Contribution of Alzheimer disease to mortality in the United States

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ABSTRACT

Objective: To assess the burden of mortality attributable to Alzheimer disease (AD) dementia in the United States.

Methods: Data came from 2,566 persons aged 65 years and older (mean 78.1 years) without dementia at baseline from 2 cohort studies of aging with identical annual diagnostic assessments of dementia. Because both studies require organ donation, ascertainment of mortality was complete and dates of death accurate. Mortality hazard ratios (HRs) after incident AD dementia were estimated per 10-year age strata from proportional hazards models. Population attributable risk percentage was derived to estimate excess mortality after a diagnosis of AD dementia. The number of excess deaths attributable to AD dementia in the United States was then estimated.

Results: Over an average of 8 years, 559 participants (21.8%) without dementia at baseline developed AD dementia and 1,090 (42.4%) died. Median time from AD dementia diagnosis to death was 3.8 years. The mortality HR for AD dementia was 4.30 (confidence interval = 3.33, 5.58) for ages 75–84 years and 2.77 (confidence interval = 2.37, 3.23) for ages 85 years and older (too few deaths after AD dementia in ages 65–74 were available to estimate HR). Population attributable risk percentage was 37.0% for ages 75–84 and 35.8% for ages 85 and older. An estimated 503,400 deaths in Americans aged 75 years and older were attributable to AD dementia in 2010.

Conclusions: A larger number of deaths are attributable to AD dementia in the United States each year than the number (<84,000 in 2010) reported on death certificates. *Neurology*® 2014;82:1045–1050

GLOSSARY

AD = Alzheimer disease; **CDC** = Centers for Disease Control and Prevention; **HR** = hazard ratio; **PAR%** = population attributable risk percentage.

Alzheimer disease (AD) is listed by the Centers for Disease Control and Prevention (CDC) as the sixth leading cause of death in the United States, accounting for 83,494 deaths in 2010.[1] This number is derived from death certificates, which are known to underreport persons dying of dementia.[2] Up to 5 million Americans are currently living with AD dementia,[3,4] a disease with an average time from diagnosis to death of 3 to 9 years.[2,5] Given these figures, the burden of mortality attributable to AD dementia is potentially much higher than the numbers posted by the CDC. A valid estimate of the number of deaths attributable to AD dementia would aid assessment of the societal burden of AD dementia, informing government and private research priorities and the development of the recently enacted National Alzheimer's Plan.[6]

Prospective follow-up of population-based cohorts can provide the most valid estimates of AD dementia incidence and is generally considered the best source for determining risk of mortality from AD dementia.[2,4,7–10] Many people with AD dementia do not come to the attention of the health care system.[11] Therefore, studies of medical records miss deaths from AD dementia. Furthermore, estimates based on observation of prevalent, rather than incident, cases may underestimate mortality risk by not including rapidly progressive AD dementia.[12,13] The study objective was to estimate the risk of mortality attributable to incident AD dementia in 2 community-based

cohort studies and produce an estimate of the number of deaths attributable to AD dementia in the United States.

METHODS **Subjects.** Two ongoing cohort studies of aging and AD, the Religious Orders Study[14] and the Rush Memory and Aging Project,[15] provided the data for these analyses. In both studies, participants without known dementia at baseline agreed to annual detailed clinical evaluation and brain donation at the time of death. Participants in the Religious Orders Study are older Catholic nuns, priests, and brothers from across the United States. From January 1994 through February 2013, 1,168 persons aged 65 years and older were recruited into the study and completed a baseline evaluation. Participants in the Rush Memory and Aging Project are older, community-dwelling persons from retirement communities and subsidized senior housing facilities across Illinois. From September 1997 through February 2013, 1,574 persons completed a baseline evaluation. Clinical and diagnostic procedures are identical across the 2 studies, allowing them to be pooled for analysis.[16] Follow-up among living participants exceeds 90%. Although participants in these studies did not have known dementia at the time of recruitment, a small portion (n = 176, 6.4%) were diagnosed with dementia upon baseline clinical examination and were excluded from these analyses, leaving 2,566 for analysis. The baseline evaluation for both studies included self-reported date of birth (used to determine age), sex, race/ethnicity (reported here as non-Hispanic white vs other), and education (years of schooling completed). Compared with the general population of older people in the United States, our study sample had proportionately fewer males and persons of minority race, and participants were more highly educated.

Standard protocol approvals, registrations, and patient consents. Both studies were approved by the Institutional Review Board of the Rush University Medical Center, and informed consent was obtained from all participants.

Clinical evaluation and diagnosis of AD dementia. Annual clinical evaluations included medical history, neurologic examination, and cognitive testing.[17,18] The medical history included questions regarding vascular disease history (e.g., claudication, stroke, and heart conditions) and vascular risk factors (hypertension, diabetes mellitus, and smoking); each were summed for analysis, range: 0–3. Clinical diagnosis of AD and other dementias at each assessment was performed using a 3-stage process with computer scoring of cognitive tests followed by clinical judgment by a neuropsychologist, and diagnostic classification by an experienced clinician.[17,18] Diagnosis of dementia and probable AD dementia followed National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.[19] Eighty-eight percent of persons diagnosed with AD dementia who died in these cohorts were given a pathologic diagnosis of AD on postmortem examination using National Institute on Aging–Reagan criteria and blinded to clinical data.[20]

Ascertainment of mortality. Both cohort studies are autopsy studies requiring brain and tissue donation. The autopsy rate is nearly 90%, thus for the majority of participants who die, the exact day of death is known. In addition to the annual clinical evaluations, participants are contacted regularly to determine vital status, and death is occasionally detected during quarterly contacts with an informant. Finally, the Social Security Death Index is regularly searched for the small number of participants we are unable to contact. Therefore, ascertainment of mortality is essentially complete, and dates of death are accurate.

Statistical analysis. We first compared persons who had an incident AD dementia diagnosis during follow-up with persons who did not for demographics and other covariates using t tests or χ^2 tests. Kaplan-Meier curves were obtained for 3 age strata (65–74 years, 75–84 years, and 85 years and older) to estimate the median time to death after a diagnosis of AD dementia. Mortality hazard ratios (HRs) for incident AD dementia were derived for the 3 age strata from proportional hazards models with age as the time scale, and participants entering the analysis at their baseline age (left truncation).[21] AD dementia status was treated as a time-varying absorbing state. Person-years for subjects who developed AD dementia contributed both to non-AD dementia (up to diagnosis) person-years and AD dementia (after diagnosis) person-years. Models included terms for sex, race, education, and parent study. We also present a model further adjusted for vascular comorbidities. Finally, we replaced the term for AD dementia with a term for all dementia to examine the mortality HR for total dementia.

Population attributable risk percentage: Excess deaths due to AD dementia. We calculated population attributable risk percentage (PAR%) to estimate the percentage of total mortality risk for the cohort that could be considered attributable to an incident diagnosis of AD dementia. PAR% as calculated here is known as the "excess fraction" and is defined as the proportion of new cases of an outcome that occurs in the exposed group that is in excess of new cases in the unexposed group (for example, the proportion of lung cancer cases in smokers that is in excess of lung cancer cases in nonsmokers).[22] In this study, the outcome is mortality and the exposure is incident AD dementia, so PAR% represents the proportion of deaths that occur after developing AD that is in excess of deaths among people without AD. Crude PAR% was calculated based on the mortality rate in the entire cohort (I_t) and mortality rate among the person-years without AD dementia over follow-up (I_n) using the following formula:

$$\text{PAR\%}_{\text{crude}} = (I_t - I_n)/I_t \times 100\%$$

We then calculated an "adjusted PAR%" using HRs from the adjusted proportional hazards models:

$$\text{PAR\%}_{\text{adjusted}} = p(r - 1)\Big/\Big[(p \times r) + (1 - p)\Big] \times 100\%,$$

where p is the prevalence (proportion with disease) of AD dementia and r is the adjusted mortality HR for AD dementia. Because prevalence cannot be accurately calculated based on the design of the cohorts used for this study in which persons with known dementia were excluded, we used recent US prevalence estimates from a study that applied AD incidence estimates from the Chicago Health and Aging Project to 2010 US census data: 3.0% for ages 65–74, 17.6% for ages 75–84, and 32.3% for ages 85 and older.[3] The Chicago Health and Aging Project, a population-based cohort study of older adults, used criteria for a diagnosis of AD dementia identical in all essential aspects to those used here.

Number of deaths attributable to AD dementia in the United States. We then applied our PAR% estimates to the reported numbers of total US deaths in these age ranges for 2010.[1] Because our estimates of HRs of mortality for incident AD dementia may not be representative of the US population, we performed a sensitivity analysis in which we calculated the number of US deaths attributable to AD dementia if the HRs for each age interval were lower or higher than the estimate from our cohort (by 10% intervals up to 50% lower or higher).

RESULTS **Mortality rates and survival after AD dementia.** Over an average of 8.0 years of follow-up per person and a total of 18,981 person-years, of 2,566 participants without dementia at baseline, 559 (21.8%) persons

Table 1   Characteristics of participants who did and did not develop AD

	Total (n = 2,566)	No AD (n = 2,007)	Incident AD (n = 559)	p For difference[a]
Age at study baseline, y, mean (SD)	78.07 (7.37)	77.27 (7.36)	80.94 (6.64)	<0.0001
Years of follow-up, mean (SD)	7.95 (4.87)	7.58 (5.00)	9.27 (4.08)	<0.0001
Female sex, n (%)	1,854 (72.3)	1,450 (72.0)	404 (73.0)	0.915
White, non-Hispanic, n (%)	2,272 (88.7)	1,762 (88.0)	510 (92.0)	0.015
Education, y, mean (SD)	16.03 (3.80)	15.96 (3.84)	16.30 (3.68)	0.057
Died, n (%)	1,090 (42.5)	692 (34.5)	398 (71.2)	<0.0001

Abbreviation: AD = Alzheimer disease.
Participants from the Memory and Aging Project and Religious Orders Study.
[a] Difference between no-AD and incident-AD groups; p values from χ^2 (categorical variables) or analysis of variance (continuous variables).

were diagnosed with AD dementia, 31 (1.2%) were diagnosed with other forms of dementia, and 1,090 (42.4%) died. The mean age at incident AD dementia diagnosis was 86.53 (SD = 6.47) years. As shown in table 1, participants who developed AD dementia were older and were followed longer. Seventy-two percent of those who developed AD dementia died, whereas 34.5% of those who did not develop AD dementia died (table 1). The median survival time from AD dementia diagnosis to death from Kaplan-Meier curves for participants who developed AD dementia was 3.8 years overall and was related to age at diagnosis. Median survival was 4.4 years for persons aged 75–84 at AD dementia diagnosis (n = 182) and 3.2 for persons aged 85 and older at AD dementia diagnosis (n = 356); only 4 persons aged 65–74 died after developing AD dementia, so Kaplan-Meier curve could not be estimated.

Figure   Predicted survival past age 75 years after a diagnosis of AD dementia vs no diagnosis of AD dementia

Estimates for white females with 15 years of education, Alzheimer disease (AD) diagnosed at age 75 years. Red = predicted survival after a diagnosis of AD; blue = predicted survival without AD.

AD dementia and risk of mortality. From a proportional hazards model adjusted for sex, race, education, and parent study with age as the time scale, the rate of mortality was more than 3 times higher after a diagnosis of AD dementia (HR = 3.13, CI = 2.74, 3.58; see the figure). After further adjustment for vascular disease and vascular risk burden, results were similar (HR = 3.17, CI = 2.77, 3.626); we therefore omitted vascular disease from subsequent analyses. Examining the data by age group, only 4 persons aged 65–74 died after developing AD dementia (table 2); therefore, HR estimates were unstable in this group. In persons aged 75–84, the rate of mortality was more than 4 times higher after a diagnosis of AD dementia, and in persons aged 85 and older, it was nearly 3 times higher after a diagnosis of AD dementia (table 2). We then repeated the models for any diagnosis of dementia. Results were similar for total dementia: HR = 3.21, CI = 2.81, 3.67 across all ages; HR = 4.54, CI = 3.54, 5.83 for ages 75–84; and HR = 2.77, CI = 2.37, 3.23 for ages 85 and older.

Population attributable risk percentage. Crude PAR% was 16.9% for ages 75–84 and 30.2% for ages 85 and older. Adjusted PAR%, based on HRs from proportional hazards models and age-specific prevalence rates from the literature,[3] was higher than crude PAR% (table 2).

Number of deaths attributable to AD dementia in the United States. We applied age-specific estimates of PAR% to the numbers of deaths in the United States in 10-year age groups[1] and obtained a figure of 503,400 excess deaths after a diagnosis of AD dementia in 2010 for Americans aged 75 and older. We then performed a sensitivity analysis in which we calculated the number of excess deaths attributable to AD dementia in the United States if the mortality HR for AD dementia was lower or higher than that which was observed (table 3). For example, if the mortality HR for AD dementia was 20% lower than the observed HR in each age strata, the number of deaths attributable to

age categories had similar findings.[5,24,25] Our observed mortality HR for AD dementia was similar to other studies, ranging from 1.7 to 3.7.[7,8,13] Our estimates of PAR%, however, were higher than earlier estimates, which ranged from 12.5% to 18.3%.[2,9,10] A possible explanation is that previous studies without annual assessments may have underestimated mortality associated with AD dementia because of "length bias" from long intervals between assessments; i.e., persons with rapidly progressive AD die before being diagnosed.[12,13] Our cohort may also be healthier and thus AD may be involved in proportionately more deaths given fewer comorbidities. Finally, a 1995 study using a lower HR for mortality reported 163,000 to 173,000 deaths attributable to AD dementia in the United States.[26]

The cohorts used in this analysis may differ in systematic ways from the general US population of older adults, in particular because of better health and more education. This would influence the up-weighting of our estimates to national mortality figures in order to estimate the number of deaths attributable to AD dementia in the United States. However, our estimates provide an approximate sense of the magnitude of the underestimation of deaths attributable to AD if relying on death certificates alone. Although our estimate of 503,400 deaths attributable to AD is crude, it is notably 5 to 6 times higher than the 83,494 AD deaths in 2010 reported by the CDC.[1] Our figure suggests that AD may be the third leading cause of death after heart disease and cancer, with nearly as many deaths as chronic lower respiratory diseases, stroke, and accidents (causes 3–5 as listed by the CDC) combined,[1] echoing a recent report indicating that dementia has an impact on survival in the range of cardiovascular disease.[23] Sensitivity analyses showed that even if our estimates of hazard of death were off by a factor of 2, this figure would be approximately 200,000, which is still substantially higher than the figure from the CDC.

It is well documented that AD and other forms of dementia are underreported on death certificates.[27–30] Dementia contributes to death insidiously over the course of years through a cascade of events. Eventually, severe dementia causes complications such as swallowing disorders and malnutrition that can lead to fatal

AD dementia in the United States in those aged 75 and older in 2010 would be approximately 400,000. By contrast, if the HR was 20% higher, the number of deaths would be nearly 600,000.

DISCUSSION In this study of older adults without dementia at the beginning of observation, the development of AD dementia significantly contributed to the burden of mortality. The rate of death was 3 to 4 times higher after a diagnosis of AD dementia and more than one-third of all deaths were attributable to AD dementia. This translates into a figure of more than 500,000 deaths attributable to AD dementia in the US population in 2010. Overall, the data indicate that the proportion of older persons who die of AD is much higher than the number indicated by death certificates, which is less than 5% of all deaths in the elderly.[1]

Some of our results are comparable to other cohort studies. Our median survival time after incident AD dementia was similar to other reports, ranging from 3.1 to 5.9 years.[2,9,12,13,23] Our cohorts were older than other cohorts; studies presenting median survival time by

conditions such as pneumonia.[31,32] These more proximate causes are listed on the death certificate as immediate cause of death, while dementia is often omitted as an underlying cause. Attempting to identify a single cause of death may not capture the reality of the process of dying for most elderly people because multiple factors may contribute to death in the elderly, some proximate and some distal. The elimination of any one of them may allow the individual to live longer. Just as the field has embraced the concept of mixed dementia, acknowledging that multiple neuropathologies may contribute to the expression of dementia beyond AD pathology alone,[33] it may be time to consider the analogous concept of "mixed mortality" to more accurately reflect the contribution of multiple disease processes to dying. This more nuanced view of "cause of death" is needed for an accurate understanding of the contributions of chronic diseases such as AD to death in rapidly aging populations.

There are several limitations to this work. Because these cohort studies are not population-based and participants agree to autopsy, mortality rates and attributable risk may not be representative of the general population. Our results may be biased if the relationship between AD dementia and death is different than for the general US population of older adults. Although we adjusted for potential confounders of the relationship between AD dementia and death, residual confounding may remain. We were only able to estimate deaths attributable to AD dementia for persons aged 75 years and older, and we did not include deaths associated with mild cognitive impairment due to AD as recognized by the newly recommended diagnostic criteria for clinical AD,[34] so we likely underestimated the true number of deaths attributable to AD; prior work has found that mild cognitive impairment is associated with mortality.[18,35] Another limitation was the use of prevalence estimates from a separate cohort, calculated using different incidence rates, death rates, and lower HRs for mortality.[3] Sensitivity analyses included halving our HR to lower than that assumed by the prevalence calculations in that study, so they are more conservative than required to overcome this limitation. AD dementia status was treated as an absorbing state, but it is possible for persons to not receive a diagnosis on subsequent assessments. Because most will eventually transition back into AD dementia, we chose not to complicate analyses by allowing such transitions. Finally, PAR% calculations have been criticized because the sum of PAR% estimates for different factors on the same outcome is often larger than 100%. However, this conforms to our concept of "mixed mortality"; indeed, many of the deaths attributable to AD dementia may also be attributable to other co-occurring conditions.

This study has a number of strengths. There are few large studies of this kind with annual clinical evaluations, robust standardized diagnostic criteria, and very high rates of follow-up of living participants. Based on this study design, these results have a high level of internal validity and results are not likely to be biased because of selective attrition. Developing a consensus around the burden of mortality imposed by AD and dementia is important for informing government and private research priorities. The estimates generated by this analysis suggest that deaths from AD far exceed the numbers reported by the CDC and may be closer in magnitude to the number of deaths reported for heart disease and cancer.

AUTHOR CONTRIBUTIONS

Dr. Bryan D. James is the primary author of this manuscript. He was responsible for the study concept and design, interpretation of data, and drafting the manuscript. Dr. Sue E. Leurgans conducted the analysis for this study and contributed to the study concept and design and interpretation of data. Dr. Liesi E. Hebert, Dr. Paul A. Scherr, and Dr. Kristine Yaffe contributed to the study design and interpretation of data. Dr. David A. Bennett is the senior author of this manuscript. He is responsible for the initial concept of the study, study supervision, contribution to interpretation of data, and obtaining funding for the cohort studies.

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