Lifetime risk of dementia in the United States

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Abstract

Dementia is increasingly recognized as a major source of disease burden in the United States, on par with heart disease and cancer. Little research has evaluated the lifecycle implications of dementia. To address this research gap, this article uses the Aging, Demographics, and Memory Study (ADAMS) to provide the first nationally representative, longitudinal estimates of the probability that a dementia-free person will develop dementia later in life. I estimate that for the 1920 birth cohort, the average dementia-free 70 year old male had a 23.7% (SE: 2.9%) lifetime probability of developing dementia, and the average dementia-free 70 year old female had a 31.8% (SE: 3.6%) probability. These estimates of lifetime risk of dementia rise for younger cohorts, and they are higher than those found in local epidemiological studies in the U.S. They suggest a widespread need to prepare for a life stage with dementia.

Introduction

Dementia is increasingly recognized as a major source of disease burden in the United States (Murray 2013). A national study estimated that 3.4 million American adults over 70 had dementia, corresponding to a prevalence of approximately 13.9% (Plassman et al. 2007). Dementia imposed a financial cost of over $40,000 per affected person per year, comparable to the financial costs of heart disease and cancer (Hurd et al. 2013). Americans over 60 reported fearing dementia more than any other disease, including cancer (Alzheimer's Association 2014). As the U.S. population ages, the number of Americans with dementia is very likely to increase in the coming decades (He and Larsen 2014; Kasper et al. 2015). Using nationally representative, longitudinal data, this study will estimate the probability that an average dementia-free person will develop dementia in the course of life.

An approach that incorporates the competing risks of death and dementia incidence in a prospective cohort allows one to estimate the risk that the average dementia-free individual will develop dementia in the future. It can also provide an estimate of the related measures of dementia-free life expectancy and life expectancy with dementia. These quantities are important for individuals, businesses, and governments as they plan for retirement, save and contribute to pensions, and assess future health care costs and caregiving needs. For demographers and epidemiologists, these quantities provide meaningful insight into the question of whether long-run gains in survivorship are being experienced in healthy or unhealthy states (Crimmins and Beltrán-Sánchez 2010; Crimmins et al. 2009).

Data from the Framingham Heart Study and from a national Canadian sample have been used to report the lifetime risk of developing dementia using a competing-risks framework (Carone et al. 2014; Seshadri and Wolf 2007; Seshadri et al. 1997). Dementia-free life

expectancy was reported for a large cohort in the Pacific Northwest, known as the Adult Changes in Thought study (ACT) (Tom et al. 2015). Though informative, the Framingham, Canadian, and ACT cohorts are not representative of the U.S. population. For example, these cohorts had a larger proportion of subjects who were white than did the U.S. as a whole. Studies have generally found that African Americans have higher age-specific rates of mild cognitive impairment and of dementia than whites (Katz et al. 2013; Sheffield and Peek 2011). As the nation gets more racially and ethnically diverse, these cohorts are decreasingly representative of the U.S. elderly population. Therefore, there is a need for estimates of lifetime risk of dementia from nationally representative data.

Data, Measures, and Methods

Sample and Definitions

This study uses the Aging, Demographics, and Memory Study (ADAMS), a nationally representative, longitudinal study of cognitive health and dementia conducted in four waves from 2001 to 2009 (Langa et al. 2005). ADAMS, a probability subsample of the Health and Retirement Study (HRS), examined adults aged 70 and older with a series of cognitive, psychological, and neurological tests, and conducted an extensive medical history, an inventory of current prescription medications, a neurology-focused physical exam, and a family/caregiver questionnaire. The testing was conducted in person by trained technicians and nurses and supervised by neuropsychologists (Langa et al. 2005). Diagnostic criteria were based on the Diagnostic and Statistical Manuals of Mental Disorders, DSM-III-R and DSM-IV, and final diagnosis of dementia was made by a consensus expert panel of physicians (Heeringa et al. 2009;

Langa et al. 2005). Detailed descriptions of the ADAMS sample and assessment tools have been previously published (Heeringa et al. 2009; Langa et al. 2005; Plassman et al. 2007).

According to the DSM, the essential feature of dementia is the development of multiple cognitive deficits that include memory impairment and at least one of aphasia (language deficit), apraxia (movement deficit), agnosia (deficit in recognition of objects or senses), or executive functioning deficit (American Psychiatric Association 2000). The cognitive deficits must represent a decline from past abilities and must be severe enough to cause impairment in occupational or social functioning (American Psychiatric Association 2000). The most common type of dementia is Alzheimer's disease (AD), which accounts for 60% to 80% of dementia cases. The next most common type is vascular dementia, which alone accounts for about 10% of cases but which is often found together with AD (Alzheimer's Association 2014).

The initial wave of ADAMS, 2001-2003, examined 856 subjects to generate baseline estimates of dementia prevalence in the U.S. (Plassman et al. 2007). The subsequent waves followed 456 dementia-free individuals for dementia incidence (Plassman et al. 2011). The second wave focused on subjects whose baseline status was "cognitively impaired, no dementia"; this second wave assessed subjects 16 to 18 months after their baseline assessment. For the third and fourth waves, all living subjects who were dementia-free at baseline were in the sampling frame. Subjects in the third wave averaged 3.7 years since their most recent assessment, and subjects in the fourth wave averaged 1.8 years since their most recent assessment (Plassman et al. 2011). Despite the relatively long intervals between assessments, ADAMS investigators could determine, based on informant reports, medical records, and clinical assessment, that a subject experienced the onset of dementia at any time since the previous assessment. For example, if a 72 year old subject was deemed dementia-free at baseline and then

assessed at age 76 and found to have dementia, investigators could determine that his age at the onset of dementia was 73. The assignment of ages at dementia onset during the inter-assessment interval allows for the estimation of dementia incidence rates, rather than probabilities. Thus the ADAMS data can be used to calculate age-specific incidence of dementia, an essential ingredient in making estimates of lifetime risk.

Mortality data come from ADAMS' link to the Health and Retirement Study's mortality tracking via the National Death Index (NDI), which provides vital status and, if deceased, month of death, as of December 2011. The 856 ADAMS subjects constitute the individuals at risk of mortality. The ADAMS study team did not attempt to diagnose dementia posthumously in subjects who had not received a dementia diagnosis during their lifetimes. I use the mortality data to generate estimates of the age-specific ratio of mortality rates between those with and those without dementia. Mortality rates for the entire U.S. population come from the Social Security Administration (SSA) cohort life tables (Bell and Miller 2005).

Demographic Methods

Disease prevalence at a point in time embodies a history of disease incidence and of the difference in mortality rates between those with and those without the disease. If age-specific incidence and mortality rate differences have been constant over time, then age-specific prevalence will also be constant. These conditions define a stationary population with respect to the disease in question. Any two parameters among disease incidence, prevalence, and differential mortality imply the third parameter (Preston, Heuveline, and Guillot 2001, chapter 4). The ADAMS data allow for the estimation of all three parameters, as discussed above; they therefore enable one to assess the stationary population assumptions of the constancy of age-

specific incidence rates and differential mortality over time. Alternatively, if there is a strong basis for assuming the constancy of rates, one can use estimates of two of the parameters along with the assumption of constancy of rates to derive the third parameter. I will use ADAMS incidence and prevalence estimates and the assumption of stationarity to derive an estimate of differential mortality and to estimate lifetime risk of dementia. Then I will relax the assumption of stationarity and estimate differential mortality directly from the ADAMS data, producing a second set of lifetime-risk estimates.

In the context of ADAMS and dementia, differential mortality is the hardest of the three parameters to estimate, and there is no "gold standard" for estimating differential mortality in this context (Guehne et al. 2005). Existing estimates of the ratio of mortality among women age 75 to 84 with dementia to mortality among same-age women without dementia vary from 4.07 in Canada (Ostbye et al. 1999) to 2.59 in Spain (Villarejo et al. 2011), with an even wider range of estimates in studies focusing on Alzheimer's disease rather than all dementias (Ganguli and Dodge 2005). Although this ratio is consistently found to decline with age, the pace of decline varies widely across studies (James et al. 2014; Ostbye et al. 1999; Tschanz et al. 2004; Villarejo et al. 2011), making estimates of the age pattern of differential mortality subject to strong parametric assumptions. The ADAMS team has published estimates of age-specific prevalence and incidence to which I can benchmark my own estimates (Plassman et al. 2007, 2011), but no comparable ADAMS-based estimates of differential mortality exist.

In this study, where ADAMS data go to 2009 and mortality data go to 2011, an additional challenge in estimating differential mortality relates to censoring. Individuals' dementia status is known as of their last ADAMS assessment, but mortality follow-up continues for several additional years, during which time new cases of dementia go unobserved. Thus the question

arises of when to censor individuals whose last ADAMS assessment categorized them as without dementia. If one follows them as long as the mortality follow-up allows, one will misclassify many deaths as deaths without dementia. If one censors these individuals too early, one under-counts deaths and person-years without dementia. In either case, the distortions to the estimated differential mortality are potentially severe. The results will show that estimated differential mortality has the largest standard error among the three parameters, and given underlying questions about functional form and the censoring of individuals not diagnosed with dementia, it is likely that standard errors of estimates of differential mortality do not capture all the uncertainty associated with those estimates.

The difficulties in directly estimating differential mortality motivate the use of the stationarity assumptions, and there is considerable evidence suggesting that age-specific dementia incidence has been constant over the last decades (Asgharian et al. 2006; Ewbank 2004; Rocca et al. 2011). Since my estimates cover only ages 70 and above, the time interval during which I would assume constancy of incidence rates and of differential mortality is relatively short. Given the evidence for stationarity and the difficulties directly estimating relative risks of death, I will begin with a method that assumes that age-specific dementia incidence and differential mortality have been constant over time, deriving differential mortality from stationary-population relations rather than estimating it directly.

Other studies do find declines over time in prevalence of moderate or severe cognitive impairment (Langa et al. 2008; Manton and Ukraintseva 2005). Declines in prevalence could be consistent with constant incidence if average duration of dementia declines, but these contrary findings provide some evidence against the stationarity assumption. I will therefore conduct additional analyses using differential mortality I estimate directly from the ADAMS data –

despite the limitations of such estimation – and not assuming a stationary population. Comparing the prevalence estimated at baseline in ADAMS to that implied by my estimated incidence and differential mortality provides an informal test of the stationarity assumptions: if the two prevalence series are concordant, then the incidence and differential mortality that gave rise to baseline prevalence closely align with the incidence and differential mortality observed longitudinally.

With either approach, once age-specific incidence rates and mortality rates by dementia status are in hand, I use multiple-decrement life table relations to track exits from the dementia-free population via death or dementia onset (Preston, Heuveline, and Guillot 2001, chapter 4). The number of exits via dementia onset features prominently in the estimates of lifetime risk of dementia.

Approach 1: Stationary-Population Approach

Because of the small sample size in ADAMS, I fit simple models to generate smooth age patterns of dementia prevalence and incidence:

$$logit(prevalence_x) = \alpha + \beta x, \quad [1]$$

$$logit(incidence_x) = \alpha' + \beta' x, \quad [2]$$

where *x* is exact age. This model broadly conforms to the functional form of the age pattern of Alzheimer's disease rates, and Alzheimer's prevalence and incidence rates have been shown to have similar functional forms (Brookmeyer and Gray 2000; Brookmeyer et al. 2011; Ziegler-Graham et al. 2008). For prevalence, I fit the model using logistic regression on the baseline ADAMS sample (n=856). Baseline age was provided in completed years ("last birthday"), so exact age (*x*) was the reported age plus 0.5.

For incidence, I fit the model using a discrete-time logistic regression on a person-year data file (Allison 1984), using the 456 subjects followed longitudinally. Age of dementia onset was reported in completed years, so, for incident cases, the exact age at incidence was set at the reported age (last-birthday) of onset plus 0.5. Subjects who never received a diagnosis of dementia from ADAMS investigators, including those who died without a dementia diagnosis, were censored. Among the censored subjects, those whose status at the end of the ADAMS study period was "alive, dementia-free" contributed dementia-free person-years up to and including their exact age (in months) at their last assessment. A sensitivity analysis that censored dementia-free survivors at the end of the ADAMS study period, rather than at their last assessment, produced implausible estimates of differential mortality, providing additional justification for the current censoring strategy (results available upon request).

Censored subjects whose status at the end of ADAMS was "died without dementia" contributed dementia-free person years until their exact age at death. For example, if a subject's status at the end of ADAMS was "died without dementia," and she died at age 78 and 5 months, then she contributed person-years of exposure until she was 78.41666. Her death would be assigned to the interval between exact ages 78.0 and 79.0. The approach of carrying the last assessment of deceased individuals forward until death is consistent with previous ADAMS reports (Plassman et al. 2011) and recommendations based on simulations of censored time-to-dementia data (Leffondré et al. 2013). It is based on the idea that if the deceased individuals had survived and developed dementia, the investigators could have been able to observe their dementia onset; decedents were therefore at risk of dementia onset until their deaths.

There is considerable evidence in the literature suggesting that age-specific incidence rates of dementia do not vary by sex (Chêne et al. 2015; Plassman et al. 2011; Ruitenberg et al.

2001). When a sex term was included in Eq. 2, its coefficient was statistically insignificant (p>0.20). This insignificant result further justifies the pooling of males and females in the estimation of dementia incidence.

Call the fitted prevalence vector $({}_nP_x)$, and the incidence vector $({}_ninci_x)$; these are assumed the same for males and females. The 1920 birth cohort would have been aged 81 to 88 over the study period of ADAMS, making this cohort's life table a good approximation of the overall level of mortality in the population the ADAMS cohort represents. The SSA life table for this cohort provides mortality rates $({}_nm_x)$, survivors to exact age x (l_x), and person-years lived at each age in the entire population $({}_nL_x)$; these values are sex-specific. In other words, the level of mortality varies by sex, which will generate sex-specific estimates of lifetime risk, but the other input quantities are constant across sex. Employing the Sullivan method (Mathers and Robine 1997; Sullivan 1971) and using single-year age intervals, the number of person-years lived without and with dementia, respectively, in the age interval (*x, x+1*) are:

$$ {}_1L_x^{ND} = {}_1L_x(1 - {}_1P_x) \quad [3] $$

$$ {}_1L_x^{D} = {}_1L_x * {}_1P_x. \quad [4] $$

The assumptions of stationarity are sufficient for the Sullivan method to generate unbiased and consistent estimates of person-years lived in each state (Imai and Soneji 2007). Taking l_{70} as the radix for the entire population, I estimate the population with dementia at exact age 70 as

$$ l_{70}^{D} = l_{70} * P_{70.0} \quad [5] $$

and the population without dementia as

$$ l_{70}^{ND} = l_{70} * (1 - P_{70.0}). \quad [6] $$

Since prevalence usually pertains to age intervals, Eqs. 5 and 6 are only approximations; they are necessary to establish the proportions in each state at exact age 70. I fill the life table as follows, assuming events occur on average halfway through intervals. For survivors:

$$l^{D}_{x+1} = (2 * \ {}_1L^{D}_{x}) - l^{D}_{x}, \quad [7]$$

$$l^{ND}_{x+1} = (2 * \ {}_1L^{ND}_{x}) - l^{ND}_{x}. \quad [8]$$

The number of new dementia cases is

$${}^{dem}_{1}d^{ND}_{x} = \ {}_1L^{ND}_{x} * \ {}_1inci_{x}. \quad [9]$$

The number of deaths without dementia is

$${}^{death}_{1}d^{ND}_{x} = l^{ND}_{x} - l^{ND}_{x+1} - {}^{dem}_{1}d^{ND}_{x}. \quad [10]$$

The death rates among those with and without dementia are not explicitly used in Approach 1, but they are implicit in the counts of new dementia cases and the person-years lived in each state, and they are essential ingredients in the underlying population processes at work. For completeness and comparison with Approach 2, I present equations for those rates in Appendix 1.

The primary quantity of interest is the lifetime risk of dementia for an age-*a* person without dementia:

$$LFTM_a = {\Sigma^{w}_{x=a} \ {}^{dem}_{1}d^{ND}_{x}} \Big/ {l^{ND}_{a}}, \quad [11]$$

where *w* is the highest age interval. Also of interest is dementia-free life expectancy, the average number of years a randomly chosen person age *a* can expect to live free of dementia, under current rates:

$$DFLE_a = {\Sigma^{w}_{x=a} \ {}_1L^{ND}_{x}} \Big/ {l_a}. \quad [12]$$

Total life expectancy is as in a single-decrement life table:

$$LE_a = {}^{\Sigma_{x=a}^{w}\ {}_1L_x}\Big/_{l_a}, \quad [13]$$

and by construction, unconditional life expectancy with dementia – that is, the average number of years an age-*a* person randomly chosen from the population can expect to live with dementia, under current rates, is

$$DLE_a = LE_a - DFLE_a. \quad [14]$$

One can also define conditional life expectancy without dementia as the average number of years a *dementia-free* person of a given age can expect to live free of dementia:

$$DFLE'_a = {}^{\Sigma_{x=a}^{w}\ {}_1L_x^{ND}}\Big/_{l_a^{ND}}. \quad [15]$$

This quantity is valuable because the number of dementia-free person-years lived above age *a* for someone who already has dementia at age *a* is zero, and the numerator of Eq. 12 includes those zeros, while that of Eq. 15 does not. The conditional DFLE is estimable using this method because all person-years lived in a dementia-free state above age *a* are experienced by people who were dementia-free at age *a*; the numerator and denominator therefore match. In contrast, $(\Sigma_{x=a}^{w}\ {}_1L_x^{D})/l_a^{ND}$ is *not* equal to the average number of years a dementia-free person age *a* can expect to live with dementia, because some of the person-years lived with dementia above age *a* – years contributing to the numerator – are experienced by people who already had dementia at age *a* and who thus do not contribute to the denominator.

Approach 2: No Assumption of Stationarity; Estimate Differential Mortality Directly from Data

The first approach used the fact that age-specific prevalence and incidence estimated in a stationary population – that is, one in which incidence and differential mortality have not changed over time – imply a unique pattern of differential mortality. However, if the population

is non-stationary, then current prevalence estimates do not necessarily convey information about current differential mortality.

To estimate a current age pattern of differential mortality directly from the ADAMS data, without assuming the population is stationary, I use a Gompertz-type model of death rates as a function of an indicator for dementia presence, exact age, and their interaction, fit with a Poisson regression on a person-year data file (Loomis 2005). Dementia status is modeled as a time-varying indicator to incorporate both baseline prevalent cases and incident cases (Palloni and Thomas 2013). The model is:

$$\ln\left(m_{x,dem}\right) = \alpha + \beta_1 x + \beta_2 dementia + \beta_3 x * dementia. \quad [16]$$

As with the estimation of dementia incidence discussed above, subjects who died without a dementia diagnosis during the ADAMS study period contribute dementia-free person years until their exact age at death, and subjects who survived ADAMS without a dementia diagnosis contributed dementia-free person years until their last ADAMS assessment. A sensitivity analysis that censored dementia-free survivors at the end of the ADAMS study period, rather than at their last assessment, produced implausible estimates of prevalence (results available upon request), providing support for the current censoring strategy. Mortality data for the period after ADAMS (2009 to 2011) was used only for those with a dementia diagnosis, whose state could not change until death. Not using mortality data from the post-ADAMS period for individuals without a dementia diagnosis avoids large misclassification errors whereby persons who develop dementia subsequent to ADAMS would wrongly contribute deaths without dementia and person-years without dementia to the calculations.

Based on Eq. 16, the ratio of the mortality rate among persons with dementia to that among persons without dementia – also known as the risk ratio, rate ratio, or relative risk (RR) – is

$$RR_x = \exp(\alpha + \beta_1 x + \beta_2 + \beta_3 x) \Big/ \exp(\alpha + \beta_1 x) = \exp(\beta_2 + \beta_3 x). \quad [17]$$

In this way, the *ratio* of the two mortality rates is estimated from the ADAMS sample, but the actual values of the mortality rates, and the mortality rate differences that generate prevalence and lifetime risk, can be adjusted to match national data with many more deaths using the SSA 1920 cohort life tables.

Consistent with most of the literature, the ratio of mortality rates between those with and those without dementia were held constant across sex (Agüero-Torres et al. 1999; Garcia-Ptacek et al. 2014; Johnson et al. 2007; Lönnroos et al. 2013; Meller et al. 1999; Villarejo et al. 2011; Witthaus et al. 1999). When a sex term and a sex-by-dementia-status interaction term were included in Eq. 2, the coefficient on the sex-by-dementia term was not statistically significant ($p>0.30$), providing additional justification for keeping differential mortality constant across sex. As with the modeling of incidence rates, pooling males and females to estimate differential mortality is useful with a small sample size such as in ADAMS. In this model, the only quantity that differed by sex was the overall level of age-specific mortality in the entire U.S. population.

The inclusion of the interaction term with the coefficient β_3 implies that the excess risk of death associated with having dementia declines (assuming β_3 is negative) with age (Helmer et al. 2001). This decline arises from two related but distinct forces. The first is the aging of all the individuals in the cohort: as the underlying risk of death rises with age for everyone, the excess risk of death associated with dementia declines. The second force is heterogeneity in frailty within each group (Vaupel et al. 1979). Heterogeneity within population groups selects out the

frailest individuals first. This force acts more strongly on the higher-mortality group (people with dementia), leaving heartier individuals remaining. In the context of dementia, heterogeneity could arise from changes with age in the average duration of dementia or changes in the prevalence of the APOE e4 allele in the dementia population relative to that in the non-dementia population (Ewbank 2004). This process is similar to the consistent finding of black-white mortality differentials, which decline at older ages (Eberstein et al. 2008).

For a given age, the mortality rate for the entire population can be decomposed into a weighted average of mortality rates of the diseased and disease-free populations, weighted by the age-specific prevalence of the disease:

$$
\begin{aligned}
{}_1m_x &= {}_1m_x^D * {}_1P_x + {}^{death}_{1}m_x^{ND} * (1 - {}_1P_x) \\
&= {}^{death}_{1}m_x^{ND} * {}_1RR_x * {}_1P_x + {}^{death}_{1}m_x^{ND} * \left(1 - {}_1P_x\right). \qquad [18]
\end{aligned}
$$

The terms can be rearranged to solve for the mortality rate in the dementia-free population:

$$
{}^{death}_{1}m_x^{ND} = {}_1m_x \Big/ \left({}_1P_x * {}_1RR_x + 1 - {}_1P_x \right) \qquad [19]
$$

and in the population with dementia:

$$
{}_1m_x^D = {}^{death}_{1}m_x^{ND} * {}_1RR_x, \qquad [20]
$$

where the overall mortality rate vector ${}_1m_x$ comes from the SSA life table, the mortality rate ratio (RR_x) is as above in Eq. 17, and the age-specific prevalence is the proportion of survivors to the middle of the age interval who have dementia, as detailed in Appendix 2.

Using the incidence rates estimated in Eq. 2 and the mortality rates found in Eqs. 19-20, I construct a multiple-decrement life table for the population without dementia, incorporating elements of the increment-decrement life table to keep track of a model population with dementia. As with Approach 1, I use single-year age groups and assume no recovery from

dementia. The life table relations I use are developed in Preston, Heuveline, and Guillot 2001 and shown in detail in Appendix 2.

Once the multiple-decrement life table is completed, the summary quantities of interest – lifetime risk of developing dementia, unconditional expectancies, and certain conditional expectancies – can be calculated as in Eqs. 11 through 15.

Simulated Reductions in Mortality, and Simulated Delays or Reductions in Dementia Incidence

Approach 2, which does not assume the constancy of rates over time, lends itself to simulations of future lifetime risk based on changes in mortality or dementia incidence. To assess lifetime risk for younger, lower-mortality cohorts, a secondary analysis used values for ${}_1m_x$ from the 1940 cohort life tables from SSA. The results estimate lifetime risk using current incidence rates and mortality rate ratios as estimated in ADAMS, isolating the role of declines in the overall level of mortality in changing lifetime risk of dementia.

I also estimate the lifecycle effects of an intervention that delays the onset of dementia. In the first scenario, the intervention delays dementia onset by one year and is effective for 50% of the dementia-free population at age 70. In the second scenario, the same intervention affects 90% of dementia-free 70 year olds. In the third scenario, the intervention delays dementia onset by five years and is effective for 50% of dementia-free 70 year olds, and the fourth scenario delays dementia onset by five years for 90% of dementia-free 70 year olds. I model these interventions by splitting the model dementia-free population in half (or, for the second and fourth scenarios, into 10%/90% groups), subjecting the first group to the dementia incidence rates as modeled in Eq. 2, and subjecting the second group to the dementia incidence rates as modeled by

$$logit(incidence'_x) = \alpha + \beta(x - K), \qquad [21]$$

where *K* is the number of years of delay of dementia onset induced by the intervention. This equation assigns what had been the age-70 incidence rate to age 70+K, what had been the age-71 incidence rate to age 71+K, and so forth.

Another type of intervention would reduce the risk of dementia at every age, rather than delaying its onset. Such an intervention generates an incidence equation such as:

$$logit(incidence''_x) = \alpha + (\beta k)x, \qquad [22]$$

where *k* is a value between 0 and 1 that represents the extent to which dementia incidence rises less steeply with age due to the intervention. The closer *k* is to zero, the more effective is the intervention in the sense of reducing the acceleration of dementia incidence. I simulate an intervention where $k = 0.9$, to reduce the (logit of) acceleration of dementia incidence with age by 10%.

Both the dementia-free and with-dementia populations are subject to the same mortality rates as before; the changing sizes of these two populations resulting from the simulated intervention are assumed to change the overall mortality rate (Eqs. 18-20).

Estimation of Standard Errors and Confidence Intervals

To generate standard errors and confidence intervals around the lifetime-probability and expectancy estimates, I considered as stochastic the parameter estimates generating the age-specific dementia incidence schedules (the fitted values of [α' β'] in Eq. 2) and either prevalence (for Approach 1 – the fitted values of [α β] in Eq. 1) or differential mortality (for Approach 2 – the fitted values for [α β_1 β_2 β_3] in Eq. 16). Total mortality, derived from the SSA cohort life tables, was treated as deterministic (i.e. having zero variance) (Abatih et al. 2008; Loukine et al.

2012), and the life table assumptions, such as linearity of survival within age intervals, were also considered not to contribute any additional variance.

For dementia incidence, I used the estimates of [α' β'] in Eq. 2, along with their associated variance-covariance matrix, as the parameters of a bivariate Normal distribution to draw 1,000 independent values of [α' β'], generating 1,000 incidence schedules. Separately, I used an analogous procedure with the estimated parameters and variance-covariance matrix from Eq. 1 or Eq. 16 to generate 1,000 age schedules of prevalence (Approach 1) or the mortality rate ratio between those with and those without dementia (Approach 2). Each incidence schedule was paired with one schedule of the second parameter (prevalence or mortality rate ratios) and run through the life table operations, producing 1,000 lifetime-probability and expectancy estimates. In figures, the median of the 1,000 estimates is shown as the point estimate, and the 2.5^{th} and 97.5^{th} percentiles are shown as the confidence bounds (Fishman 2015; Mooney 1997; Salomon et al. 2001). Tables show the means and standard errors (square roots of variances) of the 1,000 estimates.

Parameters from Eqs. 1, 2, and 16 were estimated using Stata version 14 (StataCorp, College Station, TX), using first-order Taylor Series linearization for variance estimation with the *svy* routine (Heeringa et al. 2009). Random sampling for the estimation of standard errors was conducted in R using the *mvrnorm* command in the MASS package (Venables and Ripley 2002), and life table operations were conducted using base R (R Core Team, Vienna, Austria). The HRS and ADAMS data are available to the public after a registration procedure (Health and Retirement Study 2013).

Results

There were 308 cases of dementia at baseline out of 856 unweighted sample members. All baseline sample members were at risk of death, generating 519 deaths in 3,520 person-years at risk. Among the 456 individuals without dementia at baseline who were followed longitudinally, 106 developed dementia in 2,142 person-years at risk. The estimates of the regression parameters in Eqs. 1, 2, and 16, along with the variance-covariance matrices used to sample the 1,000 simulated incidence, prevalence, and mortality rate-ratio schedules for the confidence intervals, are shown in Table 1.

Table 2 shows the estimated age schedule of dementia prevalence, which aligns closely with published estimates from ADAMS (Plassman et al. 2007), at 6.1% for age 75, 22.7% for age 85, and 38.4% at age 90. The fitted age-specific dementia incidence rates are also shown in Table 1, with 16 new cases per 1,000 person-years at age 75, 37 new cases per 1,000 person-years at age 85, and 56 to 86 new cases per 1,000 person-years at ages 90-95. The incidence rates shown here are close to those previously reported from ADAMS (Plassman et al. 2011).

The age pattern of mortality rate ratios shown in Table 2, showing a rapid decline in differential mortality with age, is largely consistent with that found in other, non-national and non-U.S. samples; however, as mentioned previously, the pace of decline of differential mortality with age varies widely in the literature (Guehne et al. 2005; Ostbye et al. 1999; Tschanz et al. 2004; Villarejo et al. 2011). The estimated mortality rate ratio (RR) at age 70 of 13.3 is highly unstable, as shown by its high standard error, arising from the low number of deaths at age 70; the true RR is probably not quite that high. Since the prevalence of dementia is very low at age 70, results are not sensitive to the RR estimate at that age. The RR implied by estimated incidence, baseline prevalence, and the stationary population assumption is around 1

for ages above 85, which is plausible given the high level of mortality in the general population at those ages.

Using Approach 1, Table 3 shows calculations of the various life table quantities of interest: total life expectancy, dementia-free life expectancy and life expectancy with dementia (for a randomly chosen person in the population), and, of most interest, the probability that a currently dementia-free person will develop dementia later in life. It also shows conditional dementia-free life expectancy (DFLE') – dementia-free life expectancy for a dementia-free person at the given ages. About 23.7% (SE: 2.9%) of dementia-free 70 year old males are expected to develop dementia later in the course of life, compared to 31.8% (SE: 3.6%) of dementia-free females age 70. The lifetime probability remains roughly constant with age for males, meaning the force of dementia incidence increases about as quickly as the force of male mortality. For females, lifetime probability declines to 25.2% at age 95, indicating that the force of female mortality increases more quickly than the force of dementia incidence. Lifetime probability is higher for females than males because females have lower overall mortality, the only input that varies by sex.

For both sexes at ages 70 to 85, the vast majority of remaining life for a randomly chosen person is expected to be dementia-free, as shown by the high ratio of DFLE to DLE at these ages. However, at the oldest ages, 90 and above, DFLE and DLE are about equal – with DLE even greater than DFLE at age 95 – because mortality, incidence, and prevalence are all high at these ages. Dementia-free life expectancy for a dementia-free person (DFLE') is slightly higher than unconditional DFLE because the latter includes people with dementia, whose DFLE is zero. The gap between DFLE' and DFLE widens with age because the prevalence of dementia rises with age.

Table 4 shows the same quantities as Table 2 – prevalence, incidence, and the mortality rate ratio (RR) – but uses estimated incidence and RR to infer prevalence (i.e. Approach 2), rather than using estimated incidence and prevalence to infer RR. For all except the youngest and oldest ages, estimated RR is higher than that implied by stationary-population incidence and prevalence in Table 2. For example, 80-year-olds with dementia are estimated to die at 4.6 times the rate of 80-year-olds without dementia, whereas the stationary population implied a multiplier of just 1.8 times. A higher estimated RR implies a significantly lower prevalence, also shown in Table 4, because exits from the population with dementia (relative to the population without) occur more quickly when RR is higher.

There are several possible explanations for the discordant prevalence estimates Tables 2 and 4. If the estimated RRs are correct, then the discordant estimates imply a departure from stationarity, i.e. a change in dementia incidence rates, such that the rates that produced baseline prevalence were higher than the rates observed longitudinally in ADAMS. Another possible, though less likely, departure from stationarity consistent with the discordant prevalence estimates is that RR has increased over time, since a higher RR implies a lower prevalence. However, if we are confident that dementia incidence rates and differential mortality have not changed, then the discordance implies a misspecification of the RR function (Eqs. 16-17). A final possibility is that the discrepancy arises from differences in the ascertainment of dementia status between the baseline study and the longitudinal follow-up study. Although the assessments of subjects were similar across waves of ADAMS, the baseline study by definition did not have access to the results of prior dementia examinations by the ADAMS team. To obtain a cognitive history of the subject (that is, measures of cognition prior to the baseline examination), the baseline study used medical records and interviews of knowledgeable informants. These methods have high

reliability and validity (Langa et al. 2005; Plassman et al. 2007), but they are not the same as observing the person's cognitive performance in detail over time, as was done for the longitudinal ADAMS incidence sample.

When using the non-stationary approach, estimated lifetime risk of dementia is higher by about 3 to 5 percentage points than when using stationary population relations. For example, Table 5 shows that at age 70, the lifetime risk for males without dementia was 26.9% and for females 34.7%. However, there is considerable overlap in the confidence intervals around the estimated-RR and stationary-population estimates of lifetime risk (Fig. 1), suggesting statistical concordance in the results of the two approaches. In other words, the lifetime-risk estimates shown in Table 3 are robust to the possible departures from stationarity implied by the discordant prevalence values in Tables 2 and 4. The higher estimate of differential mortality employed in Approach 2 means the competing risk of death without dementia is lower, raising lifetime risk of developing dementia.

Using the 1940 cohort life table rather than that of 1920 (with Approach 2) raises lifetime risk at all ages (Table 6). The increase is between 3 and 4 percentage points for both males and females. The probability that a dementia-free 70 year old male from this cohort develops dementia later in life is about 30.8%; for a dementia-free 70 year old female it is 37.4%. The increase in lifetime risk results from population-wide reductions in mortality between the two birth cohorts, reducing the competing risk of death and allowing a larger proportion of the population to survive to ages of high dementia incidence. The changes in the results based on the choice of an input life table do not negate the results for the older cohort, nor do they cast doubt on Approach 1, which requires only that incidence and mortality rate differences be constant over time. Rather, the 1940 results simply illustrate that individuals in younger, lower-mortality

cohorts face higher age-specific lifetime risks of dementia than individuals in older, higher-mortality cohorts. The percentage increase in lifetime risk across the two cohorts is larger for males than females because females have lower mortality than males to begin with (a larger base leads to smaller percentage change), and/or because mortality declined less for females than for males between these two cohorts (Preston & Wang 2006).

Table 7 shows the age pattern of incidence under the possible interventions that reduce or delay dementia onset, and Table 8 shows the lifetime-risk estimates associated with these alternative scenarios. Table 8 should be compared with the Lifetime Risk column and its standard error in Table 5. In the first two scenarios, an intervention delays the risk of dementia by one year; in Scenario 1 the intervention affects 50% of dementia-free 70-year-olds, and in Scenario 2 it affects 90%. The estimates for Scenarios 1 and 2 in Table 8 indicate that this intervention would reduce lifetime risk at age 70 by only one to two percentage points, with similar reductions at older ages. The small difference between Scenarios 1 and 2 shows that the proportion of the age-70 population for which this intervention is effective has a small effect on lifetime risk estimates. Extending the reach from 50% to 90% of dementia-free 70-year-olds reduces lifetime risk by less than one percentage point.

A larger reduction in lifetime risk is achieved by an intervention that delays dementia onset by five years and reaches 50% of the dementia-free population age 70 (Scenario 3) – now the reduction is 3.7 percentage points for males and 4.5 for females. If this five-year delay affected 90% of dementia-free 70 year olds (Scenario 4), it would reduce lifetime risk at age 70 by 6.7 percentage points for males and 8.1 percentage points for females, a 25% reduction in lifetime risk for males and a 23% reduction for females. Similar reductions in lifetime risk are achieved by an intervention that reduces the rate of acceleration of dementia incidence with age,

as in Scenario 5. This intervention achieves a 5.6 percentage-point reduction in lifetime risk for males and 7.1 percentage-point reduction for females.

Discussion

This study provides, to my knowledge, the first nationally representative estimates of the lifetime probability of developing dementia in the U.S. These estimates suggest that about 23% to 27% of dementia-free 70 year-old males and about 31% to 35% of dementia-free 70-year-old females in the 1920 birth cohort will develop (or have developed) dementia before they die. For the 1940 birth cohort, these estimates rise to about 31% for males and 37% for females. The expected number of years that a randomly chosen individual aged 70 could expect to live with dementia is only about one to 1.5 years for males and two years for females, but given the high care needs of people with dementia, this estimate still implies a large need for individuals and families to plan for a life stage with dementia.

A recent study, known as Adult Changes in Thought (Tom et al. 2015), reported dementia-free life expectancy for dementia-free cohort members (what I call DFLE') age 70, estimating 14.3 years for males and 15.7 years for females. My estimates were 11.1 years for males and 13.4 years for females (Table 3). Since the ACT cohort had much longer life expectancy overall – for example, 16.0 years for males age 70 vs. 12.3 years in the national population – it is not surprising that it also had longer conditional dementia-free life expectancy. The ACT study did not report on lifetime probability of developing dementia.

Another past study of an individual's lifetime risk of dementia that incorporated a competing-risks framework used Framingham data from 1975-1995 (Seshadri et al. 1997). It estimated that a dementia-free male age 65 had a 14.3% probability of developing dementia at

some point in his remaining life, and a dementia-free female age 65 had 21.7% probability of developing dementia at some point in her remaining life (Seshadri and Wolf 2007).

There are several reasons why my estimates of the probability of developing dementia are considerably higher than the Framingham-based estimates. First, overall mortality during ADAMS was lower than overall mortality during Framingham. The age-standardized mortality rate (ASMR) in the U.S. population age-65+ in 2005, the middle of the ADAMS study period, was 4,804 deaths per 100,000 person-years lived; this rate was much lower than the ASMR in Massachusetts for age 65+ in 1985, the middle of Framingham's study period, which was 5,679 deaths per 100,000 person-years lived (Centers for Disease Control and Prevention 2014). The comparison of the 1920 SSA cohort table to that of 1940 shows that lower mortality levels imply higher lifetime risks of dementia. Additionally, because the Framingham sample was overwhelmingly white, it produced lower dementia incidence rates than would come from a national sample, because African Americans experience higher rates of dementia incidence than whites at any given age (Seshadri and Wolf 2007).

My estimates of lifetime risk fall between those found in Framingham and those estimated for a national sample from Canada, where the authors estimated that slightly over 40% of 70-year-olds in Canada would develop dementia before death (Carone et al. 2014). The dementia incidence rates found in the Canadian study were higher than those estimated here (Canadian Health and Aging Study 2000), producing higher estimates of lifetime risk. Incidence of dementia as measured in Canada could be higher than that measured in ADAMS because of actual differences in dementia incidence between the Canadian and U.S. elderly populations, or because of differences between the two studies in the method of ascertaining dementia status. For example, the Canadian study diagnosed new cases of dementia posthumously for some

subjects, based on family reports of cognitive status three months before death (Canadian Health and Aging Study 2000).

A recent simulation study using ADAMS and HRS found that an intervention that delayed the onset of Alzheimer's disease (AD) for five years would result in a 41% lower prevalence of AD in 2050 among those aged 70+ than if onset had not been delayed (Zissimopoulos et al. 2014). Setting aside possible differences between AD and other dementias, a decline in AD prevalence could be larger than the decline in lifetime risk if the average duration of AD fell substantially as a result of the delayed onset of AD. Additionally, since the average duration of AD is longer than that of vascular dementia (Treves and Korczyn 2012), an intervention reducing the duration of AD could have a larger effect on AD prevalence than an intervention reducing the duration of all types of dementia could have on all-dementia prevalence. Further research can use increment-decrement methods to estimate age-specific average duration of dementia under different possible interventions.

Another direction for future research is the estimation of quantities associated with family members of persons with dementia, such as the risk of having a parent who develops dementia. The estimates of lifetime risk presented here imply that informal care givers will face an increasing burden in the near future (Kasper et al. 2015). Because of the generally advanced age of persons with dementia, spouses are often not available to provide care, and daughters generally provide the most care (Friedman et al. 2015). The lower parity of cohorts born in the 1940s and 1950s, relative to cohorts born in the 1920s and 1930s, implies that fewer aging Baby Boomers will have daughters who can take care of them than members of older generations have had (Human Fertility Database 2015). Research has found that middle-aged and young adults consistently underestimate their future need for personal care (Henning-Smith and Shippee 2015;

Kemper et al. 2005; Spillman and Lubitz 2002). The results shown here suggest that a large fraction of current and near-future elderly will develop dementia in their lifetimes, even if treatments delaying or reducing dementia risk become widespread.

Appendix 1: Death Rates in Approach 1

Using Approach 1, the death rate among persons without dementia is

$$ {}^{death}_{1}m_x^{ND} = {}^{death}_{1}d_x^{ND} \Big/ {}_1L_x^{ND}. \quad [23] $$

To derive the death rate among those with dementia, I first decompose the mortality rate in the entire population into a weighted average of the mortality rates of the population with and the population without dementia, where the weights are the prevalence of dementia and its complement:

$$ {}_1m_x = {}_1m_x^D * {}_1P_x + {}^{death}_{1}m_x^{ND} * (1 - {}_1P_x), \quad [24] $$

which can be rearranged as

$$ {}_1m_x^D = [{}_1m_x - {}^{death}_{1}m_x^{ND} * (1 - {}_1P_x)] \Big/ {}_1P_x. \quad [25] $$

In Eqs. 24-25, prevalence values are obtained from Eq. 1 for all ages. The ratio of mortality rates (with dementia vs. without dementia) as implied by the prevalence, incidence, and stationary population assumption is

$$ {}_1RR_x = \frac{{}_1m_x^D}{{}^{death}_{1}m_x^{ND}}. \quad [26] $$

The quantity ${}_1RR_x$ is not necessary to obtain estimates of lifetime risk using Approach 1, but it features prominently in Approach 2 and so is presented for comparison purposes.

The difference between the mortality rate among those with dementia and the mortality rate among those without dementia is also not explicitly used in the calculations of lifetime risk, but it is central to the data generating process. From Eq. 26,

$$ {}_1m_x^D = {}^{death}_{1}m_x^{ND} * {}_1RR_x. \quad [27] $$

Subtracting the death rate among those without dementia from both sides of this equation gives the mortality rate difference:

$$ {}_1m_x^D - {}^{death}{}_1m_x^{ND} = {}^{death}{}_1m_x^{ND} * {}_1RR_x - {}^{death}{}_1m_x^{ND} = {}^{death}{}_1m_x^{ND}\big({}_1RR_x - 1\big). \qquad [28] $$

Appendix 2: Multiple-Decrement Life Table Relations in Approach 2

The overall rate of decrement from the dementia-free population is the dementia incidence rate, which comes from Eq. 2, plus the mortality rate for the dementia-free population:

$$ {}_1m_x^{ND} = {}^{death}{}_1m_x^{ND} + {}_1inci_x, \quad [29] $$

and the probability of exiting the dementia-free population at a given age, assuming decrements occur on average halfway through each age interval, is

$$ {}_1q_x^{ND} = {}_1m_x^{ND} \Big/ (1 + 0.5\ {}_1m_x^{ND}). \quad [30] $$

The probability of exiting from each respective cause is

$$ {}^{Dem}{}_1q_x^{ND} = {}_1q_x^{ND} * \left({}_1inci_x \Big/ {}_1m_x^{ND} \right), \quad [31] $$

$$ {}^{Death}{}_1q_x^{ND} = {}_1q_x^{ND} * \left({}^{death}{}_1m_x^{ND} \Big/ {}_1m_x^{ND} \right). \quad [32] $$

Define l_x^{ND} as the number of dementia-free survivors to the xth birthday, so that the number of exits from the dementia-free population, by type of exit, is

$$ {}_1^i d_x^{ND} = l_x^{ND} * {}_1^i q_x^{ND},\ i = Dem, Death. \quad [33] $$

The number of dementia-free survivors to the next age is

$$ l_{x+1}^{ND} = l_x^{ND} - {}^{Dem}{}_1d_x^{ND} - {}^{Death}{}_1d_x^{ND}. \quad [34] $$

For an approximation of the prevalence of dementia at age 70, I use the fitted value of prevalence for age 70.0 from Eq. 1 in the life table, obtaining l_{70}^{ND} as in Eq. 6. After age 70, the population with dementia is tracked as follows. The only way to exit the population with dementia is death, so the probability of death with dementia is

$$ {}_1q_x^D = {}^{Death}{}_1q_x^D = {}_1m_x^D \Big/ (1 + 0.5\ {}_1m_x^D). \quad [35] $$

The size of the population reaching the *x*th birthday with dementia is defined as l_x^D, so the number of deaths is

$$ {}^{Death}{}_1d_x^D = l_x^D * {}^{Death}{}_1q_x^D \quad [36] $$

However, those who develop dementia while age *x* are subject to the risk of death m_x^D once they develop dementia. If they develop dementia halfway through the age interval on average, then the probability of death with dementia for these new cases in that interval is

$$ {}^{Death}_{new}q_x^D = {}_1m_x^D \Big/ (2 + 0.5\ {}_1m_x^D) \quad [37] $$

and the number of deaths among new dementia cases is

$$ {}^{Death}_{new}d_x^D = {}^{Dem}{}_1d_x^{ND} * {}^{Death}_{new}q_x^D. \quad [38] $$

The size of the population with dementia at the subsequent (exact) age is

$$ l_{x+1}^D = l_x^D + {}^{Dem}{}_1d_x^{ND} - {}^{Death}{}_1d_x^D - {}^{Death}_{new}d_x^D. \quad [39] $$

Person-years lived in the dementia-free state are calculated assuming exits occur linearly within age intervals:

$$ {}_1L_x^{ND} = l_{x+1}^{ND} + 0.5(l_x^{ND} - l_{x+1}^{ND}). \quad [40] $$

Person-years lived in a state of dementia are simply

$$ {}_1L_x^D = {}_1L_x - {}_1L_x^{ND}. \quad [41] $$

Filling in the table for the subsequent age (*x*+1) requires an approximation of the proportion of survivors with dementia in the middle of the age (*x*+1, *x*+2) interval, because the mortality rates in Eqs. 18-20 pertain to age intervals rather than exact ages. My approximation again uses the assumption of linearity of survivorship in small intervals: I assume that half the attrition recorded from exact ages *x* to *x*+1 will occur from exact age *x*+1 to the middle of the (*x*+1, *x*+2) interval. I denote approximated number of persons in state *i* in the middle of the age

(x+1, x+2) interval as ${}_1\hat{L}^{i}_{x+1}$, while I assume that the L column for the entire population (from SSA) records all survivors in the middle of the given age interval:

$$\begin{aligned} {}_1\hat{L}^{D}_{x+1} &= {}_1L_{x+1} - {}_1\hat{L}^{ND}_{x+1} = {}_1L_{x+1} - [l^{ND}_{x+1} - 0.5(l^{ND}_{x} - l^{ND}_{x+1})] \\ &= {}_1L_{x+1} - [1.5l^{ND}_{x+1} - 0.5l^{ND}_{x}]. \end{aligned} \quad [42]$$

Prevalence of dementia at the subsequent age is estimated as the proportion of mid-interval survivors living in a state of dementia:

$${}_1P_{x+1} = {}_1\hat{L}^{D}_{x+1} \Big/ {}_1L_{x+1}, \quad [43]$$

which is used to solve for the mortality rate in the dementia-free population for the age *x+1* interval, using Eqs. 18 and 19.

Because I use narrow (one-year) age intervals, the resulting $\hat{L}^{i}_{x}$ columns from Eq. 42 will be close to the L^{i}_{x} columns from Eqs. 40-41. The similarity of the two columns is shown as online material. The age schedule of prevalence as calculated in Eq. 43 is shown in Table 4. It can be compared to that estimated in baseline ADAMS in Eq. 1 as an informal test of stationarity, under the assumption that the model of differential mortality is correct.

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Table 1 Models of dementia incidence, prevalence, and differential mortality

A) Prevalence model:
$logit(prevalence_x) = \alpha + \beta x,$

Point estimates:

Term	Coefficient estimate
Age (*x*)	0.152565
Constant	-14.2737

Variance-covariance:

	Age	Constant
Age	0.000295	-0.02424
Constant	-0.02424	2.004415

B) Incidence model:
$logit(incidence_x) = \alpha' + \beta' x,$

Point estimates:

Term	Coefficient estimate
Age (*x*)	0.087151
Constant	-10.6868

Variance-covariance:

	Age	Constant
Age	0.000407	-0.03363
Constant	-0.03363	2.793747

(Continued on next page)

(Table 1, Continued)

C) Differential mortality
Model: $\ln(m_{x,dem}) = \alpha + \beta_1 x + \beta_2 dementia + \beta_3 x * dementia.$

Point estimates:

Term	Coefficient estimate
Dementia	6.435545
Age (*x*)	0.110955
Age*Dementia	-0.06139
Constant	-12.2631

Variance-covariance:

	Dementia	Age	Age*Dementia	Constant
Dementia	3.427942	0.027964	-0.03975	-2.35307
Age	0.027964	0.000299	-0.00033	-0.025
Age*Dementia	-0.03975	-0.00033	0.000464	0.027693
Constant	-2.35307	-0.025	0.027693	2.10715

See text for details of model fitting.

Data: Aging, Demographics, and Memory Study (ADAMS), United States, 2001-2009. For prevalence and differential mortality, n=856. For incidence, n=456. Mortality by dementia status data from Health and Retirement Study (HRS), United States, 2001-2011.

Table 2 Dementia prevalence, incidence, and differential mortality – stationary approach

	Fitted prevalence & incidence				Implied	
Age	Prevalence	(SE)	Incidence	(SE)	RR	(SE)
70	0.030	(0.007)	0.010	(0.003)	13.313	(12.999)
75	0.061	(0.009)	0.016	(0.003)	4.395	(2.107)
80	0.121	(0.012)	0.024	(0.003)	1.846	(0.121)
85	0.227	(0.022)	0.037	(0.005)	1.108	(0.300)
90	0.384	(0.043)	0.056	(0.011)	1.024	(0.295)
95	0.569	(0.061)	0.086	(0.023)	1.037	(0.271)
100	0.734	(0.064)	0.130	(0.042)	1.259	(0.346)

RR = Relative risk of death, with dementia vs. without dementia; SE = standard error.

Data: Aging, Demographics, and Memory Study (ADAMS), United States, 2001-2009. For prevalence, n=856. For incidence, n=456. Mortality data from United States Social Security Administration life tables for 1920 birth cohort. Mortality by dementia status data from Health and Retirement Study (HRS), United States, 2001-2011.

Parametric models were fitted to prevalence and incidence data to generate single-year age-specific estimates. RR was implied by the fitted prevalence and incidence estimates along with stationary-population relations.

Table 3 Life cycle quantities for dementia – stationary approach

A. Males

Age	LE	DFLE	DLE	(SE)	Lifetime Risk	(SE)	DFLE'	(SE)
70	12.31	10.83	1.48	(0.129)	0.237	(0.029)	11.14	(0.119)
75	9.65	8.04	1.61	(0.142)	0.233	(0.027)	8.53	(0.134)
80	7.26	5.54	1.72	(0.162)	0.226	(0.032)	6.25	(0.143)
85	5.20	3.43	1.76	(0.182)	0.215	(0.041)	4.37	(0.135)
90	3.64	1.91	1.74	(0.187)	0.208	(0.052)	3.01	(0.109)
95	2.61	0.96	1.64	(0.163)	0.213	(0.067)	2.15	(0.078)
100	2.02	0.47	1.55	(0.123)	0.246	(0.089)	1.71	(0.039)

B. Females

Age	LE	DFLE	DLE	(SE)	Lifetime Risk	(SE)	DFLE'	(SE)
70	15.25	13.17	2.08	(0.190)	0.318	(0.036)	13.41	(0.191)
75	11.91	9.77	2.14	(0.205)	0.304	(0.037)	10.19	(0.205)
80	8.91	6.74	2.16	(0.227)	0.286	(0.044)	7.41	(0.209)
85	6.37	4.25	2.12	(0.249)	0.267	(0.054)	5.17	(0.190)
90	4.42	2.41	2.00	(0.251)	0.253	(0.067)	3.53	(0.149)
95	3.10	1.26	1.83	(0.220)	0.252	(0.081)	2.47	(0.102)
100	2.32	0.63	1.69	(0.167)	0.277	(0.102)	1.90	(0.061)

LE = total life expectancy for a randomly chosen person in the population of given age, DFLE = Dementia-free life expectancy for a randomly chosen person in the population of given age, DLE = life expectancy with dementia for a randomly chosen person in the population of given age, Lifetime Risk = probability that a dementia-free person will develop dementia later in life, DFLE' = Dementia-free life expectancy for a dementia-free person of given age.

By construction, DFLE and DLE have the same standard error, and LE has zero variance.

Quantities calculated using fitted values of dementia incidence and prevalence and implied relative risk of death (with dementia vs. without) shown in Table 1.

Data: Aging, Demographics, and Memory Study (ADAMS), United States, 2001-2009. For prevalence, n=856. For incidence, n=456. Mortality data from United States Social Security Administration life tables for 1920 birth cohort. Mortality by dementia status data from Health and Retirement Study (HRS), United States, 2001-2011.

Table 4 Dementia prevalence, incidence, differential mortality – non-stationary approach

Age	Implied Prevalence	(SE)	Estimated Incidence	(SE)	Estimated RR	(SE)
70	0.030	(0.173)	0.010	(0.003)	8.86	(3.344)
75	0.058	(0.241)	0.016	(0.003)	6.37	(1.761)
80	0.093	(0.304)	0.024	(0.003)	4.63	(0.896)
85	0.137	(0.371)	0.037	(0.005)	3.41	(0.513)
90	0.196	(0.443)	0.056	(0.011)	2.54	(0.447)
95	0.286	(0.535)	0.086	(0.023)	1.91	(0.479)
100	0.453	(0.673)	0.130	(0.042)	1.48	(0.472)

RR = Relative risk of death, with dementia vs. without dementia

Data: Aging, Demographics, and Memory Study (ADAMS), United States, 2001-2009. For relative risk of death, n=856. For incidence, n=456. Mortality data from United States Social Security Administration life tables for 1920 birth cohort. Mortality by dementia status data from Health and Retirement Study (HRS), United States, 2001-2011.

Parametric models were fitted to incidence and mortality data from ADAMS to generate single-year age-specific estimates. Prevalence in the cohort arises from the life table relations as described in the Methods section, under Approach 2.

Table 5 Life cycle quantities – non-stationary approach

A. Males

Age	LE	DFLE	DLE	(SE)	Lifetime Risk	(SE)	DFLE'	(SE)
70	12.31	11.55	0.76	(0.220)	0.269	(0.032)	11.91	(0.190)
75	9.65	8.90	0.75	(0.228)	0.271	(0.032)	9.35	(0.154)
80	7.26	6.51	0.76	(0.223)	0.267	(0.036)	7.04	(0.123)
85	5.20	4.47	0.73	(0.211)	0.257	(0.044)	5.04	(0.094)
90	3.64	2.93	0.72	(0.200)	0.247	(0.056)	3.49	(0.080)
95	2.61	1.85	0.76	(0.200)	0.244	(0.072)	2.43	(0.082)
100	2.02	1.10	0.92	(0.207)	0.255	(0.091)	1.77	(0.084)

B. Females

Age	LE	DFLE	DLE	(SE)	Lifetime Risk	(SE)	DFLE'	(SE)
70	15.25	13.51	1.74	(0.292)	0.347	(0.037)	13.93	(0.278)
75	11.91	10.21	1.69	(0.303)	0.341	(0.038)	10.88	(0.213)
80	8.91	7.34	1.56	(0.300)	0.329	(0.043)	8.15	(0.172)
85	6.37	4.99	1.38	(0.285)	0.312	(0.052)	5.84	(0.133)
90	4.42	3.21	1.21	(0.262)	0.293	(0.064)	4.02	(0.101)
95	3.10	1.97	1.12	(0.243)	0.281	(0.079)	2.76	(0.088)
100	2.32	1.13	1.19	(0.228)	0.284	(0.097)	1.97	(0.086)

LE = total life expectancy for a randomly chosen person in the population of given age. DFLE = Dementia-free life expectancy for a randomly chosen person in the population of given age, DLE = life expectancy with dementia for a randomly chosen person in the population of given age, Lifetime Risk = probability that a dementia-free person will develop dementia later in life, DFLE' = Dementia-free life expectancy for a dementia-free person of given age.

By construction, DFLE and DLE have the same standard error, and LE has zero variance.

Quantities calculated using fitted values of dementia incidence and relative risk of death (with dementia vs. without) shown in Table 3.

Data: Aging, Demographics, and Memory Study (ADAMS), United States, 2001-2009. For relative risk of death, n=856. For incidence, n=456. Mortality data from United States Social Security Administration life tables for 1920 birth cohort. Mortality by dementia status data from Health and Retirement Study (HRS), United States, 2001-2011.

Table 6 Life cycle quantities using 1940 cohort life table – non-stationary approach

A. Males

Age	LE	DFLE	DLE	(SE)	Lifetime Risk	(SE)	DFLE'	(SE)
70	13.64	12.54	1.10	(0.262)	0.308	(0.034)	12.93	(0.237)
75	10.65	9.57	1.08	(0.272)	0.306	(0.035)	10.13	(0.192)
80	7.96	6.93	1.03	(0.268)	0.298	(0.040)	7.59	(0.156)
85	5.70	4.74	0.96	(0.253)	0.286	(0.049)	5.44	(0.121)
90	4.05	3.13	0.93	(0.239)	0.276	(0.063)	3.82	(0.101)
95	2.95	1.97	0.97	(0.233)	0.273	(0.080)	2.68	(0.098)
100	2.30	1.15	1.14	(0.227)	0.285	(0.099)	1.96	(0.095)

B. Females

Age	LE	DFLE	DLE	(SE)	Lifetime Risk	(SE)	DFLE'	(SE)
70	15.99	14.01	1.97	(0.332)	0.374	(0.038)	14.44	(0.315)
75	12.62	10.67	1.95	(0.343)	0.370	(0.041)	11.38	(0.252)
80	9.57	7.73	1.84	(0.340)	0.359	(0.047)	8.62	(0.209)
85	6.93	5.26	1.66	(0.324)	0.342	(0.057)	6.23	(0.166)
90	4.89	3.40	1.49	(0.301)	0.325	(0.070)	4.35	(0.129)
95	3.49	2.09	1.40	(0.277)	0.313	(0.087)	3.02	(0.109)
100	2.63	1.18	1.46	(0.248)	0.316	(0.105)	2.16	(0.101)

LE = total life expectancy for a randomly chosen person in the population of given age. DFLE = Dementia-free life expectancy for a randomly chosen person in the population of given age, DLE = life expectancy with dementia for a randomly chosen person in the population of given age, Lifetime Risk = probability that a dementia-free person will develop dementia later in life, DFLE' = Dementia-free life expectancy for a dementia-free person of given age.

By construction, DFLE and DLE have the same standard error, and LE has zero variance.

Quantities calculated using fitted values of dementia incidence and relative risk of death (with dementia vs. without) shown in Table 3. Mortality rates for total population come from Social Security Administration, 1940 birth cohort life tables.

Data: Aging, Demographics, and Memory Study (ADAMS), United States, 2001-2009. For relative risk of death, n=856. For incidence, n=456. Mortality data from United States Social Security Administration life tables for 1940 birth cohort. Mortality by dementia status data from Health and Retirement Study (HRS), United States, 2001-2011.

Table 7 Point estimates of incidence rates under intervention scenarios

New cases per dementia-free person-year lived

Age	Scenario 1&2	Scenario 3&4	Scenario 5
70	0.0095	0.00685	0.0058
75	0.0144	0.01032	0.0084
80	0.0220	0.01566	0.0122
85	0.0337	0.02394	0.0178
90	0.0518	0.03675	0.0261
95	0.0794	0.05648	0.0384
100	0.1201	0.08636	0.0565

Scenarios 1 & 2 delay dementia incidence by one year compared to rates estimated from ADAMS and shown in Table 1. Scenarios 3 & 4 delay dementia incidence by five years. Scenario 5 reduces the acceleration of dementia incidence with age by 10%.

Data: Aging, Demographics, and Memory Study (ADAMS), United States, 2001-2009. For relative risk of death, n=856. For incidence, n=456. Mortality data from United States Social Security Administration life tables for 1940 birth cohort. Mortality by dementia status data from Health and Retirement Study (HRS), United States, 2001-2011.

Table 8 Lifetime risk of dementia under intervention scenarios – non-stationary approach

A. Males

	Scenario 1		Scenario 2		Scenario 3		Scenario 4		Scenario 5	
Age	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
70	0.261	(0.032)	0.255	(0.032)	0.232	(0.032)	0.202	(0.032)	0.213	(0.031)
75	0.263	(0.031)	0.256	(0.031)	0.233	(0.029)	0.203	(0.028)	0.212	(0.028)
80	0.259	(0.034)	0.253	(0.033)	0.229	(0.030)	0.199	(0.026)	0.205	(0.026)
85	0.249	(0.042)	0.243	(0.041)	0.219	(0.035)	0.192	(0.029)	0.194	(0.029)
90	0.240	(0.054)	0.234	(0.052)	0.209	(0.044)	0.184	(0.038)	0.181	(0.035)
95	0.236	(0.069)	0.231	(0.068)	0.205	(0.057)	0.182	(0.051)	0.171	(0.043)
100	0.247	(0.088)	0.242	(0.087)	0.213	(0.074)	0.193	(0.068)	0.170	(0.052)

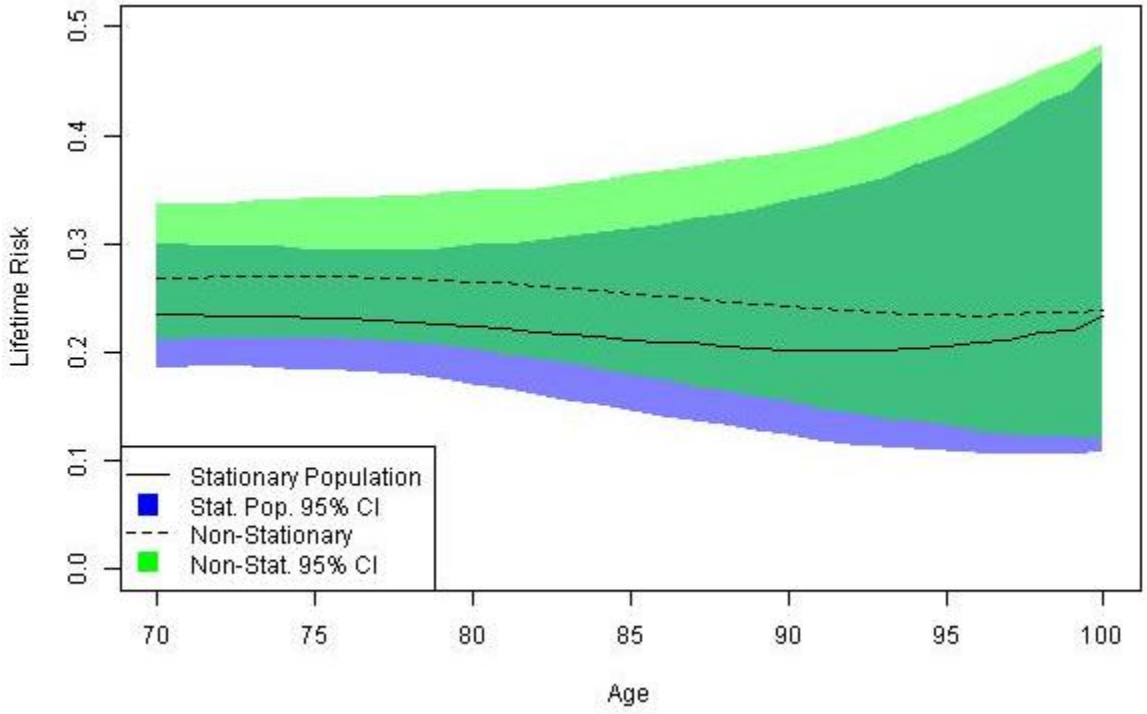
B. Females

	Scenario 1		Scenario 2		Scenario 3		Scenario 4		Scenario 5	
Age	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
70	0.338	(0.036)	0.330	(0.036)	0.302	(0.035)	0.266	(0.034)	0.276	(0.034)
75	0.331	(0.037)	0.324	(0.036)	0.296	(0.034)	0.260	(0.032)	0.268	(0.031)
80	0.320	(0.042)	0.312	(0.041)	0.284	(0.036)	0.250	(0.032)	0.255	(0.031)
85	0.303	(0.050)	0.296	(0.049)	0.268	(0.042)	0.236	(0.036)	0.237	(0.035)
90	0.285	(0.062)	0.278	(0.060)	0.251	(0.052)	0.222	(0.045)	0.217	(0.041)
95	0.273	(0.077)	0.267	(0.075)	0.239	(0.064)	0.214	(0.058)	0.200	(0.049)
100	0.277	(0.094)	0.271	(0.093)	0.240	(0.080)	0.218	(0.074)	0.192	(0.057)

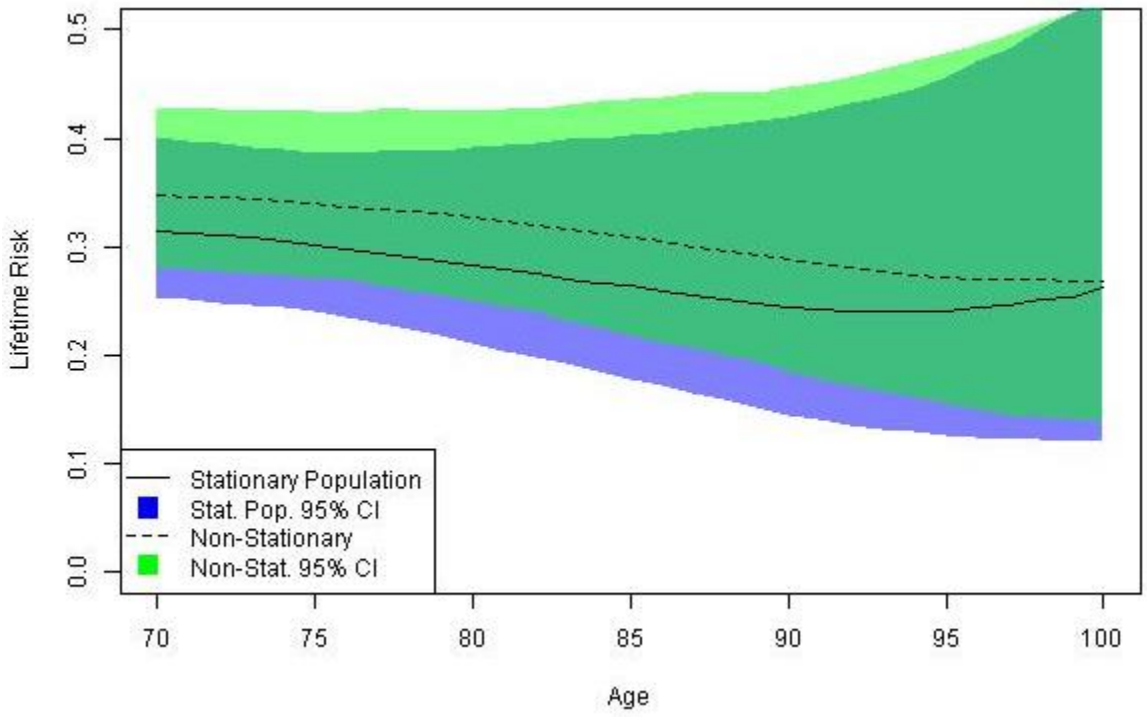
Lifetime Risk = probability that a dementia-free person of given age will develop dementia later in life.
Scenario 1: Dementia incidence delayed by 1 year, effective for 50% of dementia-free population age 70.
Scenario 2: Dementia incidence delayed by 1 year, effective for 90% of dementia-free population age 70.
Scenario 3: Dementia incidence delayed by 5 years, effective for 50% of dementia-free population age 70.
Scenario 4: Dementia incidence delayed by 5 years, effective for 90% of dementia-free population age 70.
Scenario 5: Acceleration of dementia incidence with age reduced by 10%.
Original estimates of incidence shown in Table 3.

Fig. 1 Lifetime risk of dementia, stationary approach vs. non-stationary approach

A. Males



B) Females



Notes: Lifetime risk = probability that a dementia-free person will develop dementia later in life. Stationary approach used baseline dementia prevalence and longitudinal dementia incidence along with life-table relations and 1920 U.S. birth cohort life tables. Non-stationary approach used longitudinal dementia incidence and differential mortality estimates with the 1920 cohort life tables.