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Gender and incidence of dementia in the Framingham Heart Study from mid-adult life

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Abstract

Background—Gender-specific risks for dementia and Alzheimer's Disease (AD) starting in midlife remain largely unknown.

Methods—Prospectively ascertained dementia/AD and cause-specific mortality in Framingham Heart Study (FHS) participants was used to generate 10- to 50-year risk estimates of dementia/AD, based on the Kaplan-Meier method (Cumulative Incidence) or accounting for competing risk of death (lifetime risk, LTR).

Results—Overall, 777 incident dementia (601 AD) occurred in 7,901 participants (4,333 women) over 136,266 person-years. Whereas cumulative incidences were similar in women and men, LTRs were higher in women >85. LTR of dementia/AD at age 45 was 1 in 5 in women, 1 in 10 in men. Cardiovascular mortality was higher in men with rate ratios decreasing from ~6 at 45-54 to <2 after age 65.

Conclusion—Selective survival of men with a healthier cardiovascular risk profile and hence lower propensity to dementia might partly explain the higher LTR of dementia/AD in women.

Keywords

incidence of dementia; Alzheimer's disease; gender; mortality; cardiovascular risk profile; selective survival; cohort/population-based cohort; prevention

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1. Background

The common forms of dementia, i.e. Alzheimer's disease (AD) and vascular dementia, occur more frequently with increasing age, in the presence of vascular risk factors [1], limited physical activity [2] and susceptibility genes (*APOE*, and more recently 9 other genes: BIN1, CR1, CLU, PICALM, CD33, EPHA1, MS4A4/MS4A6, ABCA7, CD2AP) [3-5].

Among other potential risk factors, a link with gender has been particularly contentious. Indeed, several studies have suggested that women are at higher risk of dementia, especially of the AD type [6-11] while others have shown no difference [12-14]. A meta-analysis of eight European population-based studies carried out in the 1990s concluded that the incidence of AD consistently tended to be higher in women [15] while in another report from the Rotterdam study, a higher incidence of dementia among women was documented only beyond age 90 years [16]. Recently, a study from the Mayo Clinic in Rochester has shown that prevalence and incidence of 'mild cognitive impairment (MCI)' are higher in men than in women [17, 18], which could be seen as inconsistent with the higher incidence of dementia reported elsewhere among women. Different hypotheses, which are not all mutually exclusive, have been proposed to explain a possible difference between the sexes in dementia risk.

First, there are several undisputed sex differences in brain development that could play a role in determining structural brain reserve and the susceptibility to cerebral diseases, including dementia. Anatomical differences between brains of women and men include lower gray matter volume and lower cortical thickness in women and, at a macroscopic level, lower brain volume and weight in women [19-23]. Each of the latter anatomical characteristics has been associated with a higher risk of cognitive decline or dementia [24] and hence could explain the apparent higher incidence of dementia in women. Secondly, molecular mechanisms through either differential exposure to sex hormones or sex specific epigenetic interactions could also play a role [25-27]. Thirdly, according to the cognitive reserve hypothesis [28], men have, on average, a higher functional cognitive reserve, measured through a proxy measure such as educational level, so that they can compensate longer for the pathological brain changes of AD (higher clinical resilience), resulting in a delayed clinical expression of dementia in men. This greater cognitive reserve might arise from the higher education and more cognitively challenging occupational opportunities open to men in the initial 6-7 decades of the 20th century. Fourth, differential diagnostic sensitivity according to gender might lead to an earlier diagnosis in women and an apparent lower incidence in men who might die undiagnosed; reflecting for instance a greater sensitivity to spousal cognitive decline among men [29, 30].

Another potential explanation is that the lower incidence of dementia and AD in men later in life is a consequence of differential mortality in men and women starting as early as mid-life. Under that hypothesis, differential mortality would lead to a selective survival of those men beyond 60 years of age, who are at lower risk of developing dementia. In order to investigate this latter hypothesis, it is essential to rely on large observational studies that have enrolled individuals starting in mid-adult life. Yet, most population-based studies on

dementia started enrollment after the age of 65, i.e. when potentially differential selection between men and women due to premature mortality has already started.

We have updated estimations of lifetime risk of dementia and AD in the FRAMINGHAM Heart Study (FHS), starting the analysis among participants 45 years of age, compared incidences of dementia and AD between women and men over up to 50 years of risk and explored the potential for differential mortality by gender before age 65 years.

2. Methods

2.1 Participants

The FHS is a longitudinal community-based cohort study initiated in 1948. Members of the Original Cohort of 5,209 residents of Framingham, Massachusetts have undergone biennial examinations including medical history, physical examination and laboratory testing through the present. In 1971, the Offspring Cohort was recruited from children of the Original Cohort and their spouses; these 5,214 participants have undergone similar examinations approximately every four years. The study design and entry criteria for both cohorts have been described in detail elsewhere [31, 32].

The ‘Dementia Cohort’ is a combined group of participants who survived dementia-free to age 45. It included participants from the Original Cohort (with entry at examination 14, 1975-1978, mean age 73) and Offspring Cohort (with entry at examination 2, 1979-1983, mean age 45), who have been under surveillance for the development of incident dementia as described below.

Original Cohort participants underwent the Kaplan-Albert neuropsychological test battery at their 14th examination cycle and their cognitive status has since been monitored at regular cycle examinations. Participants were routinely administered a screening Mini-Mental State Examination (MMSE) beginning at their 17th Exam cycle and persons who scored below education-based cut-offs or who experienced a decrement of at least 3 points on the MMSE since their most recent previous examination (or an overall decrement of at least 5 points) were flagged for an in-depth second round of neurological and/or neuropsychological assessment. Participants were also flagged by family- or self-reported symptoms of memory loss or if they were referred by a FHS physician or staff member. The Offspring Cohort has been similarly monitored since their 5th examination. In addition, a subjective memory question at examination 2 (Offspring cohort) was used to retrospectively determine if participants had been cognitively intact since this examination.

A panel of at least one neurologist and one neuropsychologist reviewed each case of possible dementia referred by the second round of in-depth assessment or when flagged through death review. The panel determined the date of diagnosis and the type of dementia using available data from neurological examination findings, neuropsychological test results, a structured telephone interview with family members or caregivers, FHS records, hospital records, information from primary care physicians, and imaging and autopsy results. The diagnosis of dementia was made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [33] and additionally required that the

participant survive for at least 6 months following the onset of symptoms. AD was diagnosed if participants met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association for definite, probable, or possible AD [34].

A separate panel of FHS physicians reviewed all participant deaths' files to assign dates and causes of death; in a small number of participants in whom cognitive decline had not been detected during their FHS examinations, any suggestion of cognitive impairment at the time of death lead to flagging of participants' records for referral to the dementia group for review following the procedure described above. Cause-specific mortality was assigned by a 3 physician review panel using previously described criteria [35, 36]. All participants gave written informed consent and the FHS study protocols and participant consent forms were approved by the Institutional Review Board of Boston University School of Medicine.

2.2 Age-specific Cohorts

We separately studied two index groups of participants who survived dementia-free to each of "index" ages, 45 and 65, and described their characteristics (specifically, potential risk factors for dementia of AD and vascular types). Individual participants contributed Person Years (PY) from entry through 2009 until they were diagnosed with dementia, died free of dementia, or were censored at the last date known to be dementia-free. Individual participants could be members of more than one index group. Characteristics were measured or recorded at the most recent examination attended within 5 years before the index age.

2.3. Clinical and laboratory measurements

Participants were categorized according to the presence of ≥1 ApoE ε4 allele. Elevated blood pressure (BP) was defined as systolic Blood Pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg and Stage 1 + hypertension was defined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) criteria as elevated BP or use of an anti-hypertensive medication [37]. Participants were classified at baseline according to documented prior occurrence of atrial fibrillation (based on review of all FHS and outside hospital electrocardiographic tracings and records) and cardiovascular disease (defined as coronary heart disease, heart failure, peripheral arterial disease or stroke). Diabetes mellitus was defined as a current fasting blood glucose ≥ 126 mg/l, random blood glucose ≥ 200 mg/l, or being on anti-diabetic therapy. Participants were categorized as current smokers or non-smokers (including past smokers). Educational achievement was classified here as high school degree or higher.

2.4. Statistical analysis

At each index age, for participants who reached the index age dementia-free, we estimated gender-specific 10-, 20-, 30-, 40- and 50-year risks, and the remaining lifetime risks of developing dementia and AD (and their 95% confidence intervals [CI]) using both conventional cumulative incidence based on the Kaplan-Meier method, which does not take into account the competing risk of mortality, i.e "Competing Mortality-Unadjusted Cumulative Incidence" (CM-UCI) and a modified double-decrement survival analysis

technique to take into account the competing risk of other causes of death, i.e Competing Mortality-Adjusted Cumulative Incidence" (CM-ACI) [38]. The conventional cumulative incidence not corrected for competing risk of death (CM-UCI) may be interpreted as the risk of developing dementia among individuals who live beyond a certain age after which dementia is diagnosed. The CM-ACI is a measure of the actual risk of developing dementia in the given follow-up period, accounting for the competing risk of death. Therefore, those who die before getting dementia are considered to have been spared dementia. ACI over remaining lifespan is also called the lifetime risk (LTR). Within each index age, we compared men and women with respect to the 10-, 20-, 30-, 40- and 50-year and remaining lifespan risks and provide p-values for the z-test comparisons. We also described age-group-specific mortality rates (per 1,000 person-years) calculated as the total number of deaths divided by person years at risk, times 1,000. In addition, among cases of dementia matched on age (5-years strata) at diagnosis, we described time from onset of MCI to diagnosis of dementia in women and men. In order to provide a rough quantitative insight on how early cardiovascular deaths in men could have impacted the difference between men and women in dementia risk after 65 years, we used a two step approach: We first made a crude estimate of how many men would have survived to age 65, had their cardio-vascular death rate been equal to that of women before 65; Next, we re-estimated CM-UCI beyond the age of 65 in men with the assumption that half or all of those added from the first step would have developed dementia [39].All statistical analyses were performed using SAS© statistical software (SAS Institute, Cary, NC).

4. Results

4.1. Study Population

From 1975 to 2009, 7,901 participants (4,333 women and 3,568 men) contributed at least one year after age 45, representing a total of 136,266 person-years of follow-up (PY) and 777 incident dementia cases were diagnosed among them. In addition, 5,937 participants survived dementia-free to at least age 65 (68,906 PY; 762 incident dementia cases). At index age 45, there was no difference between women and men regarding major risk factors for dementia and AD: 83% of women and men had obtained a high school degree, and 21% of the participants with available DNA carried an *APOE ε4* allele. When considering the subset of participants who had cardiovascular risk factors measured at age 45, the distributions were also similar (Table 1). Over time (i.e. at subsequent index ages 55, 65, 75, and 85), the proportion of *APOE ε4* carriers was stable while the proportion who achieved high school degrees decreased (similarly among women and men), possibly reflecting a birth cohort effect.

When looking at risk factors common to both dementia and cardiovascular diseases, the proportion of persons with elevated BP (>140/90 mmHg) was lower among women than men at age 45 years (15 versus 25%), but the proportions became similar at 55 years, with the prevalence of an elevated BP becoming higher in women beyond age 75 years. Across ages, the frequency of all these conditions increased in both sexes, though coronary heart disease, atrial fibrillation and stroke increased less rapidly in women than men. At age 45,

type 2 diabetes was reported in 2% of women and men. Its prevalence then increased over time as expected, though less rapidly in women than men.

In summary, at age 45, women did not differ from men in prevalence of an *APOE ε4* allele and high school diploma. In contrast, they had a lower prevalence than men of hypertension, coronary heart disease, atrial fibrillation and smoking. Overall, prevalence of risk factors for cardiovascular disease increased while the difference between women and men vanished over time.

4.2 Incidence of dementia and AD

When starting the observation at index age 45 (Table 2, Figures 1a and 1b), the risk of dementia or AD remained low until age 75 (30-year risk), whether corrected or not for competing risk of death. It then increased sharply, reaching a plateau after 95 years old in both women and men after correcting for competing causes of death. CM-UCI (i.e without correction for competing causes of death) of both dementia and AD did not differ between women and men. As far as CM-ACI (i.e corrected for competing risk of death) was concerned, the risk among women was significantly higher than among men after age 85 years (40 year risk). The proportion of AD type among dementia cases was higher in women (81%, 412/507) than in men (69%, 187/270). From 65 to 95 years of age, this proportion increased from 75% to 81% and from 57% to 69%, respectively. The overall LTR (cumulative risk corrected for competing causes of death, CM-ACI estimated for the remaining lifespan) was 1 in 5 women and 1 in 10 men who reached 45 years of age developed dementia; 1 in 5 women and 1 in 10 men developed AD.

When starting the observation at index age 65 (Table 3, Figures 1c and 1d), the same trends for cumulative incidences and lifetime risk of dementia or AD applied. The median time from onset of cognitive impairment to diagnosis of dementia in a subset of 308 men and women matched on age at diagnosis was 1.8 years in women and 2.0 years in men (p=0.083, adjusting for age at diagnosis; interquartile ranges 1.0 to 3.4 and 1.2 to 3.8, respectively).

If we restricted to those with age at diagnosis of dementia later than 70 years (n=150 for women and 150 for men), the median time intervals were 1.8 and 2.1, respectively (diagnosis age-adjusted p=0.131; interquartile ranges 1.0 to 3.4 and 1.2 to 3.8, respectively).

4.3. Age- and cause-specific mortality

We explored how a potential selection might have occurred due to differential mortality, especially before the age of 65 (Table 4). In all age categories, mortality rates were lower in women than men, ranging from 2.5 (45-54 years) to 255.2/1,000 person-years (95-104 years) in women, and from 4.0 to 310.7/1,000 person-years in men. When examining the different causes, deaths due to cardio-vascular disease represented around 30% of all deaths across all age categories, though the rate ratios for men versus women decreased with age, from around 6 (i.e men had specific-mortality due to cardio-vascular disease that was 6 times higher than women at ages 45-54) to 2 or less after age 65 years, showing that the selection from cardio-vascular disease deaths occurred in men as early as 45 years. Conversely, rate ratios for non cardio-vascular deaths in men versus women remained rather

constant across age categories (ranging from 1.3 to 1.8). To summarize, in women, competing causes of death have had an impact on estimates of dementia or AD risk later than in men. In men, a selection occurred as early as mid-life, especially (but not only) due to cardio-vascular deaths (figures 2a and 2b).

4.4. Impact of cardiovascular death in the differential LTR of dementia between men and women under counterfactual scenarios

In men, 88 cardiovascular deaths occurred before 65 years. Should cardiovascular mortality of women apply to men before 65 years (0.2 per 1,000 person-years of follow-up instead of 1.2 at age 45-54 or 0.6 instead of 3.6 at age 55-64), around 83% (5/6ths) of all deaths among men would have been spared, accounting for approximately 73 more men surviving above age 65 years. Had half of these 73 men developed dementia, an estimate consistent with the literature on post-stroke and vascular dementia in this survivor group expected to have a high prevalence of vascular risk factors [39], this would have led to an increase of the CM-UCI currently observed in men, from 60.7% (259/426) to 63.9% (259+37/426+73). If all of these 73 individuals had developed dementia, this would increase the overall cumulative incidence of dementia to 66.5% (259+73/426+73). Given that in women, CM-UCI was 76.5%, it is indeed not feasible that cardiovascular deaths before 65 years explain all the difference for dementia risk between men and women. Nonetheless, our results show that a substantial part of the difference in dementia risk between the genders (20 to 50%) may come from cardiovascular disease before age 65 years.

5. Discussion

In the FHS (Original and Offspring cohorts), a large population-based cohort with uniformly ascertained outcomes, we show that remaining life-time risk of dementia or AD did not differ between women and men, when starting the observation at mid-life. The significantly higher cardio-vascular mortality among men compared to women between ages 45 and 65 years may explain a selection of men at the lowest risk for dementia or AD, and account at least partly for the difference between gender. The higher overall life-time risk of dementia or AD in women as compared to men might therefore be interpreted as the combined effect of a longer life expectancy among women, and a selective survival to age 65 of men with the lowest risk of developing dementia. If confirmed in other studies using similar analyses or by more sophisticated modeling, this work has implications for the prevention of dementia and AD.

A large number of population-based studies consistently show that the overall incidence of dementia and AD increase with age, though the difference in risk of dementia among women and men remains controversial. A difference between women and men appears after a certain age as women continue to experience an increased dementia incidence with relatively less steep increases in men. Among the largest studies, EuroDem gathered the individual data of 4 population-based cohort studies in Europe starting from age 65 onwards, including around 530 incident cases of dementia over more than 28,000 person-years of follow up. This collaboration reported a higher risk for AD among women than men that became apparent after age 75 years, while there was no difference for vascular dementia

[15]. Nevertheless, the average follow-up period, 2 years, was short, and the studies of Eurodem included a group of women that had been less exposed to high education levels than men. Several other studies with short-term follow-up [8, 14, 40] including an earlier analysis of the FHS data [13], did not show any difference. In a recent, large study (40,441 person-years and 395 incident dementia cases) starting enrollment as early as 55 years of age, the Rotterdam investigators reported no difference of overall dementia incidence between men and women up to age 90 years, and showed that the incidence of vascular dementia was higher among men than women [16]. We now report data from a second large sample with even earlier enrollment and longer follow-up.

The observation that dementia prevalence or incidence is always higher in the oldest old individuals, especially among women compared to men, has consistently been reported [41, 42]. Among those late onset dementia cases, a mixed profile including both the degenerative features of AD and cerebrovascular disease is likely to be dominant [43, 44]. However, one important contribution of our data is to show no clear difference in terms of prevalence or incidence of subtypes among men and women in our cohort at the oldest ages (> age 85 years), consistent with other large, well designed studies [45]. There might be a synergistic effect of both disease pathologies explaining why less AD pathology is needed to result in clinical expression of the disease in the oldest-old [46, 47]. In the FHS cohort as in others [48, 49], notable gender differences exist in the prevalence of cardiovascular risk factors and incidence of cardiovascular deaths. The differential exposure of both genders to cardiovascular risk factors and disease could partly explain why the risk of dementia and especially AD emerges more strongly in women at older ages.

Therefore, our most original contribution is to suggest that beyond survival differences between men and women, a selective survival of men at lower risk of dementia may occur starting as early as mid-life, earlier than in women. Our analysis starts as early as 45 years, when differential mortality due to cardio-vascular causes starts occurring, is inclusive of those men who die earlier and might have had, had they survived, the highest risk of dementia, especially vascular or mixed subtypes [49]. More generally, our findings suggest that starting observations at age 65 years for a chronic disease of the ageing period may yield biased comparisons among categories when selective survival is explained by risk factors or components that are common to early causes of death and the chronic disease.

In addition, a higher incidence of MCI in men compared to women [18] might be explained by an earlier diagnosis of MCI in men than women as shown by a longer time period between onset of MCI and transition to dementia for men in our dataset. Precise reasons should be further explored, though a simple explanation might be that for cultural reasons men might be diagnosed earlier with MCI than women [50].

The strengths of our analysis include the use of data from a large population-based cohort, with a long follow-up (around 17 years) starting as early as 45 years before the potential selection due to cardio-vascular deaths begins to occur in men. We believe that selection occurring earlier than age 45 years is unlikely to be of sufficient importance to bias our results. The quality of follow up in Framingham is important as people are seen every two to four years and even those who miss study visits are tracked with home visits, telephone

health status updates, record reviews and retrospective status assignment if participants attend a subsequent examination, less than 2% are lost to follow-up with no data on date and cause of death. In addition, the standardized ascertainment of dementia and cause of death should avoid differential information bias among men and women. Therefore, it is unlikely that vascular dementia is misdiagnosed as AD in women. We used an estimation of life-time risk in addition to cumulative incidence, since the latter can only reliably estimate risk over a short period interval.

Among potential limitations, we acknowledge that the FHS is mainly composed of individuals of Caucasian ethnicity and who have achieved high education levels. Therefore, we caution against extrapolation to other populations unless specific studies report comparable results. Thus our findings need replication on other large databases with standardized ascertainment of dementia and AD in persons of other ethnicities, and in different countries with genetic and cultural differences, and alternative profiles of cause-specific mortality. Further, temporal trends in cause-specific mortality (such as reductions in cardiovascular death among men age 45-65 years) could alter these patterns. Our current statistical modeling methods did not consider confounding factors other than age in the models. Nevertheless, in this cohort, some other major risk factors for AD, i.e level of education and *APOE ε4* genotype, were evenly distributed among men and women and did not affect the comparison.

Among the five non-exclusive hypothesis that were raised in the introduction to explain differences in dementia risk between men and women, our data did not allow testing all of them due to lack of information. As far as the cognitive reserve concept is concerned, the original hypothesis is based on the assumptions that firstly a higher cognitive reserve does contribute to delayed onset of dementia or AD and secondly, that men have on average a higher cognitive reserve than women [28]. In the FHS, we used educational status as a proxy for cognitive reserve. Education level could indeed contribute to cognitive reserve either through a direct effect on brain development and function or through better health behaviors or health advantages for those having more wealth and social opportunities. However, an important characteristic of the FHS sample is the high average educational attainment and the absence of difference between men and women. These two specificities of the FHS sample might contribute to the apparent absence of gender differences in dementia incidence not corrected for competing causes of death. The link between vascular risk factors and brain structural imaging changes might also be different among gender [51] and require further large studies with available brain imaging data.

This work has potential consequences for future research as it could bring new insight on some recent findings, especially on the link between vascular risk factors and dementia. Indeed recent reports confirm that the association between vascular risk factors such as smoking, type 2 diabetes, hypertension, obesity [52-54] and dementia risk depends on whether these factors are measured during mid or late life. Selection bias due to differential mortality rates and differences in the underlying causes of early mortality in men and women that we have demonstrated could explain, at least partly, these discrepancies. This will also be crucial to better structure future prevention strategies [55]. We have been able to only roughly estimate the potential impact of early selection of men due to cardio-vascular

deaths (20 to 50% of dementia cases). Therefore, future methodological development will be needed in order to simulate, using more sophisticated counterfactual analyses for example through modeling, how early selection due to death, especially from cardiovascular causes, not only leads to gender differences but could bias the estimation of the dementia risk attributable to various vascular risk factors. Therefore, there is also a need for more prospective studies on the complex patho-physiological interplay between vascular and dementia diseases.

In conclusion, our results based on a large population-based cohort, followed-up as early as mid-life, show that gender differences in the incidence of dementia and AD may not work independently of vascular disease. Screening and reducing cardio-vascular risk factors to decrease the incidence of dementia applies to both genders but as mortality from cardiovascular causes declines, dementia risk might increase further, especially in men.

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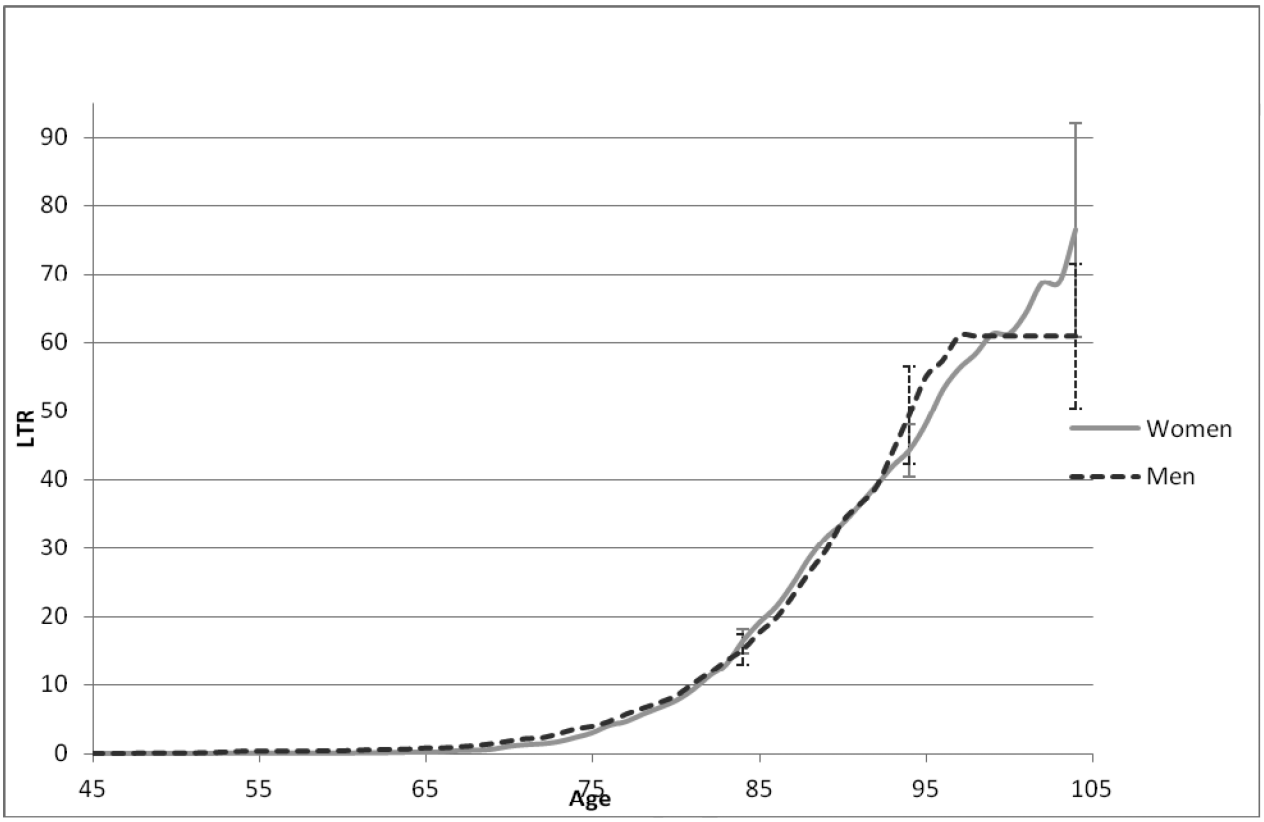

Figure 1a.
Remaining lifetime risk of dementia at index age 45, not corrected for competing risk of mortality, Framingham Heart Study.

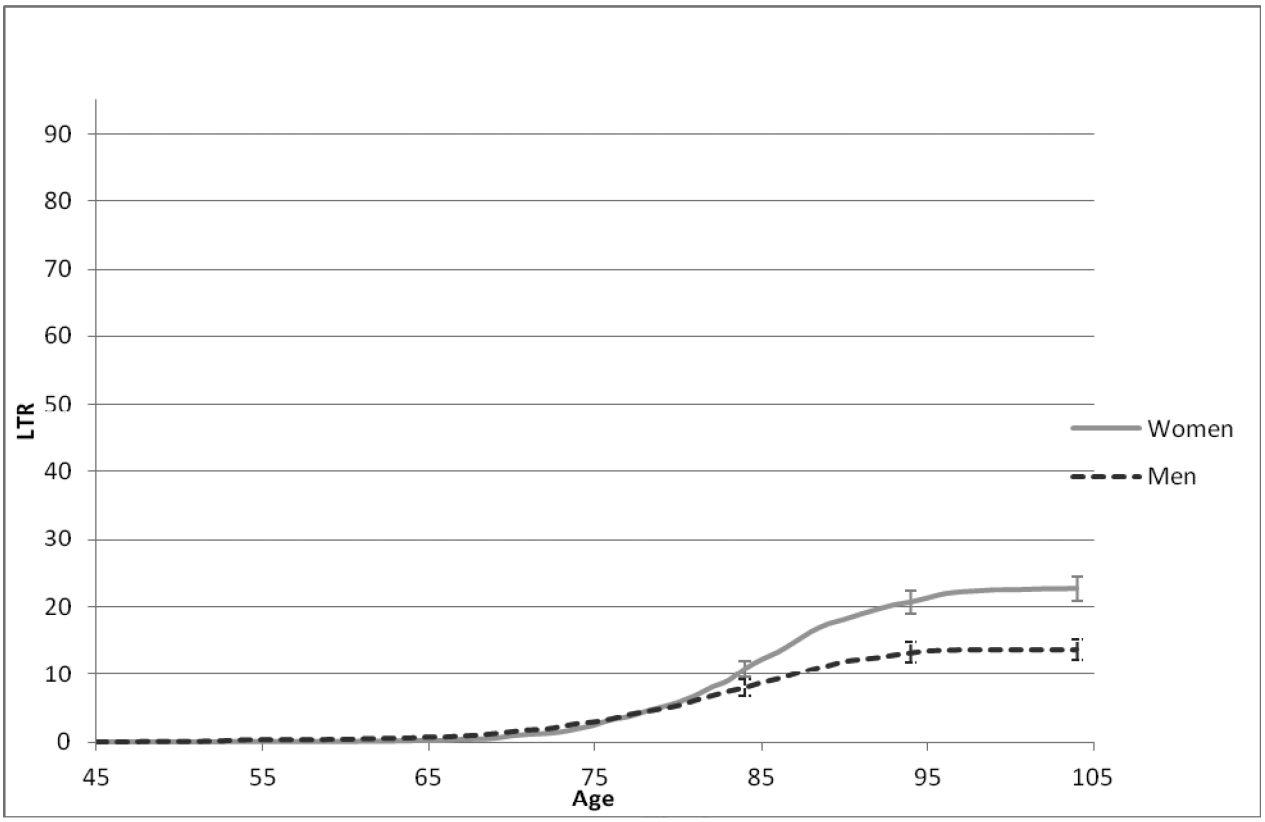

Figure 1b.
Remaining lifetime risk of dementia at index age 45, corrected for competing risk of mortality, Framingham Heart Study.

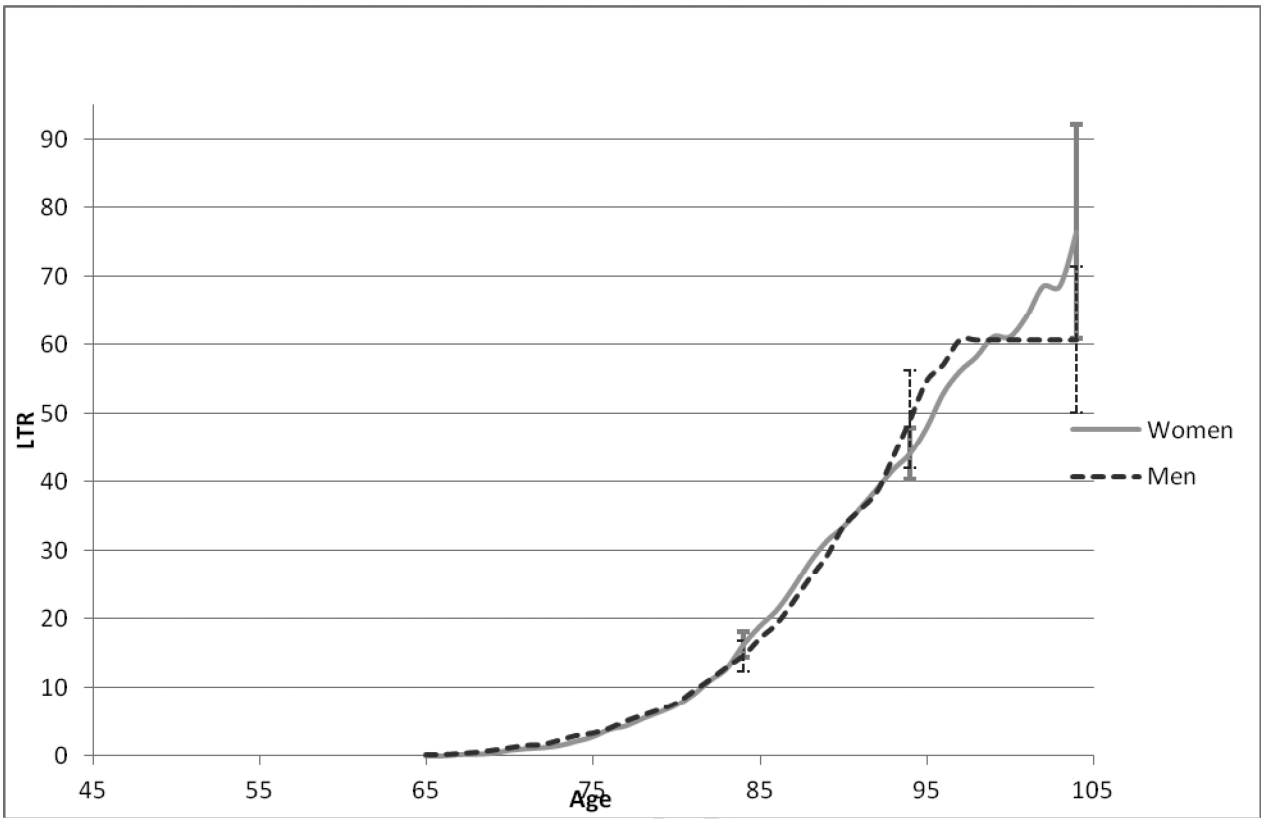

Figure 1c.

Remaining lifetime risk of dementia at index age 65, not corrected for competing risk of mortality, Framingham Heart Study.

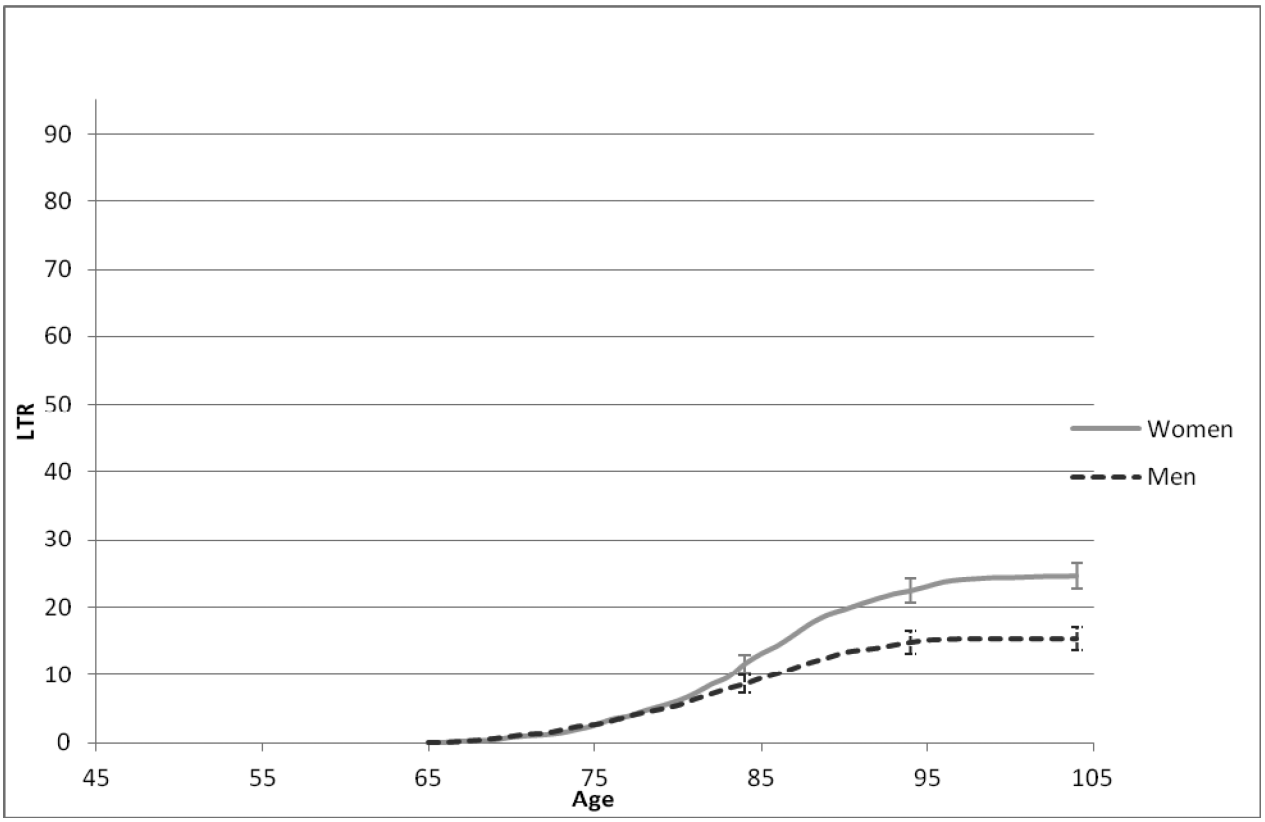

Figure 1d.
Remaining lifetime risk of dementia at index age 65, corrected for competing risk of mortality, Framingham Heart Study.

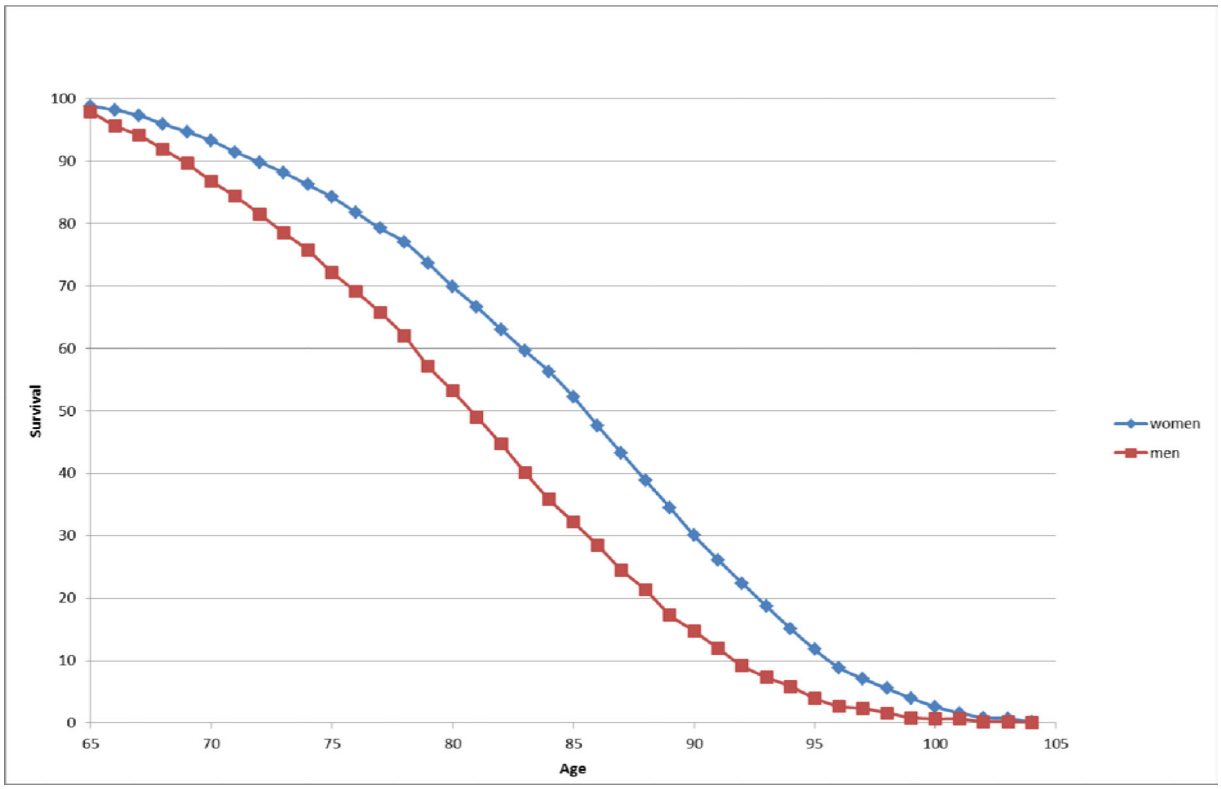

Figure 2a.
Survival after index age 45, Framingham Heart Study.

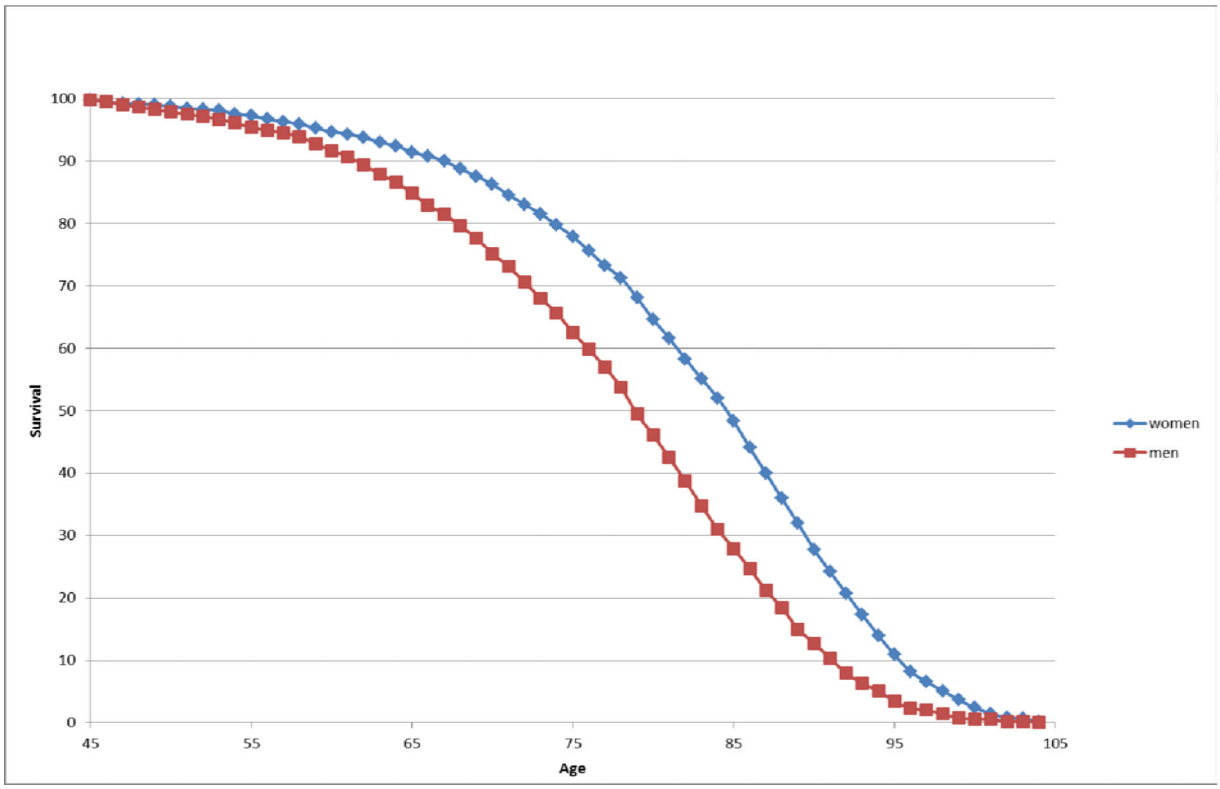

Figure 2b.
Survival after index age 65, Framingham Heart Study.

Table 1

Characteristics at index ages 45, 55, 65, 75, 85 and 95 for those participants of the Framingham Heart Study, Original and Offspring Cohorts, who were documented to be dementia-free at age 45. Individual participants could be members of more than one index group. Characteristics are shown for the subset of participants who have available measurement at the most recent examination attended within 5 years before the index age. All quantitative variables are expressed as mean ± standard deviation (SD).

Index age	45		55		65		75		85		95	
	Women (N=2679)	Men (N=2184)	Women (N=3528)	Men (N=2833)	Women (N=3243)	Men (N=2601)	Women (N=2296)	Men (N=1682)	Women (N=1273)	Men (N=744)	Women (N=292)	Men (N=96)
High School degree or higher, %*	83	83	80	80	77	77	72	71	66	64	58	52
College degree or higher, %†	22	33	18	31	16	29	13	25	10	21	9	21
ApoE4+, %* (available measurement)	21 (n=2044)	21 (n=1594)	21 (n=2510)	21 (n=1981)	21 (n=2214)	21 (n=1767)	20 (n=1520)	21 (n=1119)	19 (n=880)	19 (n=502)	20 (n=200)	8 (n=76)
Elevated Blood Pressure (>140/90 mm Hg), %†	15	25	29	30	40	38	53	47	58	46	47	40
Systolic Blood Pressure (mm Hg)†	120±17	125±15	129±20	130±17	135±21	135±19	143±22	139±20	145±23	140±22	139±23	134±21
Diastolic Blood Pressure (mm Hg)†	78±11	82±10	80±11	82±10	78±11	80±10	75±11	75±11	71±11	71±11	67±11	66±10
Hypertension Medication, %*	4	5	13	14	28	28	45	43	57	48	62	61
Stage 1+ hypertension, %†	20	31	37	40	55	54	71	67	79	70	79	77
History of cardio-vascular disease, %†	1.1	2.1	4	8	12	18	22	35	36	51	49	63
History of coronary heart disease, %†	0.5	1.7	2	7	8	15	15	26	23	35	30	35
History of atrial fibrillation, %*	0.04	0.1	0.3	0.8	1.1	3.1	3.7	7.7	9.0	16.1	19	43
History of stroke, %*	0.1	0.1	0.6	0.7	1.3	1.7	3.0	4.8	6.4	9.3	13	9
Current diabetes, %* (available measurement)	2 (n=1350)	2 (n=1240)	4 (n=1605)	8 (n=1486)	8 (n=1079)	14 (n=1040)	13 (n=688)	22 (n=631)	17 (n=145)	28 (n=123)	22 (n=85)	13 (n=39)
Smoking, %†	40	46	32	35	22	23	13	12	6	7	2	4

*p>0.05 for the comparison of women vs men at index age 45 years

†p<0.001 (except for history of cardio-vascular disease: p=0.006) for the comparison of women vs men at index age 45 years)

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Table 2

Gender-specific risk of dementia and Alzheimer's disease, conditional on survival free of dementia or AD to age 45. Framingham Heart Study, Original and Offspring cohorts, 1975-2009.

	# events		Competing Mortality- Unadjusted cumulative incidence (CM-UCI)†		p*	Competing Mortality- Adjusted cumulative incidence (CM-ACI)‡		p*
	Women	Men	Women	Men		Women	Men	
Dementia								
10 year risk	1	5	0.1 [0.0-0.2]	0.3 [0.0-0.6]	0.08	0.1 [0.0-0.2]	0.3 [0.0-0.6]	0.08
20 year risk	4	11	0.2 [0.0-0.4]	0.6 [0.3-1.0]	0.04	0.2 [0.0-0.4]	0.6 [0.2-1.0]	0.04
30 year risk	48	58	2.3 [1.7-3.0]	3.5 [2.6-4.4]	0.03	2.0 [1.4-2.5]	2.7 [2.0-3.4]	0.09
40 year risk	267	170	16.5 [14.6-18.3]	15.2 [13.0-17.4]	0.39	10.9 [9.7-12.1]	8.0 [6.9-9.2]	<0.001
50 year risk	478	264	44.2 [40.5-48.0]	49.4 [42.3-56.5]	0.21	20.7 [19.0-22.4]	13.3 [11.8-14.8]	<0.001
Lifetime risk	507	270	76.5 [60.9-92.2]	61.0 [50.4-71.5]	0.11	22.7 [20.9-24.5]	13.8 [12.2-15.3]	<0.001
AD								
10 year risk	1	5	0.1 [0.0-0.2]	0.3 [0.0-0.6]	0.08	0.1 [0.0-0.2]	0.3 [0.0-0.6]	0.08
20 year risk	3	8	0.1 [0.0-0.3]	0.5 [0.1-0.8]	0.08	0.1 [0.0-0.3]	0.5 [0.1-0.8]	0.08
30 year risk	36	33	1.7 [1.2-2.3]	2.0 [1.3-2.7]	0.53	1.5 [1.0-2.0]	1.6 [1.1-2.1]	0.74
40 year risk	212	112	13.3 [11.6-15.0]	10.6 [8.6-12.6]	0.04	8.8 [7.7-9.9]	5.5 [4.5-6.5]	<0.001
50 year risk	387	181	37.9 [34.1-41.7]	39.5 [32.1-46.9]	0.71	17.5 [15.9-19.1]	9.8 [8.4-11.2]	<0.001
Lifetime risk	412	187	72.3 [54.0-90.7]	53.3 [41.1-65.5]	0.09	19.5 [17.8-21.2]	10.3 [8.9-11.8]	<0.001

*comparison women vs men

†Cumulative incidence not corrected for competing causes of death

‡Cumulative incidence, corrected for competing causes of death

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Table 3

Gender-specific risk of dementia and Alzheimer disease, conditional on survival free of dementia or AD to age 65. Framingham Heart Study, Original and Offspring cohorts, 1975-2009.

	# events		Competing Mortality- Unadjusted cumulative incidence (CM-UCI)†		p*	Competing Mortality- Adjusted cumulative incidence (CM-UCI)‡		p*
	Women	Men	Women	Men		Women	Men	
Dementia								
10 year risk	44	47	2.1 (1.5-2.7)	2.9 (2.1-3.7)	0.13	1.9 (1.4-2.5)	2.5 (1.8-3.2)	0.23
20 year risk	263	159	16.3 (14.4-18.1)	14.6 (12.4-16.8)	0.26	11.7 (10.4-13.0)	8.7 (7.4-10.0)	0.002
30 year risk	474	253	44.1 (40.4-47.9)	49.1 (41.9-56.3)	0.23	22.4 (20.6-24.2)	14.9 (13.2-16.6)	<0.001
Lifetime risk	503	259	76.5 (60.8-92.1)	60.7 (50.0-71.4)	0.10	24.6 (22.7-24.5)	15.5 (13.7-17.2)	<0.001
AD								
10 year risk	33	25	1.6 (1.1-2.1)	1.5 (0.9-2.1)	0.90	1.5 (1.0-2.0)	1.3 (0.8-1.8)	0.72
20 year risk	209	104	13.2 (11.5-14.9)	10.2 (8.2-12.1)	0.02	9.4 (8.2-10.6)	5.9 (4.8-7.0)	<0.001
30 year risk	384	173	37.8 (34.0-41.6)	39.2 (31.8-46.6)	0.75	18.9 (17.2-20.6)	10.9 (9.4-12.5)	<0.001
Lifetime risk	409	179	72.3 (53.9-90.6)	53.1 (40.8-65.3)	0.09	21.1 (19.2-23.0)	11.6 (10.0-13.2)	<0.001

*comparison women vs men

†Cumulative incidence not corrected for competing causes of death

‡Cumulative incidence, corrected for competing causes of death

Table 4

Sex-specific mortality rates by age categories and specific causes. Framingham Heart Study, Original and Offspring Cohorts.

	All cause		Cardio-vascular deaths		Non Cardio-vascular deaths	
	# events	Rate (1,000 PY)	# events	Rate (1,000 PY)	# events	Rate (1,000 PY)
Women						
45-54	40	2.5	4	0.2	36	2.2
55-64	121	5.5	13	0.6	108	4.9
65-74	341	14.8	101	4.4	240	10.4
75-84	722	40.7	235	13.4	487	27.6
85-94	851	110.0	214	28.8	637	83.5
95-104	189	255.2	44	65.9	145	201.8
Men						
45-54	57	4.0*	17	1.2**	40	2.8
55-64	211	10.8***	71	3.6***	140	7.2**
65-74	501	27.3***	168	9.2***	333	18.2***
75-84	757	68.2***	272	25.0***	485	44.2***
85-94	455	146.7***	131	44.6***	324	106.7***
95-104	48	310.7	10	73.8	38	254.2

* P-value (women vs men in the same age category) < 0.05

** P-value (women vs men in the same age category) <0.01

*** P-value (women vs men in the same age category) <0.001