Alzheimer Disease and Mortality

A 15-Year Epidemiological Study

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Background: Alzheimer disease (AD) is considered a leading cause of death, but few studies have examined the contribution of AD to mortality based on follow-up of representative US cohorts.

Objective: To examine mortality rates, duration of survival, causes of death, and the contribution of AD to the risk of mortality in an aging community-based cohort, controlling for other predictors.

Design: Fifteen-year prospective epidemiological study. Mortality rates per 1000 person-years and the population-attributable risk of mortality were determined. Cox proportional hazards models were used to estimate relative risk of mortality due to AD, adjusting for relevant covariates. Death certificates were abstracted for listed causes of death.

Setting: A largely blue-collar rural community in southwestern Pennsylvania.

Participants: A community-based cohort of 1670 adults 65 years and older at study enrollment.

Main Outcome Measure: Mortality.

Results: In the overall cohort, AD was a significant predictor of mortality, with a hazard ratio of 1.4 after adjusting for covariates. The population-attributable risk of mortality from AD was 4.9% based on the same model. Examining the sexes separately, AD increased mortality risk only among women. Death certificates of AD subjects were more likely to list dementia/AD, other brain disorders, pneumonia, and dehydration, and less likely to include cancer.

Conclusions: Alzheimer disease was responsible for 4.9% of the deaths in this elderly cohort. Alzheimer disease increased the risk of mortality 40% in the cohort as a whole and separately in women but not in men. The mean (SD) duration of survival with AD was 5.9 (3.7) years, and longer with earlier age at onset.

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C LINICAL EXPERIENCE AND empirical data suggest that Alzheimer disease (AD) is a leading cause of death[1] and shortens life[2,3] in elderly persons. Health care providers, planners, and policy makers need to know more specifically how much AD increases or contributes to mortality risk in the population at large, with or without adjustment for the effects of other known predictors of mortality.

We report on the specific contribution of AD to mortality during a 15-year period in a prospective epidemiological study of older adults (≥65 years) in a largely rural area in southwestern Pennsylvania. Our cohort's overall mortality rates are comparable to the national average.[4,5]

METHODS

STUDY SITE AND POPULATION

The Monongahela Valley Independent Elders Survey (1987-2002) was conducted in a population with low income and education levels. Sampling and recruitment procedures have been described previously.[6] Study procedures were approved annually by the University of Pittsburgh institutional review board. A total of 1681 participants (1422 randomly selected from the voter registration list and an additional 259 volunteers from the same area) were assessed at study enrollment (wave 1, 1987-1989).[7] Participants were reexamined in a series of biennial data collection waves.

Mortality rates were estimated from wave 1 until death or the end of the study (December 31, 2002). Cohort size was 1670 after eliminating 9 participants with unknown dementia type and 2 with unknown onset date

(described later). The duration of follow-up ranged from 0.02 to 15.8 years (mean [SD], 10.3 [4.6] years).

Wave 2 (1989-1991) served as the baseline for the mortality predictor analyses because several relevant variables (described later) were first measured then. Between waves 1 and 2, 340 individuals died, relocated, or dropped out; 1 had unknown dementia type (described later); and 45 had missing data for 1 or more relevant variables. Mortality risk until study end was examined in the remaining 1295 participants.

SCREENING

Participants provided written informed consent and underwent screening, including the Mini-Mental State Examination,[8] a brief general mental status test, and a modified Center for Epidemiological Studies Depression Scale.[9] Ability to perform instrumental activities of daily living (IADL) was assessed using the Older Americans Resources and Services[10] scale. Overall morbidity was estimated by the number of regularly taken prescription medications.[11]

DIAGNOSIS OF AD

At each wave, participants operationally classified at screening as cognitively impaired or declined were asked to undergo a clinical examination for dementia.[6] A comparison group of cognitively intact participants, matched on age, sex, and education to subjects with dementia at wave 1, was randomly selected for clinical examination. The assessment protocols were those of the Consortium to Establish a Registry for Alzheimer's Disease[12] and the University of Pittsburgh Alzheimer Disease Research Center, modified for field use. Clinical examinations were performed blind to screening cognitive scores. A consensus diagnosis process established or ruled out the diagnosis of dementia according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*[13]; the presence of probable or possible AD according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria[14]; and stage of dementia according to the Clinical Dementia Rating Scale.[15] We categorized as AD all those with Clinical Dementia Rating Scale scores of 0.5 or higher also meeting the criteria for probable or possible AD. A date of onset was estimated based on all available evidence, including cognitive test scores, functional ability, self-report of memory loss, medical record information, and staff observations, at successive assessments over time.

MORTALITY AND CAUSE OF DEATH

The vital status of our cohort was ascertained completely.[16] Death certificates became available 10 to 12 months after the calendar year of death; before our study ended, they were obtained for 845 of the 852 subjects who died by December 31, 2000. Rather than arbitrarily select a single principal cause for each subject, we examined the frequencies of all conditions listed as immediate, underlying, and contributory causes of death. We separately listed individual causes/conditions of high frequency and/or specific interest, grouped the rest under organ system, and compared subjects with AD with those without dementia, adjusting for age and sex.

STATISTICAL ANALYSES

Mortality rates per 1000 person-years were calculated based on the cohort at wave 1. Proportion of population-attributable risk (PAR%) of death from AD was calculated in 2 ways. First, based on mortality rates, we used the formula typically used with longitudinal data: $PAR\% = (I_t - I_n)/I_t$, where I_t is person-years mortality rate in the entire cohort and I_n is person-years mortality rate in those without AD.

Second, to allow adjustment for covariates of interest, we calculated PAR% using the formula typically used for cross-sectional data: $PAR\% = p(r-1)/[pr + (1-p)]$, where p is the mean prevalence of AD in our cohort averaged over waves 2 to 6 as the cohort aged and r is the relative risk (hazard ratio [HR]) of mortality associated with AD, derived from the Cox proportional hazards models based on waves 2 to 6 (described later).

Mortality predictors were examined using Cox proportional hazards models. Proportionality assumptions were examined by including an interaction term for each covariate with time since wave 2. The first model examined AD alone, as a time-dependent variable, as a predictor of mortality. Fixed covariates included in subsequent models were age at wave 2, sex, education ($\geq$high school vs $<$high school), Mini-Mental State Examination score, 2 levels of IADL (disabilities in 1-3 tasks vs 0 and disabilities in $\geq$4 tasks vs 0), depressive symptoms (modified Center for Epidemiological Studies Depression Scale score, $\geq$5 vs $\leq$4), number of prescription medications, and selection status (random vs volunteer). Interaction terms for AD with each covariate were added to the main effect model one at a time. No interactions were significant in the final model. Rather than applying statistical corrections for potential length bias (ie, skewing toward longer-duration cases by including both prevalent and incident cases),[17,18] we repeated the analyses, limiting them to incident cases only. The model was then fit separately in men and women rather than merely including a sex $\times$ AD interaction term.

RESULTS

MORTALITY RATES

The wave 1 cohort (N = 1670) had a mean (SD) age of 73.4 (5.9) years; 57.8% were women. During the course of 17 209.1 person-years of follow-up until December 31, 2002, the cohort experienced 951 deaths, of which participants with AD accounted for 27.5%. Of those with and without AD, 75.3% and 52.1% died, respectively. Age-specific mortality rates, per 1000 person-years, in men and women with and without AD, are shown in **Table 1**.

AGE AT ONSET AND DURATION OF SURVIVAL WITH AD

Based on 330 incident cases with estimated onset dates, the mean (SD) age at onset of AD symptoms was 80.2 (6.0) years overall, 80.3 (5.8) years in women, and 80.1 (6.3) years in men. The mean (SD) duration of survival from onset until death was 5.9 (3.7) years overall; the duration was longer in those who, at disease onset, were younger and, therefore, had a greater remaining life expectancy (**Table 2**).

RISK OF MORTALITY ASSOCIATED WITH AD

The risk analyses included 273 cases of prevalent or incident probable or possible AD. At wave 2, in the cohort of 1295 subjects who were a mean (SD) age of 74.8 (5.4) years, covariates were distributed as follows. The mean (SD) Mini-Mental State Examination score was 27.0

Table 1. Mortality Rates per 1000 Person-years Among Participants With and Without AD, by Sex and Age at Death*

Age at Death, y	Men		Women		All	
	AD Present (n = 140)	AD Absent (n = 565)	AD Present (n = 208)	AD Absent (n = 757)	AD Present (N = 348)	AD Absent (N = 1322)
65-74 (n = 135)	38.2 (10.5-139.3)	36.8 (29.5-45.9)	39.5 (13.4-116.1)	17.6 (13.4-23.0)	39.0 (16.6-91.2)	25.6 (21.5-30.4)
75-84 (n = 474)	102.8 (76.8-137.5)	61.0 (53.0-70.3)	98.1 (76.6-125.8)	33.6 (29.0-39.0)	100.0 (82.8-120.9)	44.0 (39.8-48.8)
≥85 (n = 342)	220.4 (172.9-280.9)	129.7 (103.2-163.1)	182.5 (147.6-225.7)	93.6 (78.2-112.0)	197.2 (168.1-231.4)	104.7 (90.9-120.6)
Total (N = 951)	142.7 (118.6-171.6)	58.9 (53.0-65.4)	127.8 (108.9-150.0)	36.7 (33.0-40.8)	133.8 (118.5-151.0)	45.2 (41.9-48.7)

Abbreviation: AD, Alzheimer disease.
*Data are given as mortality rate (95% confidence interval).

Table 2. Duration of Survival in Incident Cases of AD From Symptom Onset Until Death or Censoring, by Sex and Age at Onset*

Age at Onset of AD, y	All Deceased Cases of AD (Survival Until Death)			All Cases of AD (Survival Until Death or End of Follow-up)†		
	Men (n = 100)	Women (n = 145)	All (N = 245)	Men (n = 127)	Women (n = 203)	All (N = 330)
<75	7.38 (4.01)	8.77 (4.91)	8.29 (4.62)	8.56 (4.07)	9.16 (4.81)	8.92 (4.50)
75-84	6.07 (3.10)	5.57 (3.46)	5.77 (3.32)	6.42 (3.21)	5.96 (3.36)	6.13 (3.30)
≥85	4.05 (1.90)	3.60 (1.95)	3.82 (1.92)	4.31 (2.20)	4.42 (2.66)	4.38 (2.46)
Total	5.83 (3.21)	5.95 (3.99)	5.90 (3.68)	6.39 (3.47)	6.26 (3.85)	6.31 (3.70)

Abbreviation: AD, Alzheimer disease.
*Data are given as mean (SD) survival (in years).
†Including those still alive at the end of follow-up (censored cases).

(2.3); 23.6% of subjects had IADL disability scores of 1 to 3 (ie, they were unable to perform 1-3 IADL independently), while 4.8% had IADL disability scores of 4 or more. Participants took a mean (SD) of 2.02 (2.08) prescription medications (range, 0-11). Five or more depressive symptoms (modified Center for Epidemiological Studies Depression Scale score, ≥5) were reported by 10.3% of participants.

In an unadjusted Cox proportional hazards model with AD examined alone, its HR for mortality was 2.6 (95% confidence interval [CI], 2.2-3.1). Adjusting only for age and sex, the HR for AD was reduced to 1.7 (95% CI, 1.4-2.0). When all covariates were included, the HR for AD was 1.4 (95% CI, 1.2-1.8) (ie, persons with AD had a 40% higher mortality risk than those without AD, after adjusting for the effects of the other predictors in the model). The covariates significantly associated with mortality included older age (per year: HR, 1.07; 95% CI, 1.06-1.09), male sex (HR, 1.6; 95% CI, 1.4-1.9), 1 to 3 IADL (HR, 1.4; 95% CI, 1.2-1.8), 4 to 5 IADL (HR, 2.3; 95% CI, 1.6-3.2), modified Center for Epidemiological Studies Depression Scale score of 5 or more (HR, 1.4; 95% CI, 1.1-1.8), and prescription medications (per drug: HR, 1.2; 95% CI, 1.1-1.2). Volunteer (vs random) selection status at study enrollment was negatively associated with mortality (HR, 0.7; 95% CI, 0.5-0.9).

To check for potential length bias, we fit the model previously described again, excluding 77 prevalent cases (ie, with onset before wave 2). The HRs were virtually unchanged in the new model restricted to incident cases: the HR for AD alone was 2.2 (95% CI, 1.8-2.7); it was 1.5 (95% CI, 1.2-1.9) with adjustment for age and sex and 1.4 (95% CI, 1.1-1.8) with adjustment for all remaining covariates.

MORTALITY PREDICTORS IN MEN AND WOMEN

The model with all covariates previously described was fit separately in men and women. Among the 791 women, 169 had AD and 318 died. In women, in addition to age, IADL impairment, depressive symptoms, and prescription medications, AD significantly predicted mortality (HR, 1.7; 95% CI, 1.3-2.2). Among the 504 men, 104 had AD and 271 died; significant covariates were age, IADL impairment, and prescription medications. The HR for AD in men was 1.2 (95% CI, 0.9-1.7), which was not statistically significant. All models satisfied proportionality assumptions.

POPULATION-ATTRIBUTABLE RISK

By using the mortality rate–based formula and the data in Table 1, the PAR% was 18.3%. This figure was close to the PAR% of 17.1% derived from the model-based formula using the average AD prevalence of 12.9% across waves 2 to 6, and based on the HR for AD alone. The PAR% decreased to 8.3% when based on the HR adjusting for age and sex, and to 4.9% when based on the HR also adjusting for IADL, depression, and prescription drugs.

CAUSES OF DEATH

Death certificates were obtained for 782 of 789 participants with AD or no dementia, and 63 with other de-

Table 3. Causes of Death in Those With AD vs Those Without Dementia

Conditions Listed on Death Certificates as Immediate, Underlying, or Contributory Causes of Death	Those With AD (n = 236)*	Those Without Dementia (n = 546)*	*P* Value		All Deaths Before December 31, 2000 (Those With AD, Other Dementia, and No Dementia) (n = 845)*
			Unadjusted Association†	Association Adjusted for Age and Sex‡	
Individual conditions					
Dementia/AD/senility	29 (12.3)	2 (0.4)	<.001	<.001	32 (3.9)
Stroke syndrome	22 (9.3)	57 (10.4)	.63	.40	87 (10.5)
Septicemia or sepsis	12 (5.1)	27 (5.0)	.93	.72	41 (5.0)
Dehydration	7 (3.0)	0	.001§	NA	9 (1.1)
Pneumonia‖	29 (12.3)	35 (6.4)	.006	.04	66 (8.0)
Decubitus ulcers	2 (0.8)	0	.09§	NA	3 (0.4)
Cardiac arrest¶	39 (16.5)	87 (15.9)	.84	.44	140 (16.9)
Categories					
Other brain disorder	13 (5.5)	9 (1.7)	.003	.01	25 (3.0)
Respiratory	53 (22.5)	92 (16.9)	.06	.16	156 (18.8)
Cardiovascular	112 (47.5)	275 (50.4)	.73	.36	431 (52.1)
Gastrointestinal	11 (4.7)	28 (5.1)	.78	.99	43 (5.2)
Genitourinary	13 (5.5)	37 (6.8)	.51	.34	55 (6.6)
Cancer	29 (12.3)	143 (26.2)	<.001	.005	181 (21.9)
Unknown "natural causes"	5 (2.1)	10 (1.8)	.79	.81	16 (1.9)
Other/miscellaneous	24 (10.2)	58 (10.6)	.85	.49	93 (11.2)

Abbreviations: AD, Alzheimer disease; NA, data not applicable (regression model cannot be fit because no individuals without dementia had this condition reported).
*Data are given as number (percentage) of each group.
†Data were obtained by the χ^2 test unless otherwise specified.
‡Data were obtained by multiple logistic regression.
§Data were obtained by the Fisher exact test.
‖Included within the respiratory category as well.
¶Cardiac arrest and cardiopulmonary arrest were not included in any other category.

mentias, who died between study enrollment (wave 1) and December 31, 2000. Proportions of immediate, underlying, and contributory causes of death were examined, allowing multiple conditions per subject (**Table 3**).[16] Adjusting for age and sex, AD/dementia/senility, other brain disorders, and pneumonia were listed significantly more often in those with AD than in those without dementia. Dehydration and decubitus ulcers were listed only among those with AD. Cancer was listed significantly less often in those with AD than in those without dementia.

COMMENT

Studies of mortality and AD are difficult to compare directly because some are based on volunteers or patients referred to research clinics[19,20] and others on patients in nursing homes,[21] outpatients in various settings,[22] volunteer panels,[21] or, like ours, on cases identified within community samples.[17,18,23-30] The length of follow-up has ranged from 2[25] to 14 years.[30] Some have included only prevalent,[18,26] only incident,[3,23] or both prevalent and incident cases (as in our study); some have included early-onset cases.[22] Some samples have been limited to subjects 77 years and older,[29] 85 years and older,[28] or 65 to 84 years.[24] While the end point, death, is incontrovertible, duration has been measured starting from the study baseline[20] or diagnosis,[30] the date that health services were sought,[17] or, as herein, from a reported or estimated date of symptomatic onset.[6] Some report age-specific mortality rates,[26] others standardized mortality ratios,[31] and attributable deaths have been calculated using a life table

approach[32] rather than the model-based approach used herein. Different covariates (demographics, genotype, comorbidity, and institutionalization) were adjusted for in different studies, and different instruments have been used to measure the same variables.

In our cohort, in 15 years, 27.5% of deaths occurred in individuals with AD. However, attribution of deaths to AD depends in part on how common AD is in the given sample, the relative risk of mortality associated with AD, and additional demographic and clinical characteristics of individuals that independently increase risk of death. The HR for mortality associated with AD was 2.6 when examined alone, and 1.4 after adjusting for relevant covariates. That is, overall, the presence of AD increased the risk of mortality approximately 40%. Based on these figures, the mortality risk attributable to AD is 4.9%.

The mean (SD) survival was 5.9 (3.7) years from the onset of symptoms until death, but depended on age at onset. It ranged from 8.3 (4.6) years in those with onset before the age of 75 years to 3.8 (1.9) years in those with onset after the age of 85 years. These figures are slightly higher than those reported for median survival after initial diagnosis of AD in a health maintenance organization–based registry during approximately the same period[30] and in a volunteer panel.[3] Three-year mean survival was reported from an older (≥77 years) Swedish community-based cohort in which onset of AD might have occurred up to 3 years before diagnosis.[29] Three-year survival was also reported from a large Canadian study designating onset primarily based on seeking medical attention for a memory problem.[17] The duration of survival with illness may be longer in our study than in others because

of our 15-year follow-up and because we measured survival from the estimated onset of symptoms rather than from the time of diagnosis. Over varying follow-up periods, most previous studies have shown shorter survival times in men than in women with AD, whether these studies were based on nursing home patients,[21] research center participants,[19] or community samples,[2,17,23-26,29,30] but did not examine increased mortality risk separately in men and women. In our cohort, AD increased the relative risk of mortality only in women because men in general already have an elevated mortality risk and a reduced life expectancy.[2]

Among those in whom we obtained death certificates, 3.8% had AD/dementia/senility listed as cause of death, although only 12.3% of those with AD had such a condition reported. Based solely on certification, cardiovascular conditions, cancer, acute and chronic respiratory conditions, and stroke ranked higher than AD/dementia in order of frequency as cause of death in our cohort, similar to the national rank order.[33] However, rates of mortality from or with dementia calculated from death certificates are an order of magnitude smaller than rates derived from other sources.[34] Potential reasons for the underreporting of AD or dementia on death certificates[16,35,36] might include underdetection of AD, particularly in the presence of overwhelming comorbidity, but perhaps also the certifying physician's view that AD, while present, did not cause death.[16] Our finding that dementia/AD and pneumonia were overrepresented on the death certificates of persons with AD goes beyond previous studies[31,36,37] in that our study was community based and included a comparison group without dementia. Our unexpected finding that cancer-related deaths were significantly underrepresented in those with AD might reflect competing risks or underdetection of cancer among the cognitively impaired.

Potential limitations include the few ethnic minorities in our cohort, reflective of the elderly population of the study area. With assessments performed biennially, it is possible that we missed cases of AD with exceptionally short durations. The inclusion of both prevalent and incident cases in most of our analyses could potentially skew our results toward cases with longer survival; however, HRs were virtually unchanged in analyses excluding prevalent cases.

Families of patients newly diagnosed as having AD often ask their physicians how long people commonly live with this condition, what factors predict longer or shorter survival, and what these patients usually die of. A balanced response might be based not only on the physician's clinical experience but also on data from representative community samples. Our data should also be relevant to health care planning and policy making for the growing number of individuals with AD.

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