European Journal of Epidemiology (2019) 34:1075–1083
https://doi.org/10.1007/s10654-019-00567-6

NEURO-EPIDEMIOLOGY

# A multi-state model based reanalysis of the Framingham Heart Study: Is dementia incidence really declining?

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Received: 20 May 2019 / Accepted: 9 October 2019 / Published online: 14 October 2019


## Abstract

Recent research by Satizabal and colleagues using data from the Framingham Heart Study demonstrated a linear decline in dementia incidence since the 1970s. The aim of this study is to re-examine these findings, given concerns that bias resulted from failure to account for the probability of acquiring dementia between the last dementia-free observation and death. This analysis included 5118 persons 60+ years of age, and determined the 5-year dementia incidence during four non-overlapping epochs. In addition to a replication using Cox proportional hazards, we applied separate Cox models (given unequal hazards across epochs) and a Spline-based penalized likelihood approach based on the illness-death multi-state model. In addition, we present a simulation study demonstrating the bias associated with the use of standard survival models. The simulation showed that estimates of disease incidence derived from the multi-state model-based approach were consistent with the true disease incidence, whereas Cox regression 'censoring' observations at death or at last observation consistently underestimated it. Using the Framingham data, the 5-year age- and sex-adjusted cumulative hazard rates for dementia as derived from the multi-state model-based approach were 3.84, 2.66, 3.29 and 3.13 per 100 persons in epochs 1, 2, 3 and 4 respectively. The findings do not support the conclusion that dementia incidence has declined in the Framingham Heart Study over the given time period. Previous findings of a decline may have been an artefact resulting from improper treatment of those cases in which death precluded the observation of dementia onset.

**Keywords** Dementia · Incidence · Epidemiological biases · Multi-state model · Framingham Heart Study

## Introduction

Globally, the number of people living with dementia is estimated to have more than doubled from 1990 to 2016, primarily due to population growth and ageing [1]. Although the prevalence of dementia, particularly in Western nations, is expected to continue to increase as average life expectancy increases [2], recently-reported trends in the age-specific incidence of dementia point to a possible decrease over time in high-income countries [3]. It has been suggested that this may be attributable to improvements in risk factor management (e.g., improved cardiovascular health) as a result of beneficial environments [3], although this is a complex question for which more data are urgently needed [4].

In response to the increasing recognition of dementia as a serious public health problem, research on the incidence of and risk factors for dementia has flourished in recent years. A prominent example is a paper published in the New England Journal of Medicine, in which Framingham Heart Study data was used to examine temporal trends in the incidence of dementia among

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s10654-019-00567-6) contains supplementary material, which is available to authorized users.

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individuals aged 60+ over the 30-year period from 1977 to 2008 [5]. As calculated using Cox proportional hazards models, 5-year age- and sex-adjusted cumulative hazard rates for dementia were found to have linearly declined across four non-overlapping 5-year epochs; relative to the first epoch, dementia incidence declined by 22%, 38% and 44% respectively in the three subsequent epochs. The temporal trend was observed only in those with at least a high school diploma, suggesting rising educational levels may be a contributing factor to the decline.

A pervasive problem in the study of ageing cohorts, particularly where follow-up assessments are conducted at discrete intervals, is that death may occur before the onset of disease (e.g., dementia) can be determined. Standard survival models are inadequate to analyze interval-censored illness-death type data [6, 7], as a result of their inability to account for the probability of developing a disease between the last observation and death. To the extent that this occurs, it results in an underestimate of the incidence of disease and bias in Cox model hazard ratio estimates [8, 9]. We suspect that this bias, known as missing disease information due to death (MDID) bias [10], may in part be responsible for the observed decline in dementia incidence in this study and in others which have used similar methods (e.g. [11–13]). Although the Framingham study goes to considerable lengths to minimize the number of death cases for which dementia status is unobserved (e.g. via comprehensive post-mortem medical record reviews and interviews with family members), final dementia status cannot be definitively ascertained for a substantial proportion of death cases [14, 15].

Analytic methods expressly designed to contend with the problem of MDID bias have been proposed based on the illness-death multi-state model [8]. In this underlying data model, represented in Fig. 1, each cohort member starts in the initial state (alive, no diagnosis of dementia) and may either move into the other states as indicated by the arrows, or remain in the initial state until the end of the observation period. Recent work (e.g. [8, 10, 16]) has demonstrated that analytic methods including Spline-based penalized likelihood [6] and multiple imputation of missing disease information based on the event time distribution of the available data [17]

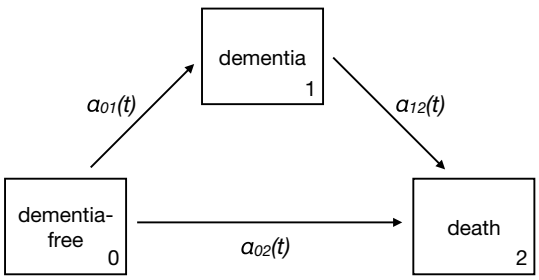


**Fig. 1** Three-state illness-death model with an initial 'dementia-free' state 0, a diseased 'dementia' state of interest 1, and the death state 'death' 2. The arrows illustrate the potential transitions between the states

result in improved disease incidence estimates, particularly where follow-up intervals are wide and the exposure has an impact on death. To date, however, methods such as this have not been widely applied to the study of dementia incidence.

The aim of this paper is to re-examine the question of whether dementia incidence declined across the four epochs of Framingham Heart Study data investigated by Satizabal et al. [5], using statistical methods based on the illness-death multi-state model. First, we conduct a simulation to illustrate the extent to which censoring of time-to-onset of disease for death cases with unobserved prior disease at death or at last observation yields biased disease incidence estimates, comparing the findings of a standard Cox proportional hazards model with those obtained using the Spline-based penalized likelihood approach based on the illness-death multi-state model. Second, we re-analyze the Framingham data to determine estimates of dementia incidence over time, as derived using the penalized likelihood approach in addition to Cox regression. In doing so, we plot the age- and sex-adjusted cumulative dementia hazards for each epoch as calculated by each analytic method, thereby making full use of the time-to-event information in the data as recommended by e.g. [18]. We hypothesize that the previously-observed decrease over time in dementia incidence [5] will be reduced, or eliminated entirely, if analytic methods designed to account for MDID bias are used.

## Simulation study

### Methods

The aim of the simulation study was to illustrate the extent to which censoring of time-to-onset of disease for death cases with unobserved prior disease at death or at last observation yields biased disease estimates when analyzed using standard survival models. We first simulated complete illness-death reference data (without any additional right-censoring or truncation), generating $N = 1000$ independent data sets with $n = 3000$ individuals each. The simulation study was driven by the hazard rates [19], which completely determine the Markovian illness-death process that we consider. We assumed the hazards for the three possible transitions in the illness-death multi-state model to be constant (for ease of illustration) and computed them as follows:

$$\alpha_{01}(t) = 0.1,\ \alpha_{02}(t) = 0.1,\ \alpha_{12}(t) = 0.3 \text{ (Epoch 1).}$$
$$\alpha_{01}(t) = 0.1,\ \alpha_{02}(t) = 0.2,\ \alpha_{12}(t) = 0.45 \text{ (Epoch 2).}$$
$$\alpha_{01}(t) = 0.1,\ \alpha_{02}(t) = 0.3,\ \alpha_{12}(t) = 0.6 \text{ (Epoch 3).}$$

These three parameterizations, envisioned as three separate epochs of observation, hold dementia incidence ($\alpha_{01}$) constant, but vary in the hazard for death with ($\alpha_{12}$) and without ($\alpha_{02}$) prior dementia. This is designed to mimic cohort studies such

as the Framingham Heart Study, in which the risk of death for individual cohort members increases over time as the cohort ages and where there is *differential mortality* meaning the risk of death is increased after dementia compared to without prior dementia, i.e., $\alpha_{12} > \alpha_{02}$. We note here that even though the choice of parametrizations does not follow a concrete realistic scenario, they are still not unrealistic, and more importantly, the findings hold for any kind of parameterization given differential mortality.

In each of the simulated complete illness-death reference data sets, we then artificially induced MDID by setting two discrete pre-specified visits in follow-up time, $t_1 = 2$ and $t_2 = 4$, representing biannual cohort examinations, and changing the complete data as if we had collected the event information only at these visits. Further information on the simulation procedure is available elsewhere [9].

For each epoch, we calculate disease incidence estimates following the application of two 'censoring' schemes for subjects dying with unobserved prior disease: censoring at death (CensDeath) and censoring at last observation (CensVisit). We note here that this type of censoring is not properly defined, as it is not predictable from the past but conditional on the future, and hence does not fulfil the condition of independent censoring [10]. Estimates derived using Cox regression using the R function coxph (R package survival) are contrasted with estimates derived from Spline-based penalized likelihood (R package SmoothHazard), the latter which also does not make any parametric assumption on the hazards and is fitted using the incomplete data with MDID.

### Results

Figure 2 shows cumulative disease incidence estimates for all three simulated epochs, as calculated using Cox regression.

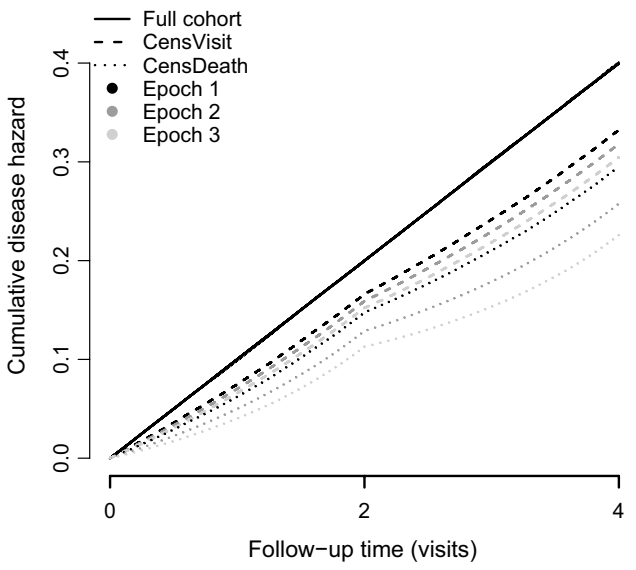


**Fig. 2** Non-parametric estimates of the cumulative disease incidence as a function of follow-up time from the simulation study

The diagonal line represents the reference estimate obtained from the full cohort, i.e., the mean estimate as obtained as an average over all complete illness-death reference data sets. It can be seen that cumulative disease incidence is underestimated to a greater extent as the hazard of death increases across the three epochs, both with and without prior disease. In addition, censoring death cases at death (CensDeath) consistently results in greater underestimation of disease incidence than censoring at last observation (CensVisit). The estimate derived from the penalized likelihood multi-state model approach did not deviate noticeably from the true disease incidence, and is therefore not displayed.

## Analysis of dementia incidence using the Framingham data

### Study sample

The Framingham Heart Study is a community-based, longitudinal cohort study initiated in 1948. At the time of the Satizabal et al. [5] study, the original cohort of 5209 residents of Framingham, Massachusetts had undergone up to 32 examinations every 2 years, involving detailed history taking by a physician, a physical examination, and laboratory testing. An offspring cohort, consisting of 5214 offspring of participants in the original cohort and their spouses, was initiated in 1971. The offspring cohort have completed up to 9 examinations, scheduled every 4 years. In both Satizabal et al. [5] and the present study, these two cohorts were combined for analysis, resulting in a similar sample size in all four epochs. We evaluated the same non-overlapping epochs as Satizabal et al. [5] (see Table 1 for the timespan for each epoch) and applied the same exclusion criteria.

A detailed description of the surveillance methods for dementia in the Framingham study has been provided in several previous publications [5, 20, 21]. Briefly, every case of possible cognitive decline, as established via screening assessments and additional neurologic and neuropsychological examinations, is reviewed by a dementia review panel to determine whether the person had dementia, the dementia subtype, and the date of onset. Data sources for this review include the aforementioned screening assessments and examinations, telephone interviews with caregivers, medical records, neuroimaging studies and autopsies. After death, the panel reviews medical and nursing records to determine whether the person may have had cognitive decline since his or her last examination, but a definitive diagnosis of dementia is often not possible; dementia case ascertainment from medical records is known to be subject to some degree of misclassification [22, 23]. Satizabal et al. [15] suggested that such individuals should be classified as 'probably dementia-free'.

**Table 1** Baseline characteristics

| Characteristic | Epoch 1 (N = 2303) | Epoch 2 (N = 2035) | Epoch 3 (N = 2268) | Epoch 4 (N = 2119) |
|---|---|---|---|---|
| Age at entry (years) | | | | |
| Mean | 69 ± 7 | 71 ± 7 | 72 ± 8 | 72 ± 9 |
| Range | 60–88 | 60–95 | 60–101 | 60–100 |
| Female sex (%) | 59 | 55 | 57 | 56 |

The baseline examination period was between 1977 and 1983 for the first epoch, between 1986 and 1991 for the second epoch, between 1992 and 1998 for the third epoch, and between 2004 and 2008 for the fourth epoch

The dataset for this study was retrieved from the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) upon request to the National Heart, Lung, and Blood Institute (NHLBI) and was current to December 2018. As a result of routine data updates, and a lack of clarity regarding the precise definition of each epoch's 'inception cohort' (see the Supplementary material for more detail), there were minor differences to the earlier data analyzed by [5]. Supplementary Figure 1 displays the number of participants contributing data to each epoch, as well as the number of participants excluded and reason for exclusion at each epoch.

Time-to-event was determined for the primary outcomes of dementia onset and death, measured in days from each epoch's baseline examination. Participants who were alive and dementia-free at the end of an epoch were censored at the end of the 5-year observation period or at the last date on which they were known not to have dementia, and could continue to contribute data to a subsequent epoch. Those who died during a 5-year observation period were classified as 'died dementia-free', 'died following dementia diagnosis', or in the case of no definitive diagnosis, 'final dementia status inconclusive'.

## Statistical analysis

We calculated dementia incidence for each of the four epochs, reporting 5-year cumulative hazard rates (the cumulative incidence of dementia per person for each epoch) as a curve over time. These estimates were derived using: (a) Cox proportional-hazards models with death cases censored at death (CensDeath), and (b) the aforementioned multi-state model approach of Spline-based penalized likelihood. All models are adjusted for age (linear continuous) and sex. The CensDeath Cox model estimates represent a replication of the primary analysis of [5]. To obtain the age- and sex-adjusted cumulative hazards from the penalized likelihood approach, we took the estimated baseline hazards, multiplied them by a constructed linear predictor from the estimated regression coefficients multiplied by the mean of the individual age and sex characteristics, and finally integrated the resulting hazards model over time. Thereby, the covariates are assumed to have Cox-type multiplicative effects on the intensities. Robust sandwich estimators were used to account for the inclusion of individual participants in more than one epoch.

## Results

In total, the sample across the four epochs consisted of 5118 individual participants who collectively contributed data for 8725 observation periods (39,506 person-years), slightly lower than the 9015 observation periods studied in [5]. Table 1 displays the distribution of age and sex at the baseline examination period for each epoch. An extended version of Table 1, including variables as reported by [5], can be found in the supplementary material (Table S1).

Table 2 displays the numbers and proportions in each epoch for each possible transition in the illness-death multistate model, corresponding with the paths displayed in Fig. 1. Overall, 402 confirmed diagnoses of dementia were observed across the four epochs, of whom 295 were alive at the end of the observation period in which the diagnosis took place, and 107 had died. This was higher than the 371 confirmed cases reported by [5] over the same period, despite the lower number of observation periods. Of the overall 1120 deaths, 64.5% ($n = 722$) were inconclusive with regard to their final dementia status, and thus were potential contributors to MDID bias. This is very similar to the number of inconclusive observations ($n = 719$) reported by [15]. It is important to note that the proportion of such cases differed across the four epochs, being notably lower in epoch 1 (4.9%) than in the other three epochs (11.8%, 8.8% and 8.1% for epochs 2, 3 and 4 respectively).

Initially we calculated 5-year age- and sex-adjusted cumulative hazard rates using a Cox model, as a direct replication of the analyses reported in [5], with epoch entered in the model as a series of dummy variables. This analysis, shown in Table 3 (expressed as cumulative hazard rates per 100 persons, along with their confidence intervals) and illustrated in Fig. 3a, replicated the primary finding of [5] of a decline over time in the incidence of dementia. The corresponding estimates from the original analysis of [5] are also displayed in the table for comparison; as expected

**Table 2** Numbers and proportions in each epoch for each possible transition in the illness-death model, corresponding with the paths displayed in Fig. 1

| | N | Alive and dementia-free | Diagnosed dementia at exams | Diagnosed dementia from death review* | Died dementia-free | Died following dementia diagnosis** | Final dementia status inconclusive |
|---|---|---|---|---|---|---|---|
| | | No transition | 0→1 | | 0→2 | 1→2 | 0→2 or 1→2 |
| Epoch 1 | 2303 | 1933 (83.9) | 100 (4.3) | 4 (0.2) | 154 (6.7) | 30 (30) | 112 (4.9) |
| Epoch 2 | 2035 | 1655 (81.3) | 88 (4.3) | 3 (0.1) | 49 (2.4) | 24 (27.3) | 240 (11.8) |
| Epoch 3 | 2268 | 1937 (85.4) | 99 (4.4) | 2 (0.1) | 31 (1.4) | 18 (18.2) | 199 (8.8) |
| Epoch 4 | 2119 | 1785 (84.2) | 104 (4.9) | 2 (0.1) | 57 (2.7) | 35 (33.7) | 171 (8.1) |
| Overall | 8725 | 7310 (83.8) | 391 (4.5) | 11 (0.1) | 291 (3.3) | 107 (27.4) | 722 (8.3) |

*Number and proportion of individuals with dementia diagnosis obtained from death review

**Proportions in this column signify the proportion of those diagnosed with dementia who died in the same epoch

**Table 3** Temporal trends in the incidence of dementia, by method for handling death cases with missing dementia status

| | Epoch 1 | Epoch 2 | Epoch 3 | Epoch 4 |
|---|---|---|---|---|
| *5-year cumulative hazard rate (95% CI)** | | | | |
| Original Satizabal analysis[§] | 3.6 (2.9–4.4) | 2.8 (2.2–3.5) | 2.2 (1.8–2.8) | 2.0 (1.5–2.6) |
| Replication Satizabal analysis | | | | |
| CensDeath Cox, single model | 4.01 (3.07–4.78) | 3.05 (2.27–3.72) | 2.42 (1.82–2.96) | 2.39 (1.76–2.96) |
| CensDeath Cox, separate models | 3.64 (2.48–4.65) | 2.6 (1.67–3.47) | 2.59 (1.66–3.44) | 2.88 (1.86–3.8) |
| Multi-state model based reanalysis | | | | |
| SmoothHazard, separate models | 3.84 (1.99–5.69) | 2.66 (1.22–4.1) | 3.29 (1.61–5.02) | 3.13 (1.58–4.69) |

*5-year cumulative hazard rates per 100 persons adjusted for age and sex

[§]Estimates and confidence intervals in Satizabal et al. [5] only provided to one decimal place

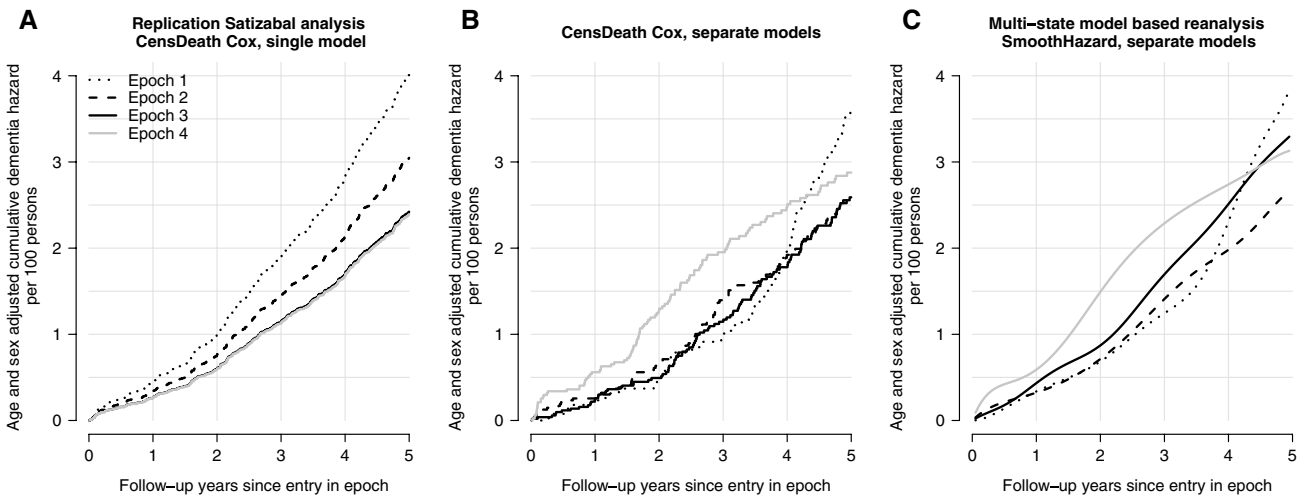


**Fig. 3** Estimates of the age- and sex-adjusted cumulative dementia hazard as a function of each of the 5-year follow-up periods, each analysis approach illustrated in a separate plot (**a**–**c**)

given the aforementioned minor sample differences, the estimates we obtained were consistently slightly higher.

However, testing the proportional hazards assumption [24] for epoch showed that this assumption was not met (all p values below 0.01), i.e., epoch did not have a certain constant multiplicative effect on an overall baseline dementia hazard. We therefore allowed the cumulative dementia hazard to differ by epoch by fitting four separate models, one for each epoch. The resultant estimates are shown in Table 3, and the non-parametric estimates of

the adjusted cumulative hazards functions are displayed in Fig. 3b, which also graphically illustrate the extent to which the PH assumption is not met when compared to Fig. 3a. When the dementia hazard was permitted to vary by epoch, the previously-observed linear decline in dementia incidence was no longer apparent. While the point estimate at year 5 was the highest for epoch 1, the difference was not statistically significant as evidenced by the overlap in the confidence intervals. Moreover, Fig. 3b shows that the cumulative dementia hazard was similar in all four epochs until year 4, and only increased in epoch 1 in the final year of the observation period.

Next, similar analyses, i.e., separately for each epoch, were conducted using the penalized likelihood illness-death model approach. The 5-year point estimates per 100 persons along with their confidence intervals are also shown in Table 3, and the semi-parametric (Spline-based) estimates of the adjusted cumulative hazards functions per 100 persons in Fig. 3c (penalized likelihood). This analysis did not find a linear decline in dementia incidence over time. However, there were notable differences between them. The shape of the cumulative hazards from the penalized likelihood approach (Fig. 3c), in finding a similar cumulative dementia hazard in all four epochs until the final year followed by an increase in epoch 1 only, closely resembled that of the separate-model Cox analysis (Fig. 3b).

Figure 4 displays the same age- and sex-adjusted cumulative hazard function estimates as illustrated in Fig. 3, however, separately for each epoch, permitting a comparison of the magnitude of the hazards within each epoch. First, comparing the two Cox model analyses, three of the four epochs differed substantially, either in terms of their course evolving over time or the final cumulative hazard rate. This confirms that assuming that the hazard is proportional across epochs is likely to lead to misleading findings. Second, we observe that as expected, the separate-model Cox analysis underestimated the cumulative dementia hazard in all four epochs compared to the penalized likelihood illness-death model-based analysis. In some instances these differences were negligible (particularly in epoch 4), but in others (e.g., epoch 3) they were clear and consistent throughout the observation period.

## Discussion

This study was designed to critically examine the recent finding of a decline in dementia incidence over the last 40 years in the Framingham Heart Study [5], by applying an analysis method developed for interval-censored illness-death-type data. Overall, our findings do not support the conclusion that dementia incidence has declined in this cohort over the given time period. We suggest that the previously reported decline in dementia incidence can be attributed to a combination of (a) failure to examine the proportional hazards assumption in Cox regression; and (b) the use of inappropriate statistical methods for analyzing interval-censored time-to-event data including cases with missing or inconclusive disease information due to death (MDID). In these circumstances, the use of multi-state model-based analytic approaches is preferred, as they yield less biased estimates than Cox models, particularly as the hazard of death (and consequently, the proportion of MDID cases) increases [8, 10].

In the two alternate analyses we conducted (Cox regression assuming non-proportional hazards by epoch, and penalized likelihood modeling), the cumulative dementia hazard rate at the end of the 5-year observation period for each epoch was highest in epoch 1, with the other three epochs similar to each other. At first glance, this would appear to provide some evidence for a decline in dementia incidence, at least from the first epoch to the second (i.e., in the 1980s and early 1990s), but not for any subsequent decline. However, in neither analysis was this decline statistically significant. Moreover, plotting the estimates of the cumulative dementia hazards as functions over time revealed that the risk for dementia was similar in all four epochs until the final year of observation, at which point the cumulative hazard in epoch 1 began to diverge from the other three epochs. It is difficult to come up with a convincing reason for this observation.

As we do not know the true underlying event time distribution, we cannot be certain that the Spline-based penalized likelihood approach resulted in less biased estimates. However, the simulation study we conducted strongly suggests this is the case, as does earlier work (e.g. [10]), suggesting that the use of standard survival models tends to underestimate disease incidence. We note here that there are alternatives to the penalized likelihood approach which are, however, all based on the multi-state model and corresponding similar likelihood contributions formulated from that model (e.g. [17, 25]).

A limitation of our analysis, and by extension that of [5], is that the original and offspring cohorts are combined into one analysis cohort. In work in progress, we have identified that the original and offspring cohorts possess markedly different distributions across a range of variables within each epoch, which calls into question the appropriateness of combining them in a single analysis. A more suitable approach to answering the question of how dementia incidence has evolved over time may be to consider the two cohorts separately and dispense with the epoch structure. Where a cohort is ageing over time and more death cases are expected, the effect of MDID bias would be to underestimate the incidence of dementia cases over time, a problem

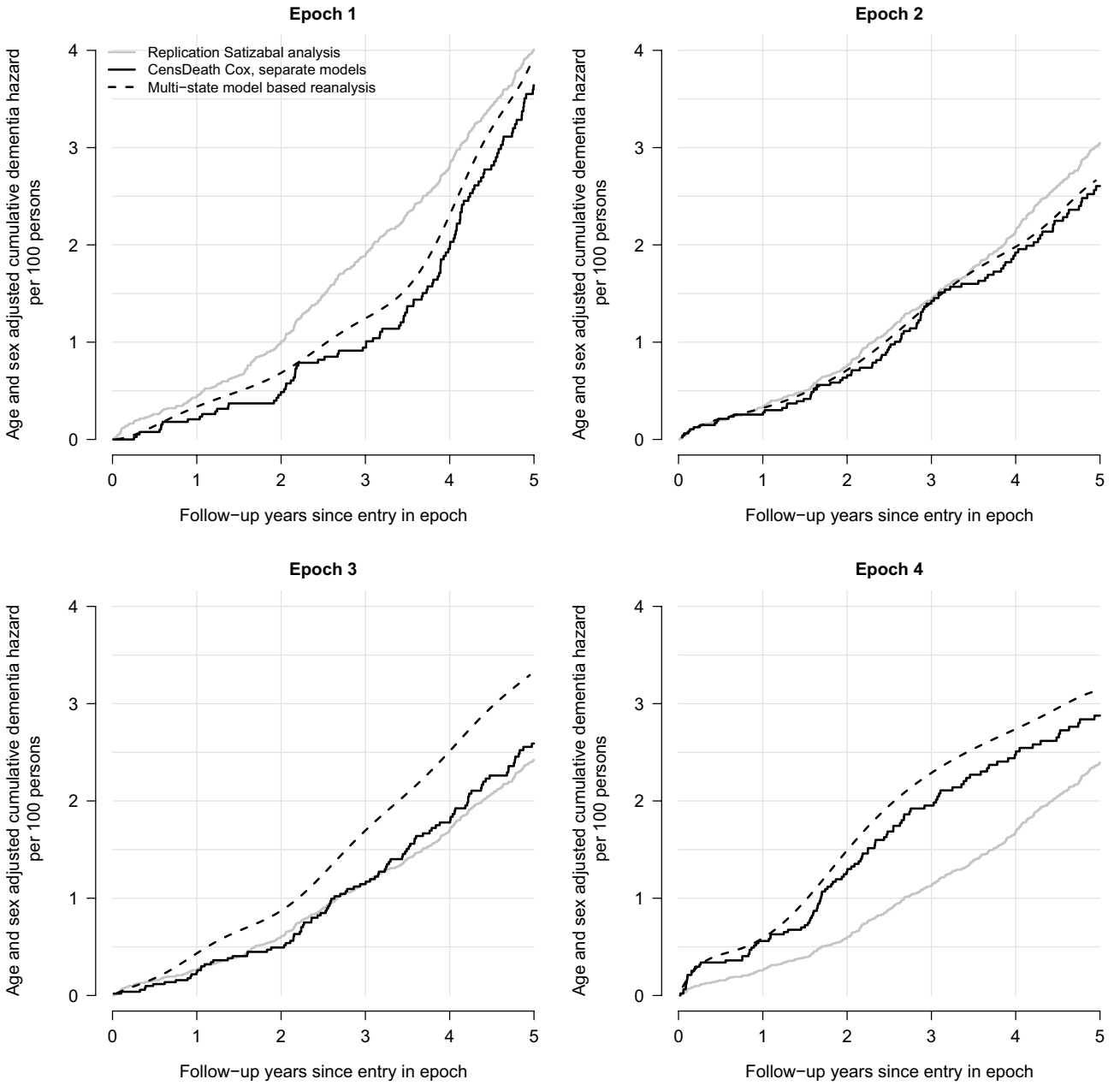


**Fig. 4** Estimates of the age- and sex-adjusted cumulative dementia hazard as a function of each of the 5-year follow-up periods, each epoch 1–4 illustrated in a separate plot

which requires the appropriate use of statistical methods based on the illness-death multi-state model. A re-analysis of these data in which the cohorts are considered separately, taking age as a base time, is a focus of our ongoing investigations. An anonymous reviewer suggested observing participants across longer epochs, however the main effect of this would be to increase the number of death cases per epoch. If the proportion of these for whom final dementia status was uncertain remained similar, this would only result in greater MDID bias within each epoch.

We are not the first to have applied multi-state models to the study of trends in dementia incidence and/or mortality. Recently, Grasset et al. [26] used illness-death models to analyze mortality with and without dementia in two French populations within the PAQUID cohort (surveyed in 1989/90 and 1999/2000, and followed up over 10 years). Decreases in mortality without dementia over time were found to have occurred in both genders, whereas mortality with dementia decreased in women only. This is in line with an earlier finding by this group, in the same cohort,

of decreasing dementia incidence in women only [27], and a German study of two more recent cohorts (from 2004–2007 and 2007–2010) which found a statistically significant decline in mortality with dementia in women only, although a decline in incidence was apparent in both genders [28]. In our ongoing work, we are also exploring whether gender functions as an effect modifier.

In an ageing cohort, greater underestimation of disease incidence over time in cohort studies is a natural consequence of censoring death cases, whether this is at death, at last disease-free observation, or at some other time point. As we have shown, the use of analytic approaches to cohort data based on the illness-death multi-state model, which effectively account for the probability of individuals developing a disease between the last observation and death, result in cumulative disease incidence estimates which do not appreciably deviate from the true incidence estimates. Previous findings of a decrease over time in the incidence of dementia in the Framingham Heart Study may have been an artifact resulting from the improper treatment of a proportion of cases in which death precluded the observation of dementia onset.

**Acknowledgements** This manuscript was prepared using the FRAMCOHORT and FRAMOFFSPRING Research Materials obtained from the NHLBI Biologic Specimen and Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the FRAMCOHORT, FRAMOFFSPRING or the NHLBI. We would like to thank Renee Marie Kingma for assistance in constructing the analysis data sets.

**Funding** This work was supported by the German Research Foundation (Grant No. DFG SCHU 756/12). The funding agreement ensured the authors' independence in designing the study, collecting, analyzing, and interpreting the data, writing of the manuscript, and in the decision to submit the manuscript for publication.

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