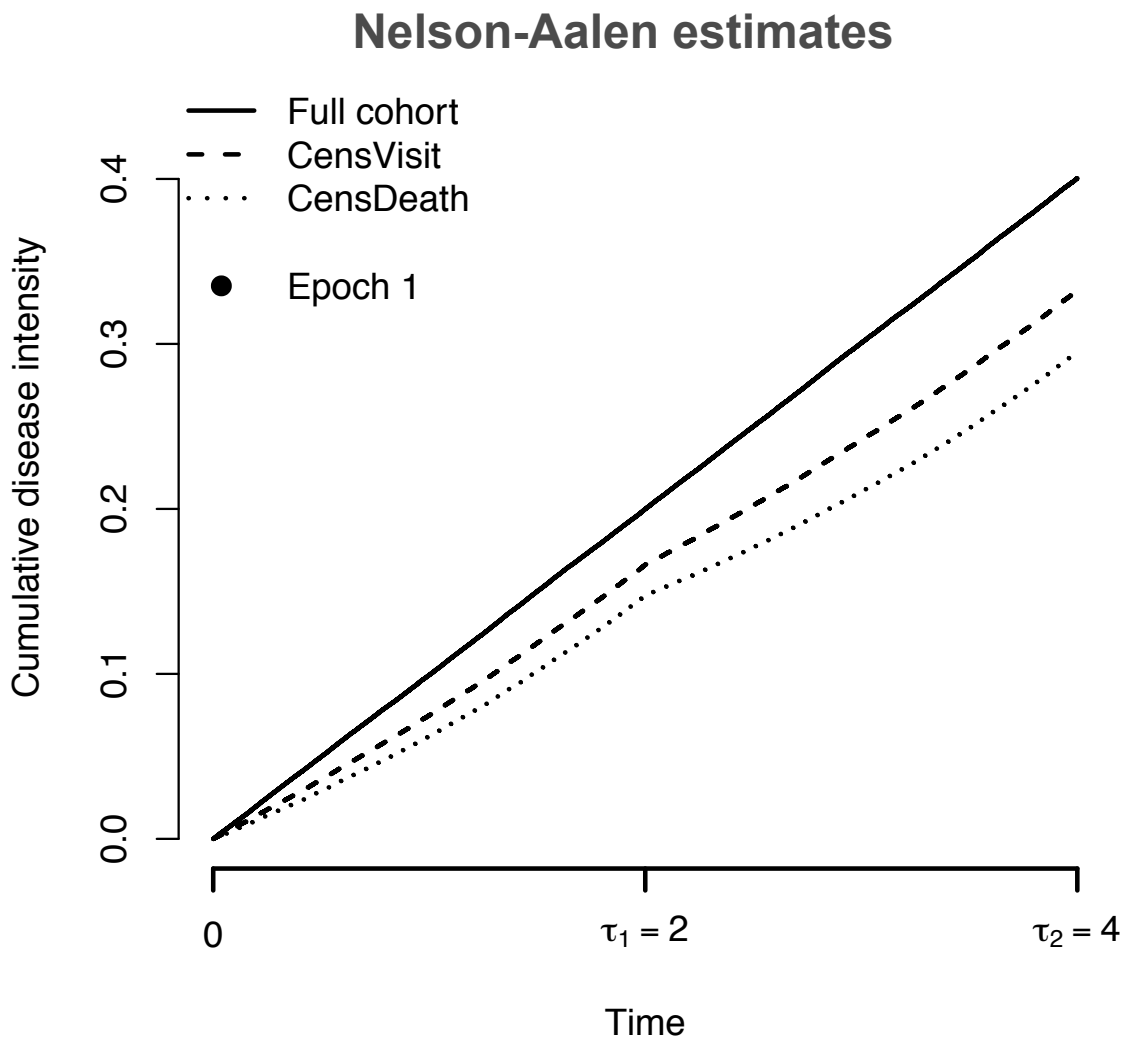

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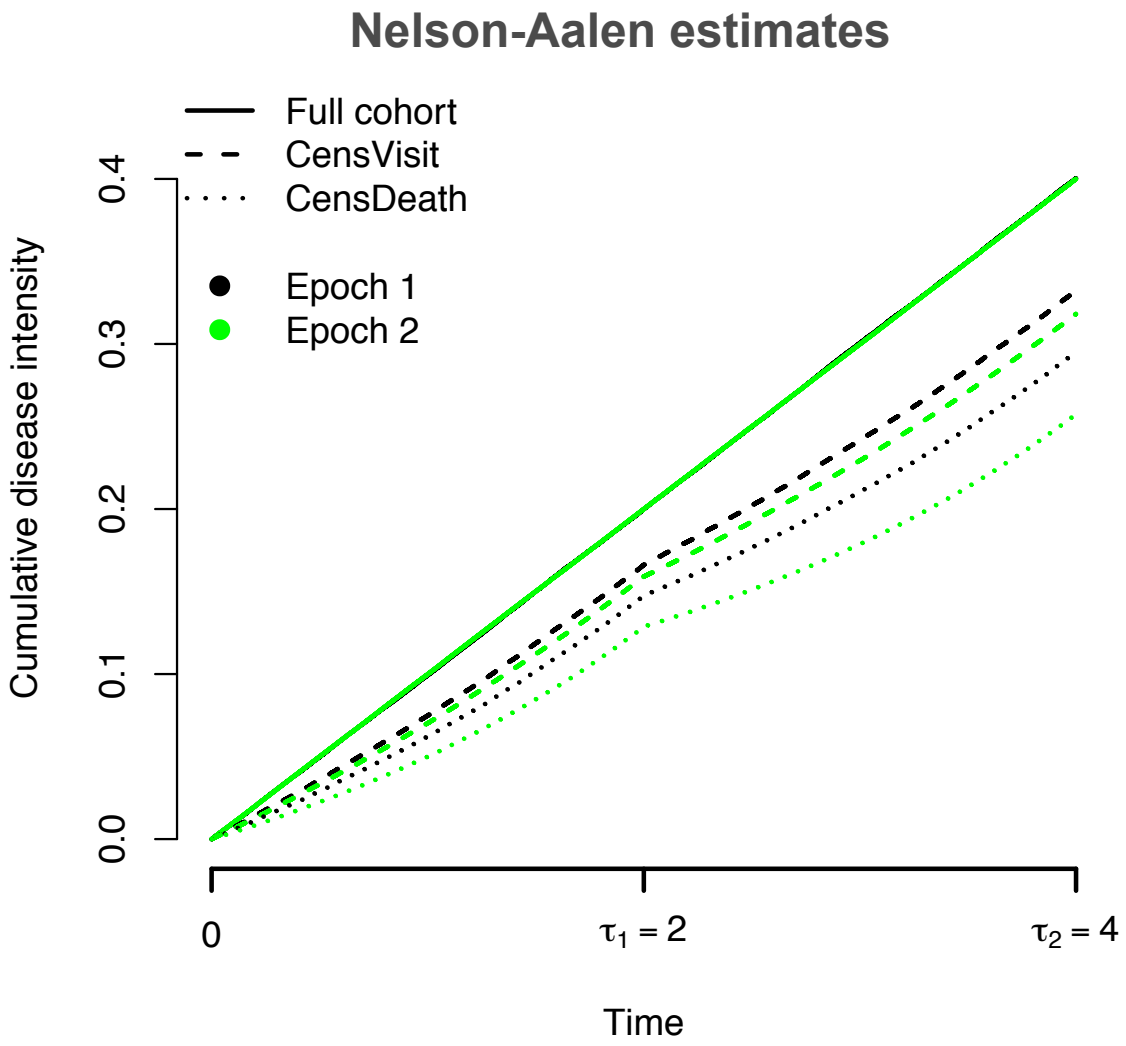

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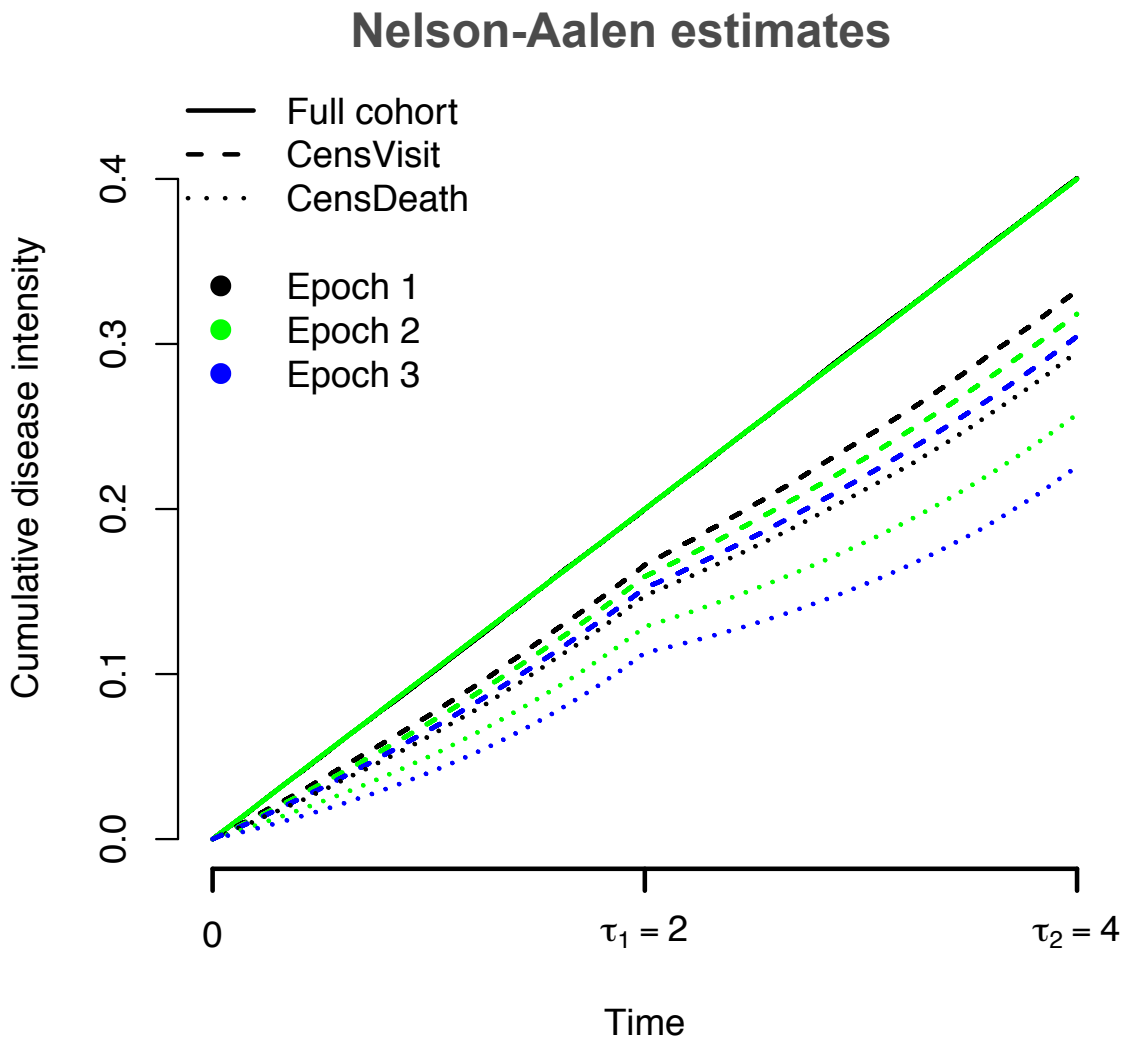

‘Censorings’ are common choice

Literature review, six journals, 2011-2012 — epidemiologic, geriatric, and environmental

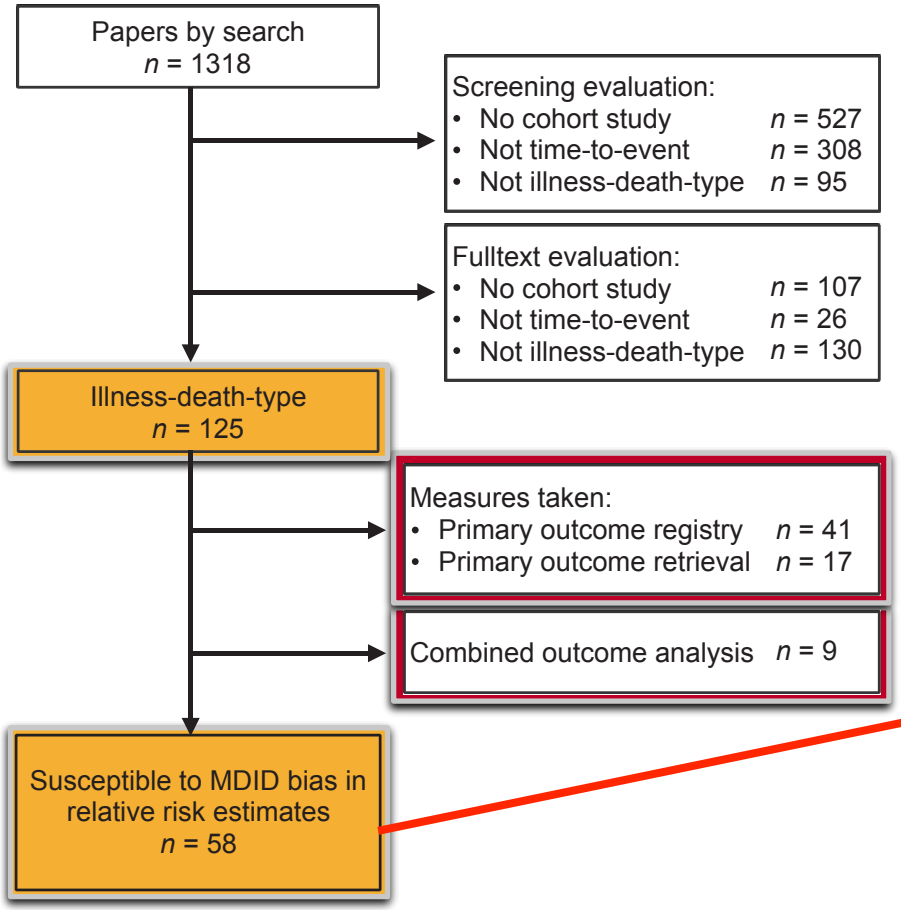

Fig. 2. Flow chart of study classification.

studies **CensDeath** = 25
studies **CensVisit** (incl. exclusion of death cases) = 31
studies **AllDiseased** = 1
studies **approach unknown** =1

‘Censorings’ are common choice

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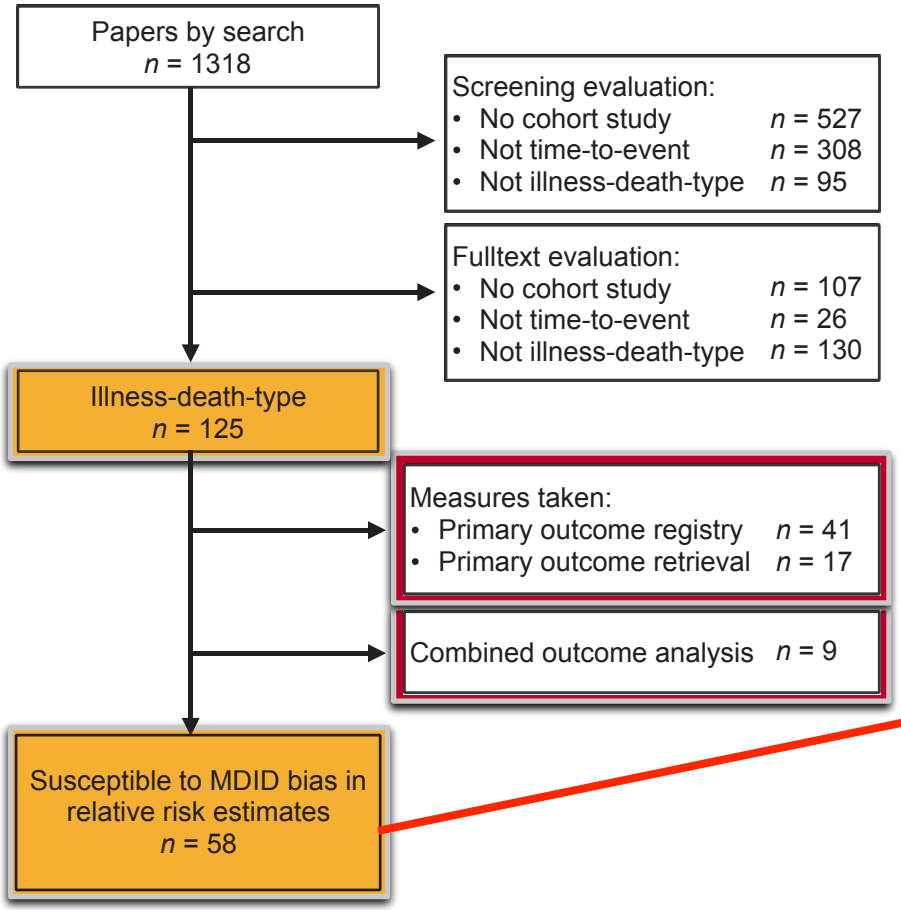

Fig. 2. Flow chart of study classification.

‘Censoring’ is the standard choice rather than the exception

studies **CensDeath** = 25
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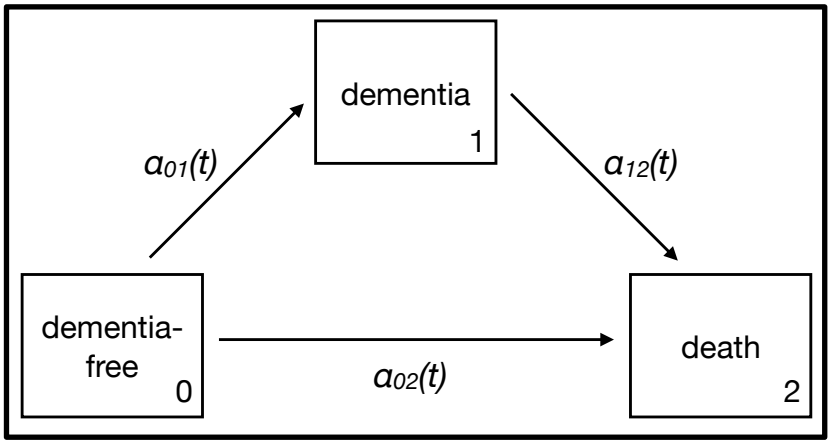
Which other method would be adequate?

Likelihood contributions for observation cases

$$T = \inf\{t > 0 \mid X(t) \neq 0\}$$
$$T_D = \inf\{t > 0 \mid X(t) = 2\}$$

$$P_{hj}(s,t) := P(X(t) = j \mid X(s) = h, \mathcal{F}_{s-})$$
$$= P(X(t) = j \mid X(s) = h)$$



Case 1 : For $i \in S_1 = \{i : T^i, T_D^i > \tau_2\}$:

$$\mathcal{L}_I = P_{00}(\tau_0, \tau_2)$$

Case 2 : For $i \in S_2 = \{i : \tau_0 < T^i \leq \tau_2, T_D^i > \tau_2\}$:

$$\mathcal{L}_{II} = P_{00}(\tau_0, T-)\alpha_{01}(T)P_{11}(T, \tau_2)$$

Case 3 : For $i \in S_3 = \{i : \tau_0 < T^i < \tau_1 < T_D^i < \tau_2\}$:

$$\mathcal{L}_{III} = P_{00}(\tau_0, T-)\alpha_{01}(T)P_{11}(T, T_D)\alpha_{12}(T_D)$$

Case 4 : For $i \in S_4 = \{i : \tau_{k-1} < T^i \leq T_D^i < \tau_k, k = 1, 2\}$:

$$\mathcal{L}_{IV} = P_{00}(\tau_0, T_D-)\alpha_{02}(T_D) + P_{00}(\tau_0, \tau_{k-1})P_{01}(\tau_{k-1}, T_D-)\alpha_{12}(T_D)$$

Multistate model approaches (& dementia)

	Fully parametric likelihood	**Penalized likelihood** (Joly et al. Biostatistics. 2002)	**Multiple imputation** (Yu et al. BiomJ. 2010)
Developed for	Estimating dementia incidence and risk factors for dementia and death		
Likelihood	All approaches build on identical likelihood contributions (tailored for interval-censored data) allowing for differential mortality		
Estimation requirements	Weibull intensities $\alpha_{hj}(t)$ (parametric)	Smooth intensities $\alpha_{hj}(t)$ (Splines)	(1) $\alpha_{02}(t) \propto \alpha_{12}(t)$ and (2) $\beta_{02} = \beta_{12} = \beta_2$.
Advantage	Converges even with sparse data information	More flexible than fully parametric model	Data imputed based on Cox model can be analyzed with any model
Disadvantage	Weibull distribution may be too restrictive	May fail to converge in sparse data	Estimation requirements may be too restrictive
Software	`SmoothHazard`	`SmoothHazard`	Binder et al. (Biom J. 2017)

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Disadvantage	Weibull distribution may be too restrictive	May fail to converge in sparse data	Estimation requirements may be too restrictive
Software	`SmoothHazard`	`SmoothHazard`	Binder et al. (Biom J. 2017)

NIH National Heart, Lung, and Blood Institute

Biologic Specimen and Data Repository Information Coordinating Center

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#5467 - Dementia incidence Data Request

Request Status
Fulfilled

Requestor (Institution)
Nadine Binder (Medical Center, University of Freiburg)

Currently Requested Studies
FHS-Cohort , FHS-OS

Date Requested
September 27, 2017

Last Modified
November 09, 2018

Related Requests
N/A

Dataset Download Links
Framingham Heart Study-Cohort (FHS-Cohort) default (ZIP - 172.5 MB)
Framingham Heart Study (FHS) Offspring (OS) and OMNI 1 Cohorts default (ZIP - 353.6 MB)

View Request | Comments | RMDA | Progress Report | More

We did not receive analysis dataset as used by Satizabal et al !

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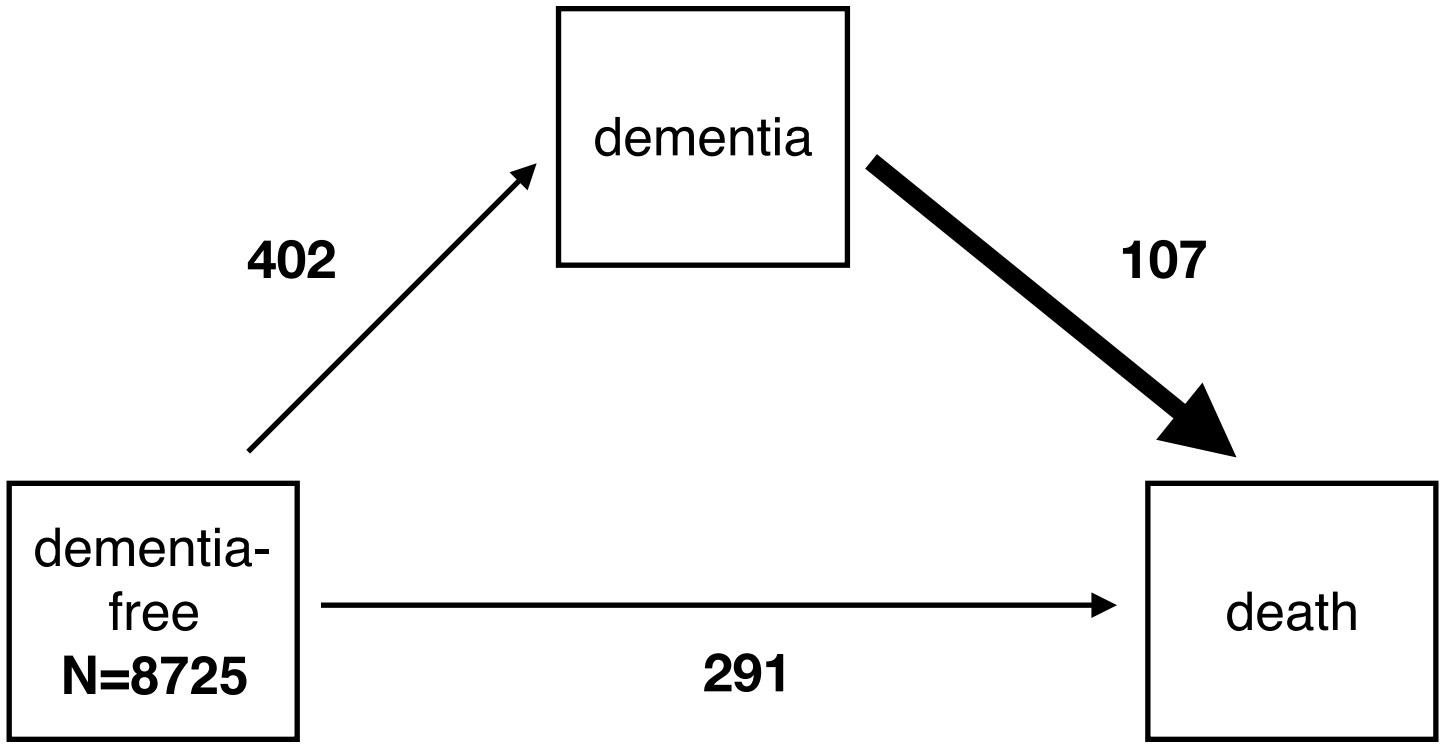
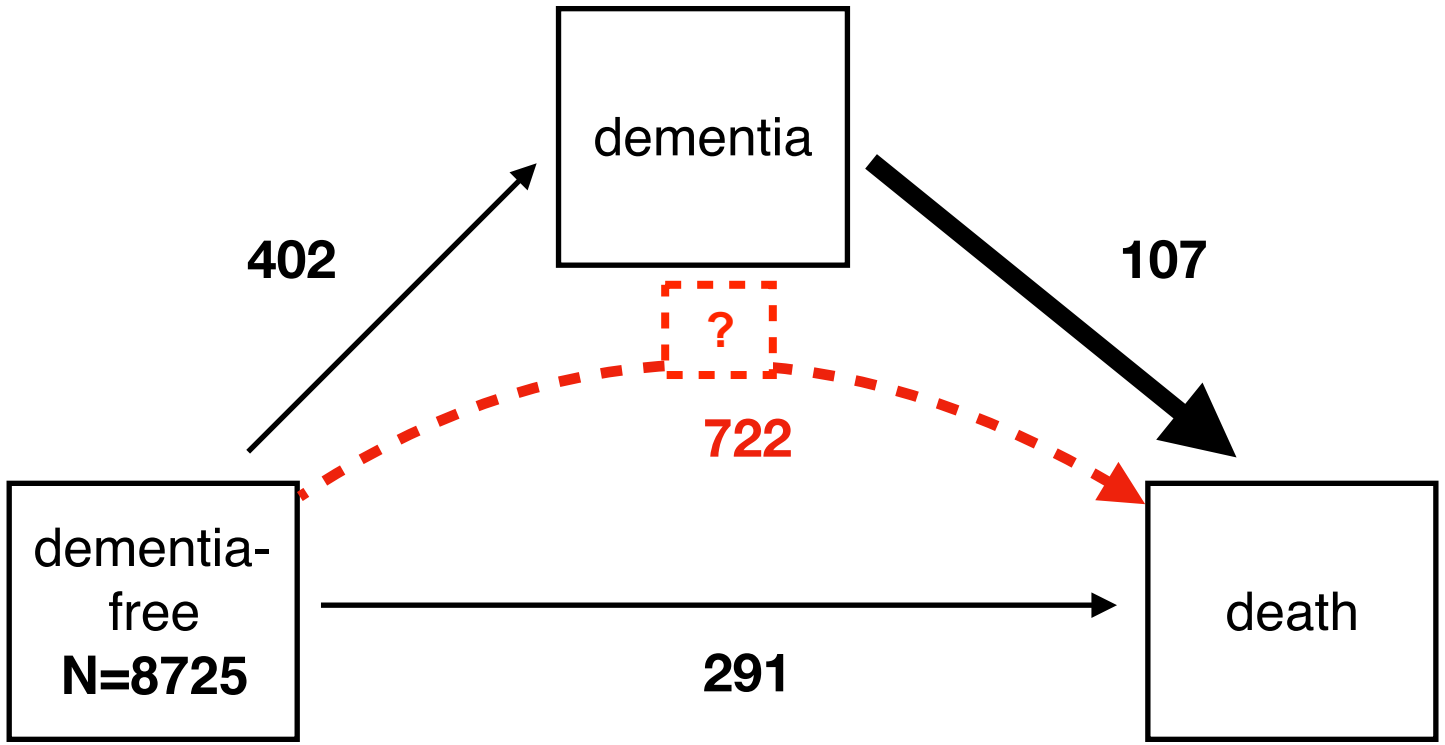
The illness-death-type data

Epoch 1 — Epoch 4

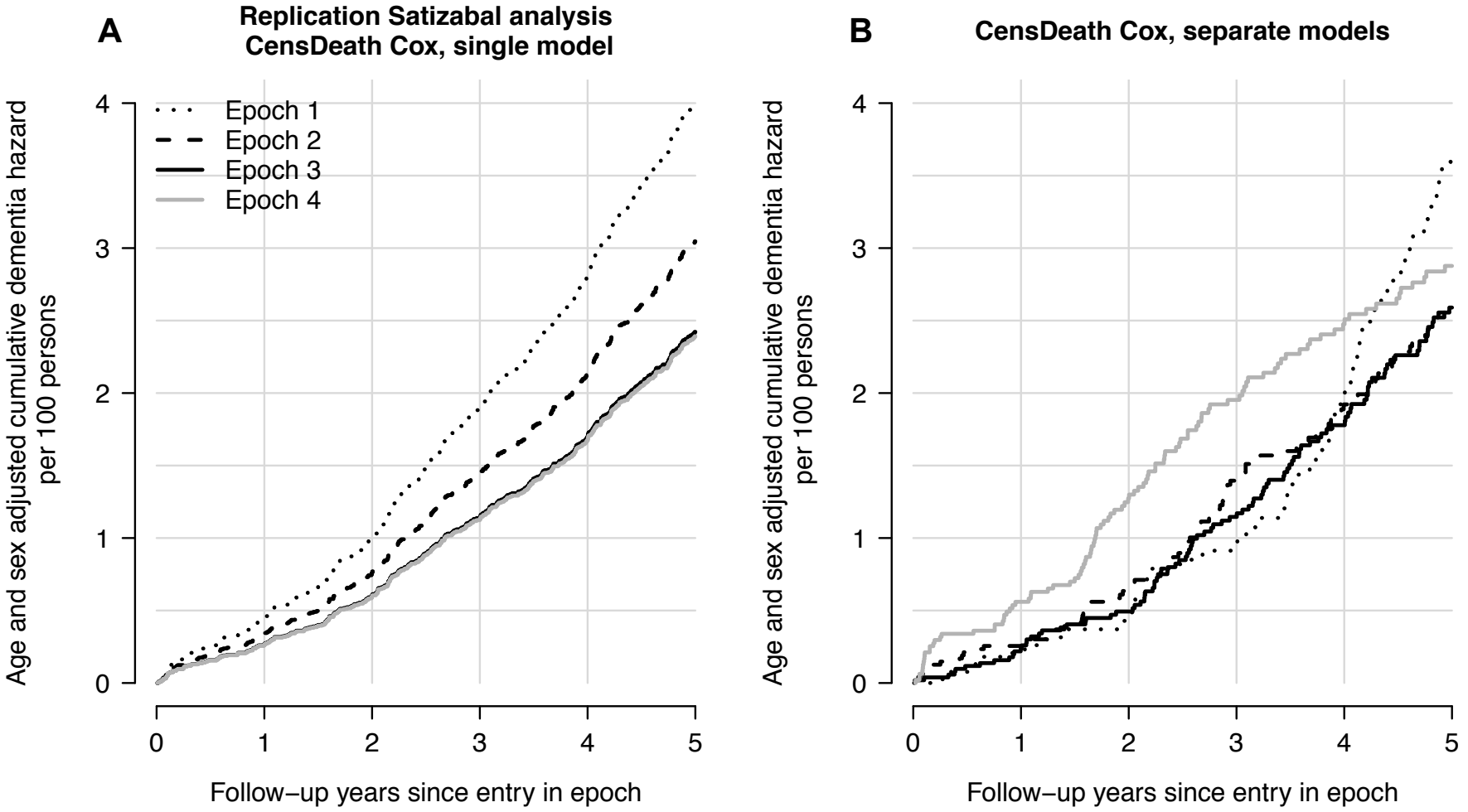


The illness-death-type data

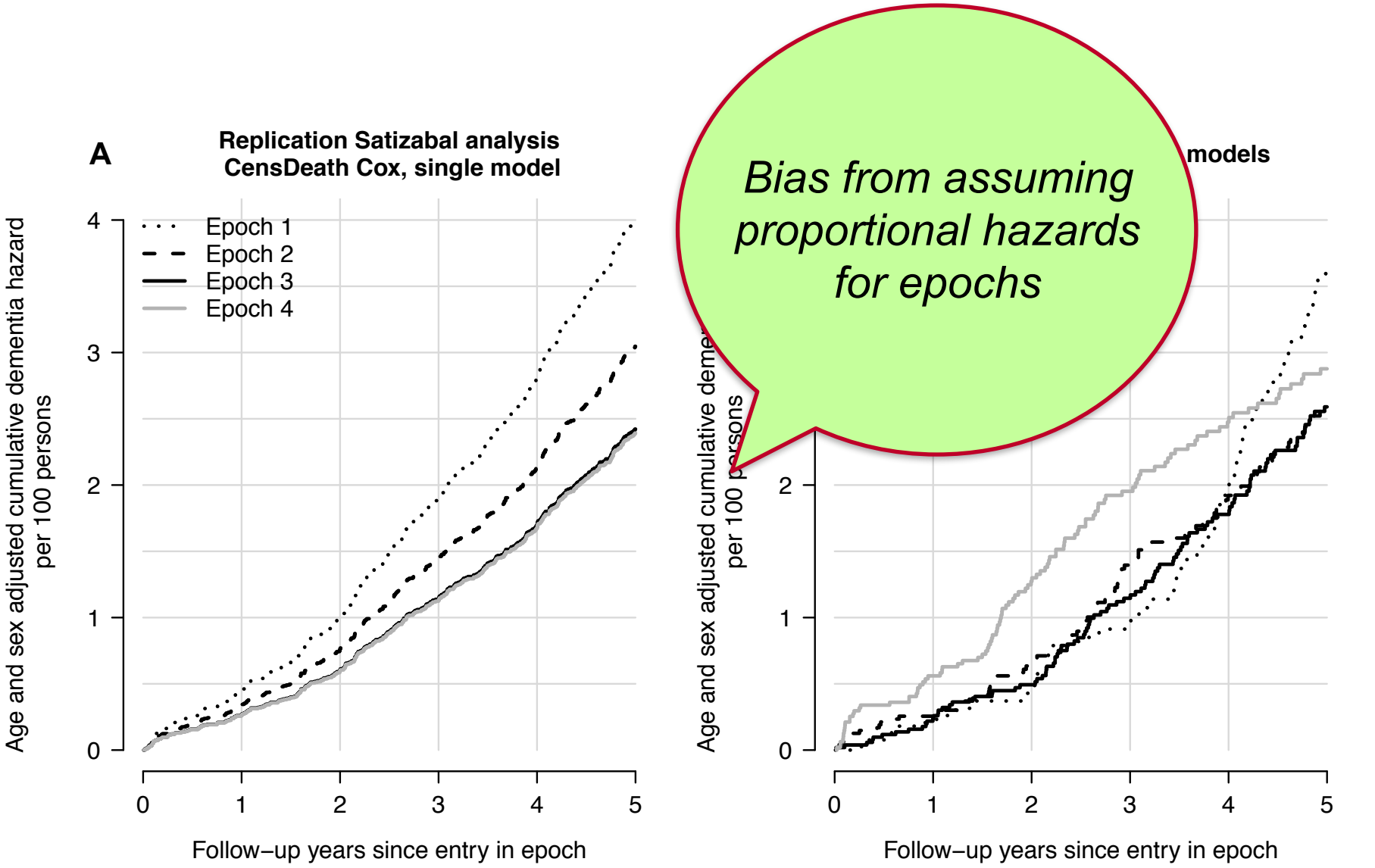
Epoch 1 — Epoch 4



Satizabal et al. reply NEJM 2016:
"719 observation periods had censoring of data with the comment 'dead and probably dementia-free'"

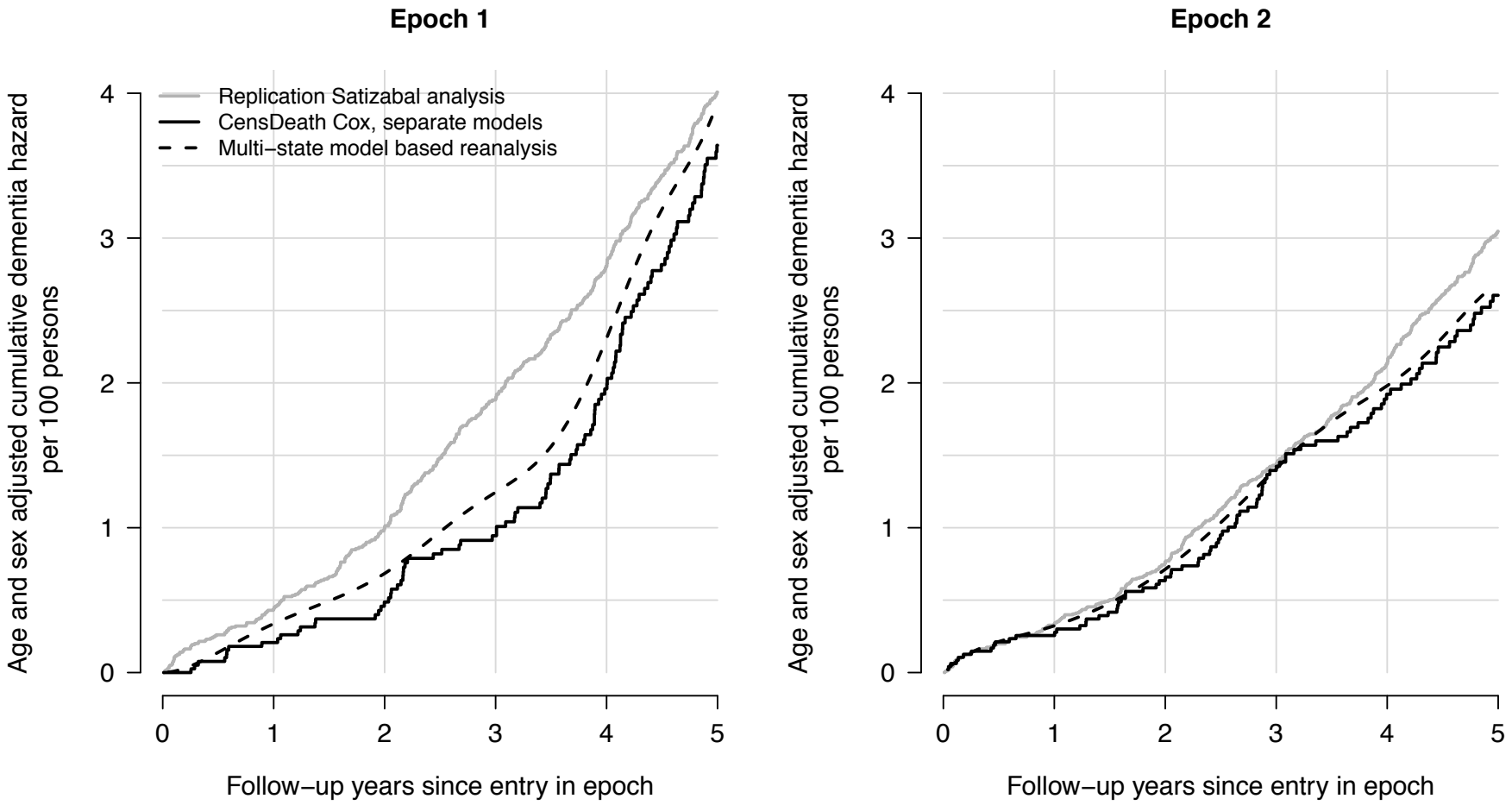


Binder et al. *Eur J Epidemiol.* 2019. Epub. ahead of print



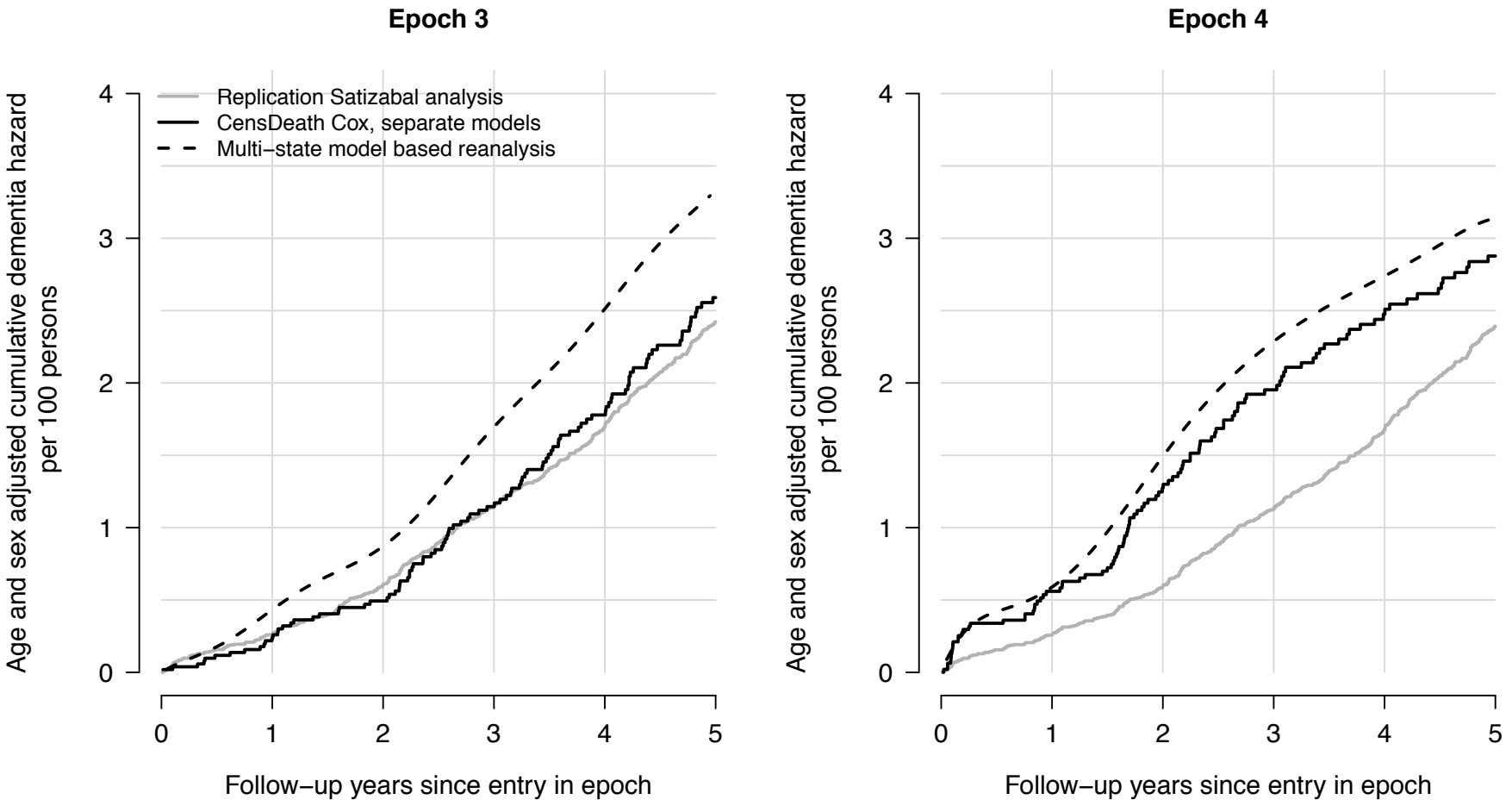
Binder et al. *Eur J Epidemiol.* 2019. Epub. ahead of print

PL multi-state model based reanalysis



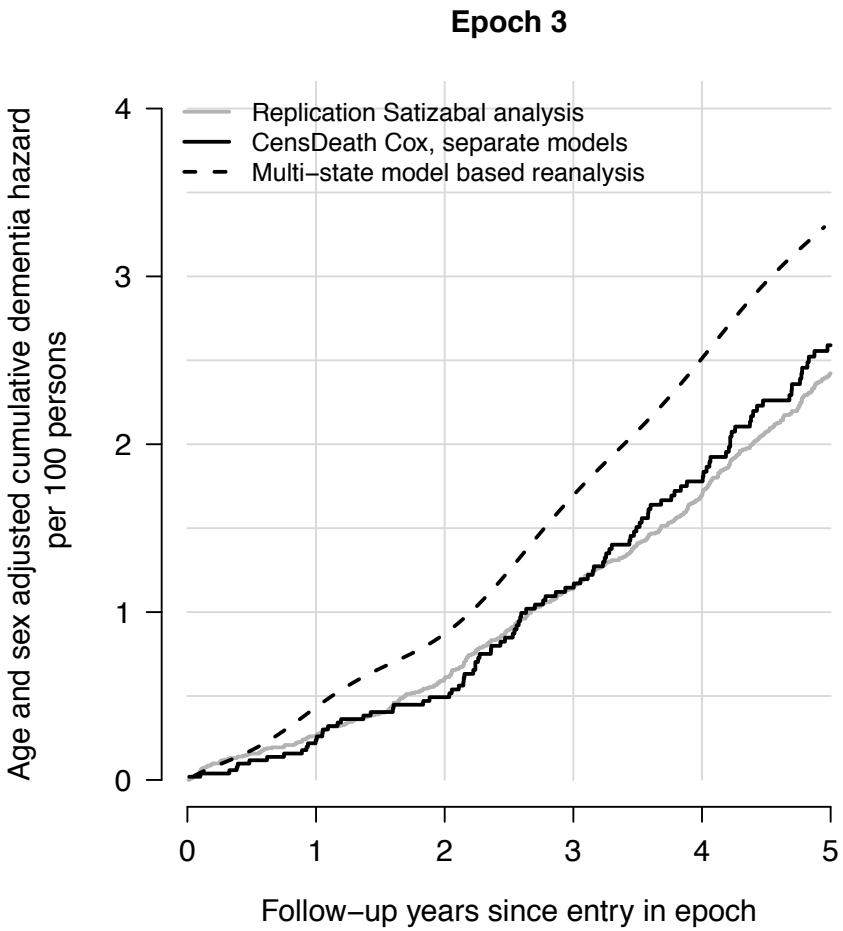
Binder et al. *Eur J Epidemiol.* 2019. Epub. ahead of print

PL multi-state model based reanalysis

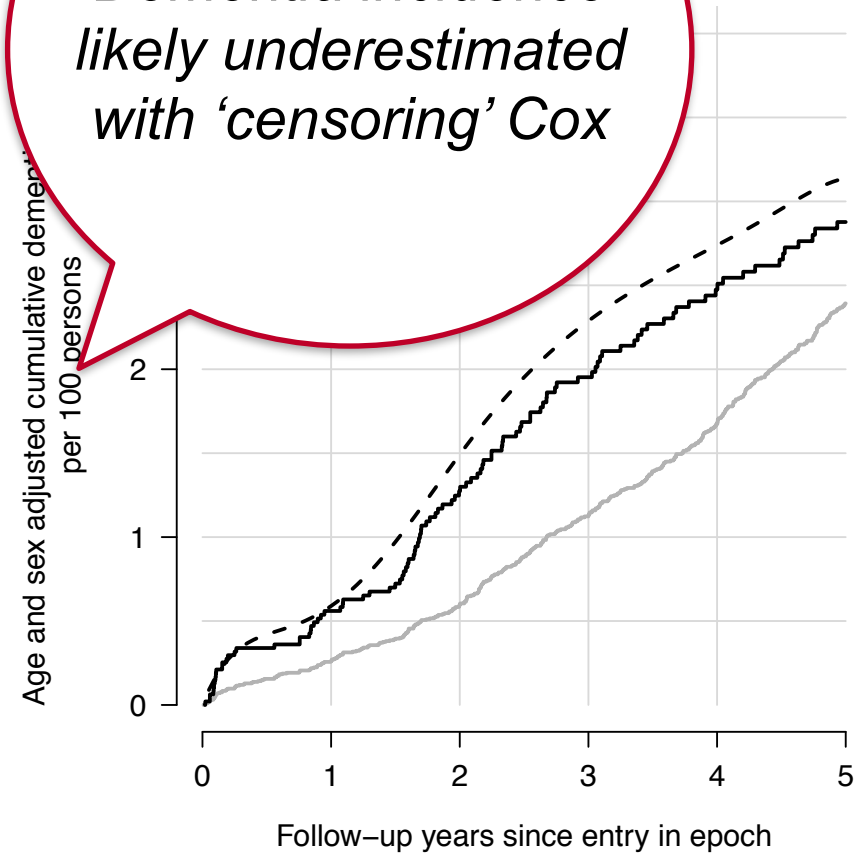


Binder et al. *Eur J Epidemiol.* 2019. Epub. ahead of print

PL multi-state model b ysis



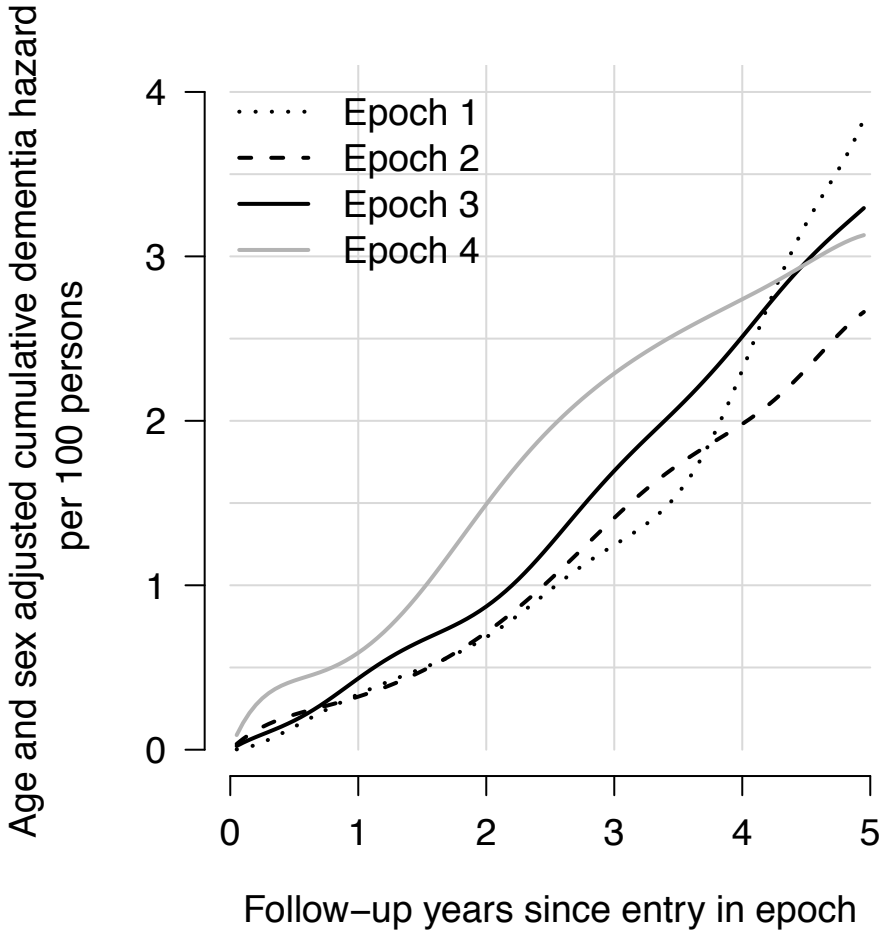
Dementia incidence likely underestimated with 'censoring' Cox



Binder et al. *Eur J Epidemiol.* 2019. Epub. ahead of print

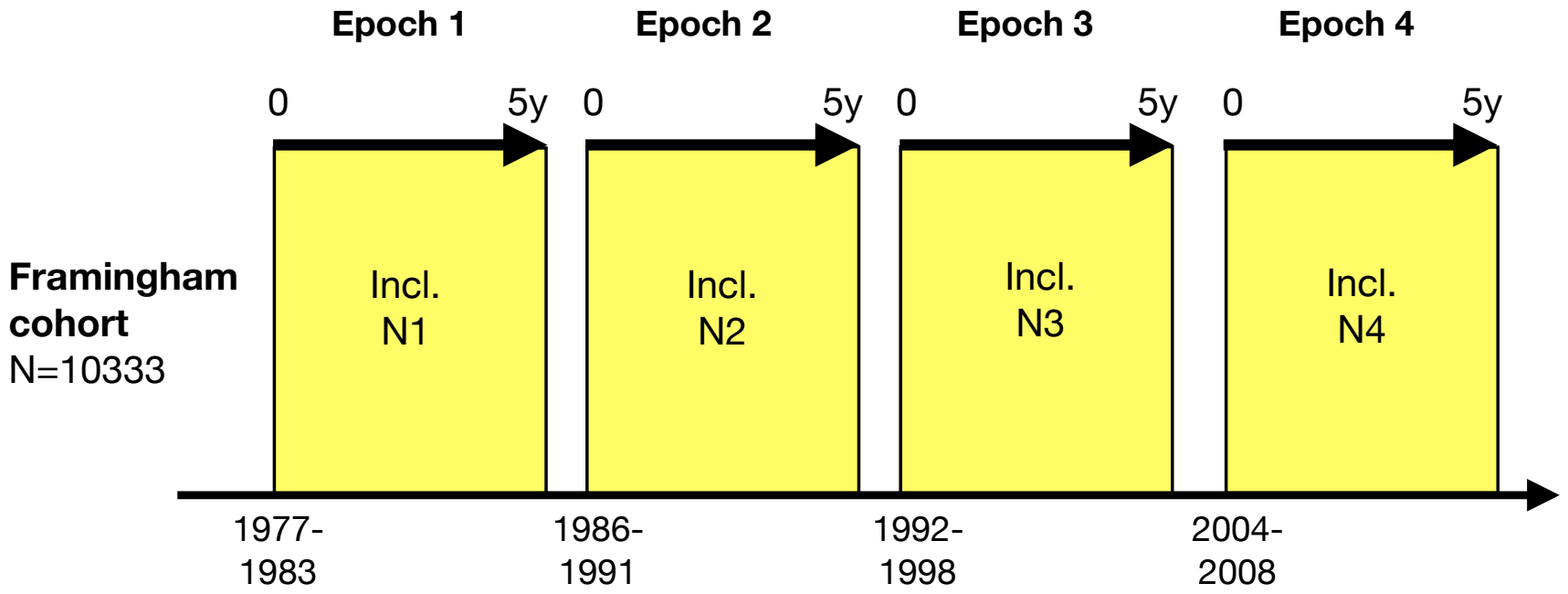
Has the dementia incidence declined?

Multi-state model based reanalysis did not show decline in dementia incidence



Binder et al. *Eur J Epidemiol.* 2019. Epub. ahead of print

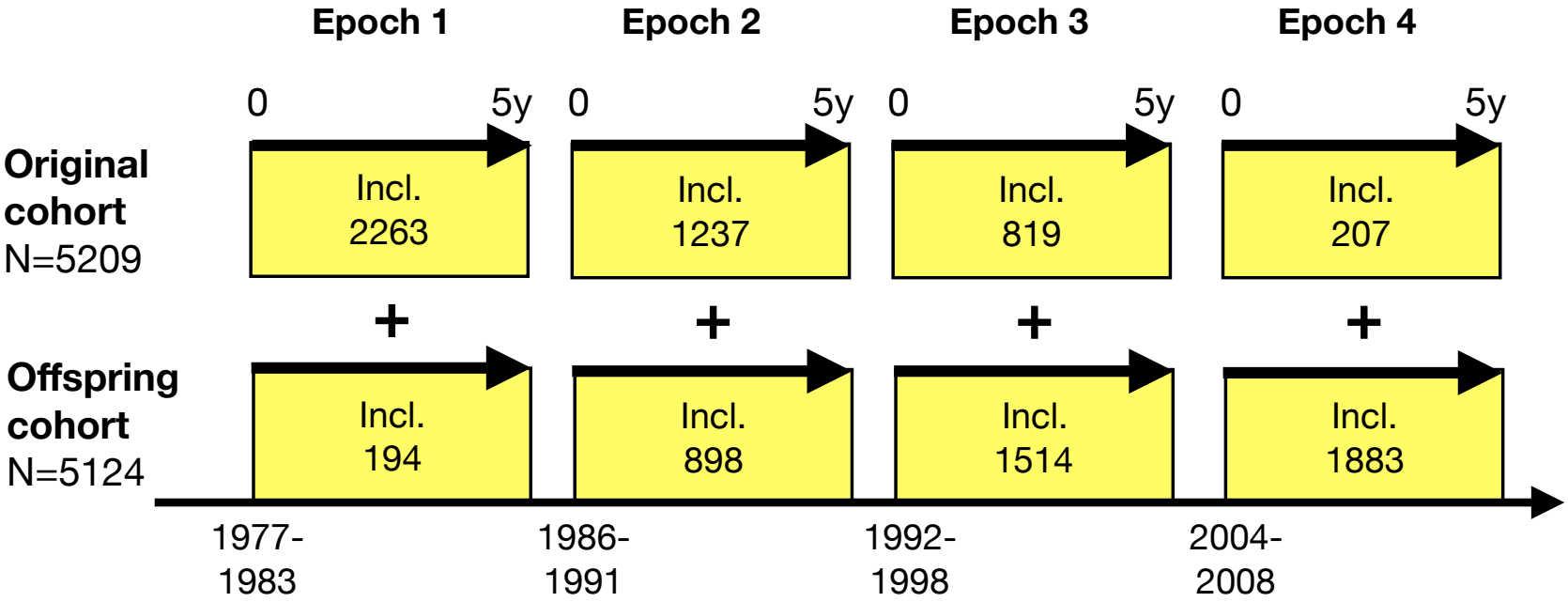
Still something left …



Incl. = age > 60
+ free of dementia at entry to epoch
+ follow-up

Outcome of interest: time from epoch entry to dementia

The actual design



Incl. = age > 60
+ free of dementia at entry to epoch
+ follow-up

Outcome of interest: time from epoch entry to dementia

Summary

MDID bias

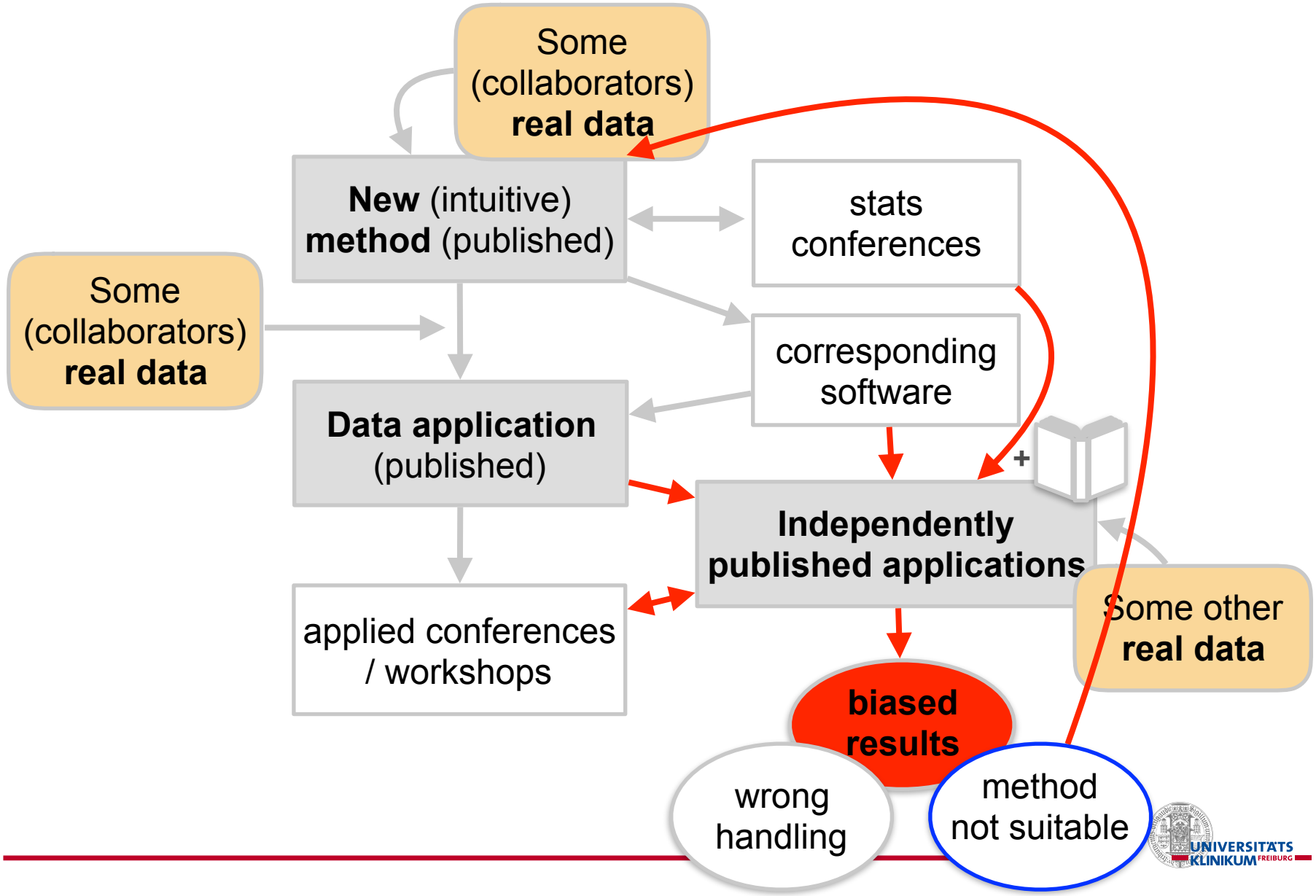
1. **What does a conventional Cox analysis estimate that retrospectively censors deaths with unknown disease status?**
   - 'Censoring' not well defined; Biased depending on differential mortality (Binder and Schumacher, J Clin Epidem. 2014)
2. **To what extent can approaches based on full likelihood of a multi-state model avoid bias in effect estimates?**
   - Multi-state model-based approaches are adequate choice for this type of data and generally yield less biased effect estimates
   - Approaches should be applied side by side as they are based on different statistical assumptions (Binder et al., Biom J. 2017)
3. **How often are ad-hoc analyses carried out in practice or which studies are susceptible to bias in estimates of disease risk?**
   - Data often not recognized as of type with Illness-death structure
   - Conventional analyses performed even in leading medical journals (Binder et al., J Clin Epidem. 2019)

Summary

Dementia study within Framingham Heart Study

- **Aim:** critically examine recent finding of a decline in dementia incidence by applying an analysis method developed for interval-censored illness-death-type data
- **Reported decline can be attributed** to
  - (a) failure to examine the proportional hazards assumption for epochs in Cox regression
  - (b) use of inappropriate statistical methods for analyzing interval-censored time-to-event data including cases with missing or inconclusive disease information due to death
- **Still, a trend analysis within Framingham could be possible** by dispensing with the epoch structure and comparing the original with the offspring cohort in a multi-state model analysis

Translation from biostatistics to epidemiology



Implications for the methods development community

STRATOS INITIATIVE

Topic Group 8: Survival analysis

Chairs: **Michal Abrahamowicz, Per Kragh Andersen, Terry Therneau**
Members: **Richard Cook, Pierre Joly, Torben Martinussen, Maja Pohar-Perme, Jeremy Taylor, Hans van Houwelingen**

TG8 attempts to help the understanding of the analytical issues, frequently encountered in real-life applications of survival analysis, and provide practical guidance regarding the validated methods and the user-friendly software that can be used to address these issues. To this end, we will draw on both earlier published reviews of the main issues and methods of survival analysis (e.g., Andersen et al 2012[3], Clark et al 2003[4], Clayton 1988[5]) and expertise of the TG8 members.

Thanks

To all who contributed to this research

Freiburg (incl. IMBI, Cochrane)
Martin Schumacher
James Balmford
Anette Blümle
Edith Motschall
Patrick Oeller
Renée M. Kingma

The sponsor

DFG Deutsche Forschungsgemeinschaft
German Research Foundation

Collaborating partners
Pierre Joly
Per Kragh Andersen

To the providers of the Framingham study data:
NHLBI BioLINCC Research Resources