

Survival Following a Diagnosis of Alzheimer Disease

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Context: Survival following a diagnosis of Alzheimer disease (AD) is important information for health planners, caregivers, patients, and their families.

Objectives: To estimate the duration of survival following a diagnosis of AD and to determine the effect of AD on life span.

Design, Setting, and Participants: Follow-up of participants of the Baltimore Longitudinal Study of Aging who were older than 55 years (January 1, 1985-September 30, 1999).

Main Outcome Measures: Survival duration.

Results: The median survival time following a diagnosis of AD depended strongly on the patient's age at diagnosis. The median survival times ranged from 8.3 years

for persons diagnosed as having AD at age 65 years to 3.4 years for persons diagnosed as having AD at age 90 years. There were no significant differences between men and women in survival after having a diagnosis of AD. Diagnoses of AD at ages 65 and 90 years were associated with approximately a 67% and 39% reduction in median life span, respectively.

Conclusions: The effect of a diagnosis of AD on life span depends crucially on the age of the person when AD is diagnosed. Caregivers, patients, and their families could plan on a median life span as long as 7 to 10 years for patients whose conditions are diagnosed when they are in their 60s and early 70s, to only about 3 years or less for patients whose conditions are diagnosed when they are in their 90s.

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LIFE EXPECTANCY following a diagnosis of Alzheimer disease (AD) is important information for health planners, caregivers, patients, and their families. Such information is useful for planning the resources needed for the care of patients with the disease as well as for evaluating the effect on public health and for forecasting the future prevalence of the disease. However, there have been conflicting estimates of the duration of survival following a diagnosis of AD.¹⁻⁷ A study in 2001 indicated the overall survival of patients with dementia was only 3.3 years.¹ As pointed out by Wolfson et al,¹ some estimates are biased because they are based on the follow-up of individuals who were found to be prevalent with AD. This can lead to overestimation of survival because persons who die rapidly following a diagnosis of AD are excluded from the study. The resulting bias is called "length" or "survivor" bias, and as described by Wolfson et al,¹ a statistical adjustment is necessary to correct the bias.

The present study uses the Baltimore Longitudinal Study of Aging (BLSA)⁸ to determine survival following the diagnosis of AD. For the last 15 years, we have been following up the participants in the BLSA to identify incident cases of AD.⁹ Unlike earlier studies, this study is not affected by length bias resulting from inclusion of only prevalent cases of disease because we have prospectively identified newly diagnosed incident cases of AD in the cohort of BLSA participants which is an important strength of this study.

METHODS

PARTICIPANTS

The Intramural Research Program of the National Institute on Aging administers the BLSA,⁸ which began in 1958 to study the effects of normal aging. The study, which was initially limited to men but began enrolling women in 1978, had enrolled 2476 subjects (1566 men and 910 women) as of September 1999. The participants were asked to return for follow-up visits every 2 years. The analyses in this article

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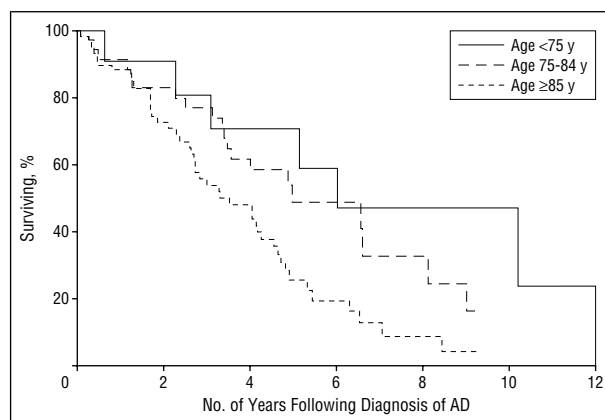
are based on all 921 BLSA participants who had at least some of their longitudinal follow-up at age 55 years or older after January 1, 1985, when vigorous efforts were made to identify incident cases of AD. Our methods for detection of incident cases of AD have been previously described.⁹ Briefly, active participants who continued to return for follow-up visits every 2 years and who were older than age 65 years were administered a battery of neuropsychological tests and underwent a neurological examination. Individuals between the ages of 55 and 64 years were first screened using the Blessed Information Memory Concentration Test,¹⁰ and those with 3 or more errors were administered the full battery of neuropsychological tests and underwent a neurological examination. If participants had not returned for a follow-up visit for 3 years, then they were contacted by telephone and screened using the Blessed Telephone Information–Memory–Concentration Test,¹¹ family informants were administered the Dementia Questionnaire,¹² and those participants with 3 or more errors on the Blessed Telephone Information–Memory–Concentration Test or those who reported cognitive decline received home visits. Diagnoses were made by consensus conferences using information from all sources and established criteria for dementia (*Diagnostic and Statistical Manual of Mental Health Disorders, Revised Third Edition [DSM-III-R]*)¹³ and AD¹⁴ and the dates of diagnoses were assigned as the estimated times that subjects met these criteria.⁹ Cases of dementia that had evidence of significant cerebrovascular disease contributing to the cognitive loss were not classified as AD. Dates of death of all participants were updated through September 1999.

STATISTICAL ANALYSIS

Kaplan-Meier survival curves of AD cases stratified by age at diagnosis (<75, 75–84, >85 years) were calculated. To estimate median remaining life span for patients with AD following diagnosis for each year of age of diagnosis (rather than the Kaplan-Meier analysis that grouped patients into broad age intervals), a Weibull parametric regression model with age of diagnosis and sex as covariates was fit to the AD cases.¹⁵ Quadratic terms in age were also considered to account for nonlinear effects of age. We obtained 95% confidence intervals (CIs) for the median based on the Weibull regression model. We compared these estimates to the median remaining life span at each year of age from among all 921 BLSA participants. This was accomplished by fitting Weibull parametric models separately to male and female BLSA participants where chronological age was taken as the fundamental time scale, and subjects entered the analysis at their age at enrollment into the BLSA or January 1, 1985, which ever came later,¹⁵ and the end point was death or last follow-up visit. Because the survival of participants in the BLSA may not be representative of the broader US population, we also compared these results to the median remaining life span at each year of age based on US life tables.¹⁶ The statistical analyses were performed using the S-Plus and SAS Statistical (SAS Inc, Cary, NC) software packages.

RESULTS

Of 2476 BLSA participants, 350 died before January 1, 1985, 371 were lost to follow-up before January 1, 1985, and 834 were younger than 55 years at last follow-up visit resulting in 921 BLSA participants who had at least some of their longitudinal follow-up at age 55 years or older after January 1, 1985 (352 women and 569 men) and did not have dementia at the time of enrollment. During the course of follow-up of these 921 BLSA participants, there were 151 incident cases of dementia of which 108 were



Kaplan-Meier survival curves following the diagnosis of Alzheimer disease stratified by patient's age at the time of the diagnosis.

classified as AD. The mean age of diagnosis was 85.0 years. The numbers of cases diagnosed prior to age 75 years, ages 75 through 84 years, and age 85 years or older were 11, 36, and 61, respectively. There were 269 deaths among the 921 BLSA participants and 72 deaths among the 108 incident cases of AD. Follow-up times among the 108 incident cases ranged up to 14.7 years.

The **Figure** shows the Kaplan-Meier estimates of the survival curves following diagnosis of AD stratified by age. The median survival times for cases diagnosed prior to age 75 years, ages 75 through 84, and age 85 years or older were 6.0, 5.0, and 3.5 years, respectively.

The **Table** gives the median remaining survival for men and women following a diagnosis of AD by individual year of age based on the regression models. The relative risk of death associated with a 5-year increase in age of diagnosis was 1.28 and was highly significant ($P=.006$). The median remaining survival ranged from 7.8 (95% CI, 4.4–13.6) and 8.9 (95% CI, 5.0–15.8) years for 65-year-old men and women, respectively, to 3.2 (95% CI, 2.5–4.1) and 3.7 (95% CI, 2.8–4.9) years for 90-year-old men and women, respectively. The relative risk of death among male relative to female patients with AD was 1.21; however, that effect was not significant ($P=.42$). Seventy-five percent of the 108 incident AD cases were college graduates. However, education (college graduate relative to nongraduate) was not a significant predictor of survival (relative risk, 0.88, $P=.71$).

The Table also shows the median remaining survival for individuals alive at the indicated age based on all BLSA participants. A diagnosis of AD at age 65 years indicated a decrease in median remaining life span for men and women compared with all BLSA participants of 15.7 years and 18.6 years, respectively, or approximately a 67% reduction. A diagnosis of AD at age 90 years indicated a decrease in median remaining life span for men and women of 1.9 and 2.7 years, respectively, or approximately a 39% reduction. A diagnosis of AD was associated with a significant decrease in survival ($P<.01$). For comparison, the Table shows the median remaining life span based on US life tables. As expected, the life span of BLSA participants is longer than indicated by US life tables. On average, the median

Median Remaining Survival Time (Years) of Alzheimer Disease Cases Following Diagnosis and Comparison With BLSA Participants and US Life Tables*

Age, y	Men			Women		
	Cases of Alzheimer Disease†	BLSA‡	US Life Tables§	Cases of Alzheimer Disease†	BLSA‡	US Life Tables§
60	9.3	28.5	20.0	10.6	32.5	24.1
65	7.8	23.5	16.1	8.9	27.5	19.8
70	6.5	18.7	12.5	7.5	22.6	15.6
75	5.5	14.1	9.4	6.3	17.7	11.9
80	4.6	10.3	6.7	5.2	13.2	8.6
85	3.8	7.3	4.7	4.4	9.4	5.9
90	3.2	5.1	3.3	3.7	6.4	4.1
95	2.7	3.6	3.2	3.1	4.3	2.8

*Data are given in years. BLSA indicates Baltimore Longitudinal Study of Aging.

†Median remaining survival for individuals at the indicated ages of diagnosis based on the Weibull regression model for survival time following diagnosis that included age at diagnosis and sex as covariates. There was no significant difference between males and females in survival following diagnosis ($P = .42$). The median remaining survivals based on a model that did not adjust for sex were 8.3 and 3.4 years at ages 65 and 90 years, respectively. A likelihood ratio test for inclusion of a quadratic term in age at diagnosis was not significant ($P > .20$). The 95% confidence intervals of median survival among men at ages 65, 75, 85, and 95 years were 4.4-13.6, 3.9-7.7, 3.1-4.8, and 1.9-3.7, respectively. The 95% confidence intervals of median survival among women at ages 65, 75, 85, and 95 years were 5.0-15.8, 4.4-9.0, 3.4-5.7, and 2.2-4.4, respectively.

‡Median remaining survival based on 921 BLSA participants. Estimates based on a Weibull regression model with chronological age as the time scale with guarantee time of 60 years using maximum likelihood methods that accounted for study enrollment at different ages.¹⁵ Regressions were performed separately for men and women.

§Median remaining survival among individuals alive at the indicated age based on the 1998 US life tables.¹⁶

remaining life span based on US life tables is approximately 33% shorter than that based on BLSA participants.

An additional analysis based on all 151 incident dementia cases yielded very similar results as that based on only the 108 incident AD cases. The median survival times (Table) decreased on average by less than 3% while there was a corresponding increase in precision (width of CIs for the median decreased on average by almost 20%).

COMMENT

It is projected that in the next 50 years, the prevalence of AD will nearly quadruple when approximately 1 in 45 Americans will be living with the disease.¹⁷ Information on survival following a diagnosis of AD is important, not only for predicting future prevalence of the disease but also for planning the resources necessary to care for patients during a life span of increasing disability.

The duration of survival following a diagnosis of AD depends critically on the subject's age at diagnosis. The results of this study indicate that the median survival of patients with AD could range from nearly 9 years for persons diagnosed at age 65 years to approximately 3 years for persons diagnosed at age 90 years. Persons diagnosed at age 65 years could anticipate approximately a 67% reduction in median remaining life span, while persons diagnosed at age 90 years could anticipate a 39% reduction in median remaining life span. Alzheimer disease is associated with a greater proportionate reduction in life span among patients affected at younger ages compared with older ages, presumably because patients at older ages are at high risk of dying of other causes.

Our estimates of survival referred to time following diagnosis, but the onset of AD is gradual and insidious with onset frequently occurring months or years be-

fore diagnosis. The mean duration between reported onset of symptoms and diagnosis of the 108 AD cases in this study was 2.8 years. The means for men and women were 3.2 and 2.4 years, respectively, while the means for those younger and older than age 75 years at diagnosis were 4.1 and 2.7 years, respectively. Thus, the total duration of disability that caregivers, patients, and their families must plan for could well be longer than suggested by the Table. This study is based on the BLSA, which is a volunteer cohort of participants with relatively high socioeconomic status and their life expectancy is greater than the broader US population as indicated by the comparison with US life tables in the Table. Thus, the median life span of patients with AD in the Table may not be applicable to the entire US population of patients with AD. Even though our population was well educated, age-specific incidence rates of AD in our cohort are consistent with other US studies¹⁷ suggesting that diagnoses were not delayed. Thus, it is reasonable that the proportionate reductions in life span associated with a diagnosis of AD (eg, 67% reduction for a 65-year-old) would be applicable more generally.

A recently published study indicated that the overall survival of patients with dementia was only 3.3 years.¹ While our study also attests to the malignancy of AD in elderly persons,¹⁸ our results also emphasize that the life span of patients with AD depends crucially on the patients' ages at diagnosis. Patients and caregivers should plan on median life spans as long as 7 to 10 years for patients whose conditions are diagnosed in their 60s and early 70s. Several prevention strategies are being investigated including hormone replacement therapy and anti-inflammatory drug therapy. If any of these prevention strategies could delay the onset of AD even modestly, the total years of disabled life in the population that results from AD could potentially be significantly reduced.

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