# Lifetime risk of dementia and Alzheimer's disease

## The impact of mortality on risk estimates in the Framingham Study

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**Article abstract**—We estimated the remaining lifetime risks of developing Alzheimer's disease (AD) and dementia from all causes, based on data from longitudinal population studies. The risk of developing AD during one's lifetime depends on both disease incidence and life expectancy. Conventional estimates of cumulative incidence overestimate the risk when there is a substantial probability of mortality due to competing causes. A total of 2,611 cognitively intact subjects (1,061 men, 1,550 women; mean age, 66 ± 7 years) were prospectively evaluated for the development of AD or other dementia. A modified survival analysis was used to estimate both cumulative incidence and the sex-specific remaining lifetime risk estimates for quinquennial age groups above age 65 years. Over a 20-year follow-up period, 198 subjects developed dementia (120 with AD). The remaining lifetime risk of AD or other dementia depended on sex, being higher in women, but varied little with age between 65 and 80 years. In a 65-year-old man, the remaining lifetime risk of AD was 6.3% (95% CI, 3.9 to 8.7) and the remaining lifetime risk of developing any dementing illness was 10.9% (95% CI, 8.0 to 13.8); corresponding risks for a 65-year-old woman were 12% (95% CI, 9.2 to 14.8) and 19% (95% CI, 17.2 to 22.5). The cumulative incidence between age 65 and 100 years was much higher: for AD, 25.5% in men and 28.1% in women; for dementia, 32.8% in men and 45% in women. The actual remaining lifetime risk of AD or dementia varies with age, sex, and life expectancy and is lower than the hypothetical risk estimated by a cumulative incidence in the same population.

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Dementia is a common and widely feared affliction of later adult life. The most common cause of dementia is Alzheimer's disease (AD). In a recent survey reported in the popular press,[1] over half of all mature adults were extremely fearful of developing AD. Typically, a concerned adult will consult a physician to help address these fears in a rational manner. If this adult performs normally on cognitive testing, what are the chances of developing AD at a later date? Incidence data can only provide an estimate of the risk of AD (given the subject's age and gender) over a short time interval. The prevalence of the disease in a given population or age group is also not equal to the lifetime risk, in part because patients die at a different rate than their healthy peers. Therefore, a cumulative estimate of the probability of ever manifesting AD over the remainder of one's lifespan is required to answer this question; such an estimate has been called a remaining lifetime risk or simply the lifetime risk at a given age.[2-5]

Estimating the lifetime risk for a condition such as AD is a complex task because of two important features of the disease. First, the incidence of AD rises steeply with age so that the average annual risk increases with each successive year as subjects grow older. Second, the age group "at risk" is elderly, and within this group, the mortality due to competing causes rises exponentially with age. Thus, we have two competing risks to reconcile to obtain a valid estimate of the remaining lifetime risk.

A number of studies have estimated the cumulative incidence of AD (or dementia due to any cause) in men and women as a function of age, and some have extended such estimates to a sufficiently advanced age, such as 90 years, to cover the lifetime of most adults.[4,6-10] The cumulative incidence from birth to this advanced age may be called a lifetime cumulative incidence. For any given subject, such data may be used to estimate the remaining lifetime cumulative incidence by subtracting the cumulative incidence at the subject's current age (e.g., 70 years) from the lifetime cumulative incidence for the cohort. This method overestimates the risk when the population prevalence of a condition is more than 10% or

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the competing risk of mortality is high.[11] While calculating a cumulative incidence, it is presumed that those who did not live to the upper age limit of the period of cumulative estimation represent "censored" observations (i.e., they would probably have developed the disease at the same rate as those who survived). Such an assumption is appropriate for studying the pathophysiology of a disease. However, for purposes of estimating individual risk or the likely population burden of a disease, we need to know how many subjects would actually develop the condition of interest rather than how many have a predilection to do so. We require remaining lifetime risk estimates that reflect the experienced risks given the actual lifespan of members of the cohort.

There is a compelling need to generate estimates of the lifetime risk of dementia and AD, so that we may inform the public and put this risk in perspective for them as compared to available lifetime risk estimates for developing other illnesses, such as hip fracture and cancer.

**Methods.** *Subjects and case ascertainment.* The Framingham Study cohort is a population-based cohort that has been evaluated biennially since 1948. Each biennial period is called an examination cycle. By December 31, 1995, 23 such cycles had been completed. In 1975 (at the start of examination cycle 14), 3,330 subjects from the original cohort were still alive and 2,828 of these subjects (85%) attended that biennial examination. Of these, 2,611 subjects (1,061 men, 1,550 women; mean age, 66 ± 7.4 years; range, 54 to 85 years) were identified as cognitively intact using either a standardized neuropsychological test battery[12] administered between 1976 and 1978 (in 2,082 subjects) or a normal performance on a Folstein Mini-Mental Status Examination[13] (MMSE) (in 529 subjects). Starting in 1975, these subjects were prospectively evaluated for the development of dementia; since 1982, this has been done using a biennial screening MMSE test. Individuals who performed poorly on the MMSE were subjected to further evaluation. A fall in the MMSE of greater than three points between successive examinations, a decline of more than five points as compared with any previous examination, or an absolute MMSE score ≤ 24 was considered indicative of possible dementia. In addition, subjects underwent a detailed evaluation if there were self- or family-reported symptoms of memory loss or upon referral by a physician (usually the primary care provider or the physician conducting the biennial follow-up Heart Study evaluation) for neurologic symptoms.

Detailed evaluation consisted of an examination by a neurologist and a neuropsychologist. The records of subjects identified as unequivocally demented by the neurologist were sent to a review committee, which made the final decision regarding the presence of dementia, the type of dementia, and the year of onset of symptoms. This review committee comprised at least two neurologists and one or more neuropsychologists and used data obtained during neurologic and neuropsychological evaluation, information from primary care physicians, hospitalization records, brain imaging (CT or MRI were obtained in more than 60% of subjects), and data obtained by telephone interview of next of kin to arrive at a clinical consensus. Criteria used for the diagnosis of dementia were similar to the DSM-IV criteria,[14] which require memory impairment, with a decline in at least one other area of cognitive functioning and significant functional impairment in the occupational or social spheres. In addition, the Framingham criteria require the presence of unequivocal dementia (of at least a moderate degree) for a follow-up period of at least 6 months.

All subjects identified as having AD satisfied the NINCDS-ADRDA criteria[15] for probable AD. Subjects with possible AD (i.e., those in whom an alternative cause could be identified as perhaps contributing to the dementia) were classified separately. Details regarding the dementia subtype classification used in the Framingham Study have been discussed previously.[16,17] Those subjects who had suffered a stroke (usually after the onset of dementia) but did not meet the DSM-IV criteria for multi-infarct dementia were classified as "dementia complicated by stroke, relationship unknown" (n = 21). This category included subjects with so-called "mixed dementia." Data from subjects in this category was combined with data on "pure" (probable) AD to estimate the upper limit of the risk of AD in the Framingham population.

*Statistical analysis.* A modified technique of survival analysis was used. In a standard Kaplan-Meier survival analysis, subjects who die are considered to provide information up to the date of their death. In our analysis, these subjects were considered "escapees," that is, they did not develop dementia at any time during their lifetime. Methods of generating a maximum likelihood estimate of cause-specific failure (the specific cause in this case being dementia or AD) in the presence of competing risks have been described earlier.[18,19] These techniques were modified as outlined below.

Each of the 2,611 people in the study cohort was followed from 1975 through 1995 to either the year of onset of dementia, the year of death, or the last year in which they passed the dementia screening evaluation. Some subjects who died (n = 190) but whose records have not been reviewed for the presence or absence of dementia at any time between their last formal cognitive assessment (MMSE or neurologic/neuropsychological examination) and death are censored at the year of the last formal cognitive evaluation.

For further analyses, we included only those subjects who were 65 years and older in 1975, along with those who survived and reached the age of 65 years at some point during the 20-year follow-up period. Using this criterion, 2,560 subjects (98% of the study cohort) contributed at least one person-year of risk. Because the onset of dementia is insidious, the date of onset was defined by the calendar year rather than a specific date. Therefore, survival times and ages were recorded in whole years. For example, a subject whose year of onset of dementia was 1976 contributed 2 years of follow-up, with an event in the second year.

The risk set at any age j contained all $R_j$ subjects who were age j at some point during their follow-up. Therefore, subjects who became demented, died, or were censored at age j were removed from the risk sets for ages j + 1 and older, whereas subjects who were age j + 1 at entry in 1975 were added to the risk set for age j + 1. For example, there were 103 subjects who were 65 years old at entry in 1975 and an additional 1,241 subjects who turned 65 during their follow-up ($R_{65}$ = 1,344). None of these subjects became demented at 65, 13 died at 65, and 3 were censored

at 65, so that 16 subjects were removed. The risk set at age 66 years contains the original 1,344, minus the 16 who were removed, plus the 110 subjects who were 66 at entry in 1975 ($R_{66}$ = 1,428).

Hazards ($h_j$), age-specific incidences ($f_j$), cumulative incidence ($F_j$), and survival probabilities ($S_j$) were calculated in the usual (Kaplan-Meier) way as

$$h_j = e_j/R_j, \quad f_j = h_j \times S_{j-1},$$

$$F_j = \sum_{i=65}^{j} f_i, \quad S_j = 1 - F_j,$$

where $e_j$ = number of events at age j, $F_{64} = 0$, and $S_{64} = 1$.

*Adjusting for competing risk.* The cumulative incidence of dementia, $F_j$, as calculated above, applies to people who live through age (j − 1) and does not reflect the competing risk of death. Deaths are counted as withdrawals and are thus assumed to have the same (unmeasured) future risk of dementia as those who are censored alive. However, those who die have "escaped" becoming demented and have a zero future risk of dementia. To adjust for the competing risk of death, we first calculated a separate survival curve, $U_j$, as above with death included alongside dementia as an event rather than as a withdrawal. Then we calculated an adjusted incidence[19] as follows:

$$f_j^* = h_j \times U_{j-1}, \quad F_j^* = F_{j-1}^* + f_j^*, \quad S_j^* = 1 - F_j^*,$$

where $h_j$ was from the original survival curve with deaths counted as withdrawals. This method yields a true remaining lifetime risk.

We used the same process to generate curves for index starting ages other than 65 years. To do this, for index starting age T, we set $F_{T-1}$ and $U_{T-1}$ to 0 and used the original hazards, $h_j$, to calculate $U_j$ for $j \geq T$. The adjusted $F_j^*$ were calculated as above. These calculations were repeated separately for men and women, for AD, and for all-cause dementia.

**Results.** *Description of subjects.* During a follow-up period of 20 years, 198 subjects (63 men, 135 women) developed dementia and 120 of these (34 men, 86 women; mean age at onset, 82 years) had probable AD. During this follow-up period, 1,015 subjects died without developing dementia, 188 subjects died but were censored at their last follow-up examination, 51 died or were censored before reaching the age of 65 and were not included in the lifetime risk calculations, and 1,159 were alive and cognitively intact until their last follow-up examination. The distribution of various types of dementia in this cohort is shown in figure 1. Of the 198 subjects who developed dementia, the age of onset of symptoms was ≥90 years in 18 and ≥95 years in 4. At the time of diagnosis, patients typically had an overall Clinical Dementia Rating scale[20] score of ≥1.

*Remaining lifetime risk.* The remaining lifetime risks of AD and of dementia due to any cause, in the various age and sex groups, and the 95% CIs are shown in table 1. These remaining lifetime risks varied little between 65 and 80 years of age and declined slightly thereafter. Among subjects aged 65 to 80 years, the average remaining lifetime risk of AD was 6.6% in men and 12.4% in women. When patients with "mixed" dementia (AD + stroke) were included, the remaining lifetime risk of AD

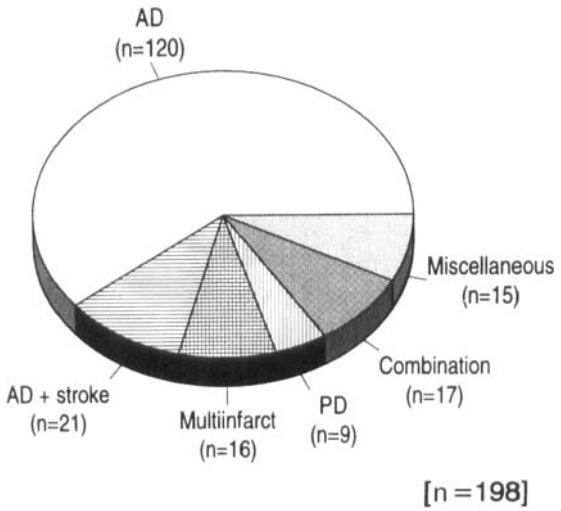


*Figure 1. Distribution of the various types of dementia in the Framingham Study cohort.*

over this age range increased to 7.4% in men and 14.9% in women. At any given age, the remaining lifetime risk of mixed dementia was approximately 20% higher than the corresponding age- and sex-specific remaining lifetime risk of pure AD. The risk of developing any dementing illness was about 1.5 times the risk of AD, averaging 10.9% in men and 19.5% in women. Whether we considered the development of AD or all-cause dementia, the remaining lifetime risk was roughly twice as high in women as in men.

*Comparison of the remaining lifetime risk with the cumulative incidence.* The Framingham data clearly illustrate the difference between the theoretical (uncensored) cumulative incidence and the remaining lifetime risk. Figure 2 shows that as the risk of dementia rises and the period of follow-up increases, the cumulative incidence increasingly overestimates the lifetime risk of the disease as measured by the actual disease experience of the cohort. In table 1, estimates of cumulative incidence for each age and sex group are contrasted with the corresponding lifetime risk estimates for the same group. The greater the ratio between the risk of mortality and the risk of dementia in a given age and sex group of the population, the larger is the numerical difference between the cumulative incidence and the lifetime risk.

*Five-year risks of AD and dementia due to any cause.* The 5-year risks of developing AD or dementia due to any cause (detailed in table 1) depended largely on the age at the time of risk estimation and to a lesser extent on the individual's sex. They were greatly dependent on the age-specific incidences but were not equal to these because of the effect of mortality among cohort members. This effect became increasingly prominent as the age at time of risk estimation increased. Thus, the difference between the corrected (for mortality) and uncorrected 5-year risk of developing AD was 4% of the uncorrected risk at age 65 years and 23% of the uncorrected risk at age 85 years. In the "young-old" (i.e., 65 and 70 years), the 5-year risks of all-cause dementia and AD were actually higher in men than in women; at subsequent ages, these risks were higher in women than men, the magnitude of the gender difference increasing with increasing age.

***Table 1*** *Age- and sex-specific 5-, 10-, 15-, 20-year, and lifetime risk estimates for the development of Alzheimer's disease and dementia due to any cause and comparison of remaining lifetime risk with theoretical cumulative incidence for age "x to 100"*

| | | All-cause dementia | | | | | | Alzheimer's disease | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gender | Age (y) | 5 y | 10 y | 15 y | 20 y | Lifetime risk (95% CI) | Cumulative incidence | 5 y | 10 y | 15 y | 20 y | Lifetime risk (95% CI) | Cumulative incidence |
| Male | 65 | 0.7 | 2.1 | 4.3 | 7.3 | 10.9 (8.0–13.8) | 32.8 | 0.3 | 0.8 | 2.2 | 3.6 | 6.3 (3.9–8.7) | 25.5 |
| | 70 | 1.5 | 3.9 | 7.1 | 8.9 | 11.0 (8.0–14.1) | 32.3 | 0.6 | 2.0 | 3.6 | 4.8 | 6.5 (3.9–9.1) | 25.3 |
| | 75 | 2.8 | 6.6 | 8.7 | 10.3 | 11.2 (7.7–14.6) | 31.2 | 1.7 | 3.5 | 5.0 | 6.1 | 6.9 (4.0–9.8) | 24.9 |
| | 80 | 4.7 | 7.4 | 9.5 | — | 10.5 (6.4–14.6) | 29.1 | 2.3 | 4.1 | 5.5 | — | 6.6 (3.1–10.1) | 23.5 |
| | 85 | 4.0 | 7.2 | — | — | 8.8 (3.4–14.1) | 25.0 | 2.8 | 4.9 | — | — | 6.5 (1.7–11.2) | 21.5 |
| | 90 | 6.0 | — | — | — | 9.2 (0.5–17.9) | 20.9 | 4.0 | — | — | — | 7.1 (0.0–15.1) | 18.7 |
| Female | 65 | 0.3 | 1.0 | 4.0 | 8.6 | 19.0 (15.4–22.5) | 45.0 | 0.2 | 0.6 | 2.5 | 5.4 | 12.0 (9.2–14.8) | 28.1 |
| | 70 | 0.6 | 3.9 | 8.6 | 14.4 | 19.5 (15.8–23.3) | 44.8 | 0.4 | 2.3 | 5.4 | 9.3 | 12.3 (9.4–15.2) | 28.0 |
| | 75 | 3.5 | 8.6 | 14.8 | 17.9 | 20.1 (16.2–24.0) | 44.5 | 2.1 | 5.4 | 9.5 | 11.6 | 12.8 (9.7–15.9) | 27.7 |
| | 80 | 5.9 | 13.2 | 16.9 | — | 19.4 (15.0–23.8) | 42.4 | 3.9 | 8.6 | 11.1 | — | 12.5 (9.0–15.9) | 26.1 |
| | 85 | 9.6 | 14.4 | — | — | 17.8 (12.4–23.2) | 38.4 | 6.3 | 9.5 | — | — | 11.4 (7.2–15.6) | 22.8 |
| | 90 | 7.9 | — | — | — | 13.4 (5.9–20.8) | 30.9 | 5.2 | — | — | — | 8.2 (2.6–13.7) | 16.7 |

All risk values are expressed as percentages.

*Ten-, 15-, and 20-year risks of AD and dementia due to any cause.* These data are provided in table 1. The magnitude of the risk became increasingly dependent on the gender of the individual and less dependent on the age at time of risk estimation as the period of follow-up increased. Thus, at age 70 years, the 10-year risk of AD was 1.2 times higher in women than in men (2.3% versus 2.0%), but the 20-year risk was 1.9 times higher in women than in men (9.3% versus 4.8%).

**Discussion.** The concept of a lifetime risk is widely used by oncologists to assess cancer[11,21-24] and by endocrinologists studying osteoporosis[25,26] in the elderly, but the present study provides the first cohort-based estimate of the remaining lifetime risk for developing dementia and AD. The strengths of our study are the use of a population-based cohort, the prospective design, rigorous case ascertainment methods, the completeness of mortality ascertainment, and the availability of both incidence and mortality data in the same population. Furthermore, because the Framingham cohort was assembled before the age of interest, "sicker" subjects were less likely to have been excluded than if a cohort with a mean age of 65 years had been assembled de novo.

The distinction between the theoretically computed cumulative risk and the real lifetime risk of

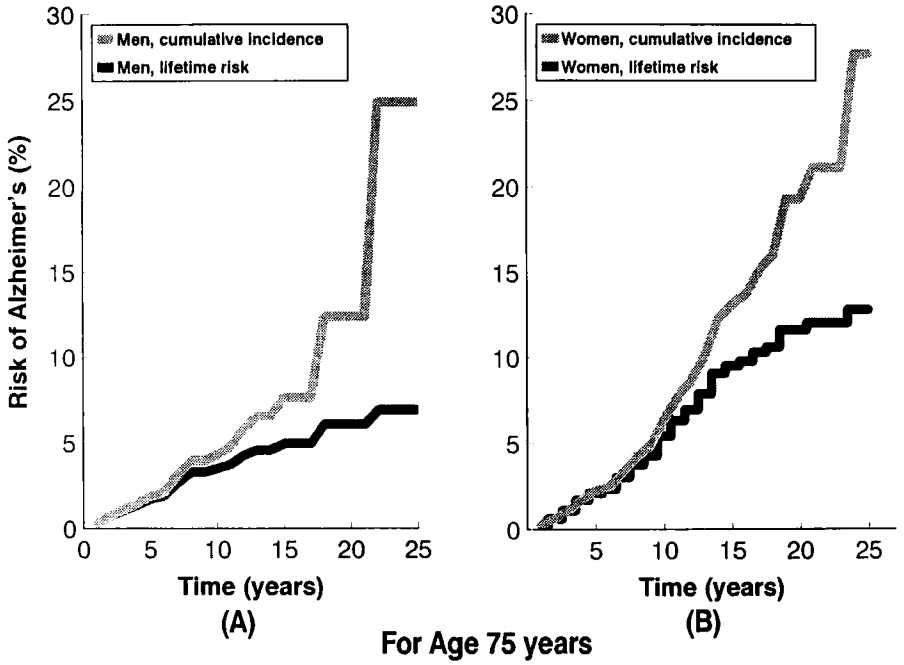


*Figure 2. Comparison of the cumulative incidence (theoretical) and lifetime risk (actual remaining lifetime risk) of Alzheimer's disease for 75-year-old subjects (A, men; B, women) over a 25-year follow-up period.*

*Table 2 Comparison of risk estimates for Alzheimer's disease from different population-cohort studies*

| Study | Statistic used to describe risk | Age group for which risk computed | Risk of Alzheimer's disease |
|---|---|---|---|
| Farrer and Cupples[6] (based on ref. 7) | Cumulative incidence | Birth to 90 y | 25% in women, 21% in men |
| Hagnell et al.[8,9] | Cumulative incidence | Birth to 90 y | 31.9% in women, 25.5% in men |
| Hebert et al.[10] | Cumulative incidence | 65–90 y | 49.6% (sex-pooled analyses) |
| Sayetta[4] | Lifetime risk | 60 y to death | 27% (sex-pooled analyses) |
| Current study | Lifetime risk | 65 y to death | 12% in women, 6.3% in men |

AD was elegantly discussed by Breitner,[2] who used the 1980 U.S. census data on survival to calculate that the actual lifetime risk of AD among first-degree relatives of probands with the disease would be only 19%, a third of the estimated theoretical cumulative risk of 55%. Most earlier studies on population cohorts, however, only reported the theoretical cumulative incidence of AD, and their results are summarized in table 2.[4,6-10] These risks are, as expected, substantially higher than our lifetime risk estimates and range from 21% to 49.6%. One study, the Baltimore Longitudinal Study,[4] reported a "residual lifetime morbid risk" (risk from age "x" to death), which is similar to what we call the remaining lifetime risk. However, their risk estimates are also higher than ours (27% at age 65), perhaps due to diagnostic misclassification in a significant proportion of their cases.[27] The remaining lifetime risk estimates, as calculated for the Framingham cohort, are relatively less alarming. The actual lifetime risk in the Framingham cohort is approximately 40% of the theoretical cumulative incidence; the higher ratio (compared with the 33% calculated by Breitner[2]) is probably due to an increased life expectancy in the past decade.

Our figures suggest that the risk of dementia in elderly individuals is comparable with their risk of developing other medical problems commonly associated with aging. Although the estimated lifetime risk of dementia for a 65-year-old woman is certainly high at 19%, it is comparable with the 16% lifetime risk of hip fracture[25] and 23% lifetime risk of developing cancer.[23] In men, the 11% lifetime risk of dementia is approximately twice the 6% lifetime risk of a hip fracture[26] but only a third of the 29% lifetime risk of manifesting a cancer.[23]

*Attributes of the lifetime risk in the Framingham cohort.* Estimating the lifetime risks of AD (or dementia) provides us with some interesting insights into the disease burden and age- and sex-specific risks in a given population. The differences between the cumulative incidence and lifetime risk in a given cohort reflect the demographic characteristics of that cohort (i.e., its age distribution and pattern of age- and cause-specific mortality). Thus, in our cohort, the lifetime risk of AD or dementia is approximately twice as high in women (12% and 19%) than in men (6.3% and 10.9%). This is largely because women live longer and hence experience a longer period of risk; in the Framingham cohort, the average remaining life expectancy at age 65 was 22.7 years for women and only 18.8 years for men. This parallels the longer life expectancy of women in most American populations.[28]

It is commonly assumed that the risk of dementia keeps increasing with age. In the Framingham cohort, however, we find that between the ages of 65 and 80 years, the increased risk of developing dementia or AD reflected in a rising age-specific disease incidence is offset by the decreasing residual life expectancy so that the lifetime risk of dementia or AD remains relatively static over this period. Thus, the lifetime risk of developing AD provides a single relatively invariant risk figure applicable in a gender-specific manner to most of the at-risk population (i.e., adults over the age of 65). However, in the very old (above 80 years of age), alternative-cause mortality rates rise so rapidly that despite the continuing rise in the incidence of dementia, the lifetime risk estimates gradually begin to decline. The lifetime risk at the age of 85 years is marginally lower than it is at 65 years (8.8% versus 10.9% for men; 17.8% versus 19% for women).

*Generalizability (external validity) and utility of the remaining lifetime risk estimates.* The generalizability of our remaining lifetime risk estimate to other populations and its utility in clinical risk prediction is limited by the fact that the Framingham cohort is an overwhelmingly white population. Also, the lifetime risk estimate is sensitive to changes in life expectancy and needs to be periodically reevaluated as the life expectancy of the American population continues to rise and the risk of mortality due to alternative causes, such as cardiovascular illness and cancer, varies. It is suggested that similar remaining lifetime risk estimations should be undertaken for different cohorts.

Consensus estimates of remaining lifetime risk would serve as the most appropriate a priori risk figures, when using Bayesian analysis to assess the prognostic utility of putative "biomarker" tests. Consideration of the age-dependent risks of AD versus other cause of death has been recognized as an important factor in pretest counseling for apolipoprotein E genotyping.[29,30] The lifetime risk also gives an estimate of the dementia burden in a community and can be used in assessing the need for and estimated cost of a variety of health services. The short-term

risk figures (5- or 10-year risks) can be used for power calculations while planning epidemiologic studies or evaluating potentially protective therapies. Finally, the statistical techniques we have used in estimating the lifetime risk can also be used in epidemiologic analyses to accurately assess the impact of putative risk factors for AD such as smoking,[31] apolipoprotein E genotype,[32] and vascular disease[33] because a trait that modifies the risk of AD may also modify mortality due to competing causes.

Our remaining lifetime risk estimates, however, have limited utility in predicting the risk of AD in a given individual. This is because the term "lifetime risk" as described in this study is an estimate of the number of "cases" (of AD or other dementia) expected in the lifetime of a cohort. In an individual subject, the remaining lifetime risk would be modified by the estimated individual life expectancy and the presence or absence of other risk factors, notably the family history and apolipoprotein E status. The most important predictor variable remains the cognitive examination, and our risk estimations only apply to subjects who are cognitively intact at the time of risk estimation.

*Limitations of this study.* It is possible that we have underestimated the risk of dementia because subjects who had "possible" or "mild" dementia at the time of death and subjects who had "moderate" dementia of less than 6 months duration were excluded. Autopsy confirmation is not available in many of our subjects clinically diagnosed to have AD; however, earlier studies have shown that a clinical diagnosis of AD made using the NINCDS-ADRDA criteria is confirmed by pathologic examination in more than 85% of patients.[34] Finally, our risk estimates become less reliable in the very old because our risk set consisted of less than 50 subjects above the age of 91 years.

**Conclusions.** The lifetime risk of AD is an important statistic defining the actual experience of the disease in a population at risk. It varies significantly from the cumulative incidence because the lifetime risk estimate adjusts for disease-free survival and remaining life expectancy. In the Framingham Study cohort, the cumulative incidence of AD between the ages of 65 and 100 years is 25.5% for men and 28.1% for women, differing little between the sexes. On the other hand, the remaining lifetime risk of AD for an adult aged 65 years or more is approximately twice as high in women (12%) as in men (6.3%) and varies little with age between 65 and 80 years of age. The lifetime risk of AD is approximately two thirds the risk of dementia due to any cause. The remaining lifetime risk of all-cause dementia averages 10.9% in men and 19% in women over the age range of 65 to 80 years. Such lifetime risk estimates should be computed for different populations because they would be valuable to clinicians, health planners, and the general public.

## References


1. Snyder Sachs J. Worrying yourself sick: Alzheimer's anxiety can hit anyone. *Longevity,* October 1995.
2. Breitner JC. Clinical genetics and genetic counseling in Alzheimer disease. Ann Intern Med 1991;115:601–606.
3. Drachman DA. If we live long enough, will we all be demented? Neurology 1994;44:1563–1565.
4. Sayetta RB. Rates of senile dementia-Alzheimer's type in the Baltimore Longitudinal Study. J Chronic Dis 1986;39:271–286.
5. Seshadri S, Drachman DA, Lippa CL. Apolipoprotein E ε4 allele and the lifetime risk of Alzheimer's disease: what physicians know and what they should know. Arch Neurol 1995;52:1074–1079.
6. Farrer LA, Cupples LA. Estimating the probability for major gene Alzheimer disease. Am J Hum Genet 1994;54:374–383.
7. Schoenberg BS, Kokmen E, Okazaki H. Alzheimer's disease and other dementing illnesses in a defined United States population: incidence rates and clinical features. Ann Neurol 1987;22:724–729.
8. Hagnell O, Ojesjo L, Rorsman B. Incidence of dementia in the Lundby study. Neuroepidemiology 1992;11(suppl 1):61–66.
9. Hagnell O, Franck A, Grasbeck A, et al. Senile dementia of the Alzheimer type in the Lundby study. I. A prospective, epidemiological study of the incidence and risk during the 15 years 1957–1972. Eur Arch Psychiatry Clin Neurosci 1991;241:159–164.
10. Hebert LE, Scherr PA, Beckett LA, et al. Age-specific incidence of Alzheimer's disease in a community population. JAMA 1995;273:1354–1359.
11. Schouten LJ, Straatman H, Kiemeney LALM, Verb ALM. Cancer incidence: life table risk versus cumulative risk. J Epidemiol Comm Health 1994;48:596–600.
12. Farmer ME, White LR, Kittner SJ, et al. Neuropsychological test performance in Framingham: a descriptive study. Psychol Rep 1987;60:1023–1040.
13. Folstein M, Folstein SE, Mchugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
14. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association, 1994.
15. Mckhann G, Drachman DA, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939–944.
16. Bachman DL, Wolf PA, Linn R, et al. Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham Study. Neurology 1992;42:115–119.
17. Bachman DL, Wolf PA, Linn RT, et al. Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. Neurology 1993;43:515–519.
18. Aalen O. Nonparametric estimation of partial transition probabilities in multiple decrement models. Ann Stat 1978;6:534–545.
19. Gaynor JJ, Feuer EJ, Tan CC, et al. On the use of cause-specific failure and conditional failure probabilities: examples from clinical oncology data. J Am Stat Assoc 1993;88:400–409.
20. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–572.
21. Bryant HE, Brasher PMA. Risks and probabilities of breast cancer: short-term versus lifetime probabilities. Can Med Assoc J 1994;150:211–216.
22. Feuer EJ, Wun LM, Boring CC, Dana Flanders W, Timmel MJ, Tong T. The lifetime risk of developing breast cancer. J Natl Cancer Inst 1993;85:892–897.
23. Brenner H, Stegmaier C, Ziegler H. Magnitude and time trends of the life-time risk of developing cancer in Saarland, Germany. Eur J Cancer 1990;26:978–982.
24. Bender AP, Punyko J, Williams AN, Bushhouse SA, and the Section of Chronic Disease and Environmental Epidemiology, Minnesota Department of Health. A standard person-years approach to estimating lifetime cancer risk. Cancer Causes and Control 1992;3:69–75.

25. Black DM, Cummings SR, Melton JL III. Appendicular bone mineral and a women's lifetime risk of hip fracture. J Bone Miner Res 1992;7:639–646.
26. Lauritzen JB, Schwarz P, Lund B, McNair P, Transbol I. Changing incidence and residual lifetime risk of common osteoporosis-related fractures. Osteoporosis Int 1993;3:127–132.
27. Arenberg D. Misclassification of "probable senile dementia of the Alzheimer type" in the Baltimore Longitudinal Study of Aging. J Clin Epidemiol 1990;43:105–107.
28. National Center for Health Statistics. Vital Statistics of the United States, 1989: Mortality, part A. Washington, DC: Public Health Service; 1993;2:2. [Public Health Service publication 93-1101.]
29. National Institute on Aging/Alzheimer's Association Working Group. Apolipoprotein E genotyping in Alzheimer's disease—consensus statement. Lancet 1996;347:1091–1095.
30. Myers RH, Schaefer EJ, Wilson PWF, et al. Apolipoprotein E ϵ4 association with dementia in a population-based study: the Framingham Study. Neurology 1996;46:673–677.
31. Lee PN. Smoking and Alzheimer's disease: a review of the epidemiological evidence. Neuroepidemiology 1994;13:131–134.
32. Petersen RC, Smith GE, Ivnik RJ, et al. Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. JAMA 1995;273:1274–1278.
33. Hofman A, Bots ML, Breteler MMB, Ott A, Grobee DE. Atherosclerosis and dementia: the Rotterdam Study [abstract]. Neurology 1995;45(suppl 4):A214.
34. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part X. Neuropathology confirmation of the clinical diagnosis of Alzheimer's disease. Neurology 1995;45:461–466.

# Quantitative MR volumetry in Alzheimer's disease

## Topographic markers and the effects of sex and education

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**Article abstract**—We determined topographic selectivity and diagnostic utility of brain atrophy in probable Alzheimer's disease (AD) and correlations with demographic factors such as age, sex, and education. Computerized imaging analysis techniques were applied to MR images in 32 patients with probable AD and 20 age- and sex-matched normal control subjects using tissue segmentation and three-dimensional surface rendering to obtain individualized lobar volumes, corrected for head size by a residualization technique. Group differences emerged in gray and white matter compartments particularly in parietal and temporal lobes. Logistic regression demonstrated that larger parietal and temporal ventricular CSF compartments and smaller temporal gray matter predicted AD group membership with an area under the receiver operating characteristic curve of 0.92. On multiple regression analysis using age, sex, education, duration, and severity of cognitive decline to predict regional atrophy in the AD subjects, sex consistently entered the model for the frontal, temporal, and parietal ventricular compartments. In the parietal region, for example, sex accounted for 27% of the variance in the parietal CSF compartment and years of education accounted for an additional 15%, with women showing less ventricular enlargement and individuals with more years of education showing more ventricular enlargement in this region. Topographic selectivity of atrophic changes can be detected using quantitative volumetry and can differentiate AD from normal aging. Differential effects of sex and years of education can also be detected by these methods. Quantification of tissue volumes in vulnerable regions offers the potential for monitoring longitudinal change in response to treatment.

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Alzheimer's disease (AD), the leading cause of dementia, presents an increasingly formidable challenge to health care systems as we enter the next century. The need for diagnostic accuracy and for biological and behavioral measures to monitor disease progression and response to therapy has never been more compelling. The present criteria for diagnosis, proposed in 1984,[1] depend heavily on clinical and behavioral analysis. In vivo volumetric and morphometric MR studies can provide sensitive indices of brain anatomy,[2-5] including computer-assisted tissue classification,[6] which in conjunction with appro-

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