

Familial Patterns of Risk in Very Late-Onset Alzheimer Disease

Jeremy M. Silverman, PhD; Christopher J. Smith, MA; Deborah B. Marin, MD; Richard C. Mohs, PhD; Cathi B. Propper, BA

Background: The incidence of Alzheimer disease (AD) peaks after 85 years of age. Although genetic factors are implicated in AD with substantially earlier onset, the familial characteristics of high-incidence very late-onset AD (VLOAD, defined here as AD with onset age ≥ 85 years) remain unknown.

Methods: We collected information pertaining to the cognitive status and demographics of 809 parents and siblings of 144 VLOAD probands, 4235 parents and siblings of 793 earlier-onset AD probands, and 7646 parents and siblings of 1493 nondemented elderly probands. Cumulative risks and 5-year interval-specific hazard rate ratios were calculated for AD in relatives of the 2 AD proband groups and relatives of the nondemented elderly group.

Results: The cumulative risk for AD in the relatives of VLOAD probands was significantly different than that in the relatives of earlier-onset AD probands ($P < .001$), but

not in the relatives of nondemented elderly probands. Also, the relatives of earlier-onset AD probands had hazard rate ratios ranging from 19.7 in those aged 50 to 54 years to 1.2 in those aged 90 to 94 years. Rates successively dropped as age intervals increased.

Conclusions: At least through the middle of the ninth decade of life, relatives of VLOAD probands have a lower risk for AD than those of earlier-onset AD probands. In addition, the relatively increased risk of relatives of earlier-onset AD probands is highest at younger ages and diminishes with increasing age. In counseling family members of patients with AD concerned about their own risk, the onset age of the patient and the age of the concerned relative should be considered. Very late-onset AD may be a good target for investigating environmental factors associated with AD.

Arch Gen Psychiatry. 2003;60:190-197

ALZHEIMER DISEASE (AD) is a highly age-dependent, late-onset disorder, although how long the initial pathophysiology predates clinical onset is unknown. The incidence of AD is still low at 60 to 65 years of age, but it then approximately doubles every 5 years at least until 85 to 90 years of age.^{1,2} Hence, compared with earlier ages, AD with onset after 85 years of age (hereafter referred to as *very late-onset AD* [VLOAD]) represents the highest-incidence AD, and it remains unclear to what extent the incidence rate continues to rise after 90 years of age.³ As longevity increases^{4,6} and the age structure of the US population shifts increasingly upward,⁷ the significant public health problem already presented by AD will grow and make delineating the complicated mix of genetic and nongenetic causes of AD increasingly urgent. Although the prevalence of VLOAD is not currently greater than that of earlier-onset AD, future increases in lon-

gevity will tend to shift the ratio of cases from the earlier-onset group toward VLOAD. Despite the many studies of familial aggregation in AD,⁸⁻¹⁵ the familial characteristics of VLOAD have not been previously investigated. Even studies specifically concentrating on late-onset AD have primarily examined samples of probands with onset of clinical symptoms after 60 or 65 years of age and included very few with onset as late as the ninth decade of life.^{12,14-16} To our knowledge, the relatives of VLOAD probands have never been examined as a separate group. Despite its frequency, VLOAD is less likely to be ascertained at tertiary care clinical facilities, the setting for most of these studies,¹⁷ and the familial characteristics of AD cases emerging at the highest levels of incidence are essentially unknown.

Nevertheless, it can be hypothesized that VLOAD has different familial or genetic underpinnings than earlier-onset AD. The role of genetic factors in earlier-onset AD is far from uniform. In rare

From the Department of Psychiatry, Mount Sinai School of Medicine, New York, NY (Drs Silverman, Marin, and Mohs, Mr Smith, and Ms Propper), and the General Medical Research Service, Veterans Affairs Medical Center, Bronx, NY (Drs Silverman and Mohs, Mr Smith, and Ms Propper).

cases, AD is caused by a mutation on 1 of at least 3 genes, any one of which leads to very early onset of illness.¹⁸ In an older and much more substantial proportion of cases, the apolipoprotein E (APOE) $\epsilon 4$ allele, although not a sufficient cause of AD, markedly increases its risk in a dose-response fashion.¹⁹ Other genetic risk factors are also probable in AD,^{20,21} and a variety of candidates have been suggested as risk factors independent of APOE or factors that interact with it.²² Finally, at least some role for nongenetic factors is likely, given the documentation of long-lived monozygotic twins discordant for AD^{23,24} and the variety of possible environmental risk factors that are currently under investigation.^{25,26}

Age at onset has been a useful organizing phenotype for identifying cases of AD in which genetic factors have a greater or a reduced influence. Very early-onset AD (ie, at <50 or <55 years of age) characterizes most AD cases with autosomal dominant, familial AD. In contrast, APOE- $\epsilon 4$ appears to exert its strongest influence on AD at later ages but especially at younger than 70 or 75 years,²⁷⁻³⁰ although some studies have found an APOE- $\epsilon 4$ effect among the very old as well.³¹ More generally, familial or genetic risk factors appear to be most influential in AD at relatively early onset ages, with diminishing impact as age increases.¹⁰ Beyond its utility for teasing apart groups with potentially different proportions of familiarity, assessment of the extent of familial aggregation in VLOAD is also important for families of patients with VLOAD who are concerned about their own risk for AD. In the present study, the risk for AD in the first-degree relatives of VLOAD probands is examined and compared with the risk among relatives of earlier-onset AD and those of nondemented elderly probands.

METHODS

AD PROBANDS

To identify AD probands with a wide range of onset ages, we used clinic and nursing home settings. The former only rarely ascertains patients with VLOAD, and earlier-onset AD is less common in the latter. Probands with a clinical diagnosis of AD (n=932) were ascertained from the Jewish Home and Hospital (JHH) (n=303) and the memory disorders clinics associated with the Mount Sinai Alzheimer's Disease Research Center (ADRC; n=629), New York, NY. The ADRC patients are routinely referred to the Department of Psychiatry Family Studies Research Center for a family history assessment. Consecutively admitted demented patients or those with mild cognitive impairment are referred without regard to the proband diagnosis or any prior information concerning family history. In the present study, we included all probands with a probable AD diagnosis; those with other dementia diagnoses or mild cognitive impairment were excluded. At the JHH, we contacted family members of the current residents in the order of their admission dates, beginning with the earliest admissions. Histories were obtained for probands regardless of diagnosis. For the present study, only those with a clinical diagnosis of AD were included in the AD proband groups.

The ADRC and the JHH are affiliated but independent institutions that use different diagnostic systems to clinically diagnose AD. The National Institute of Neurological and Com-

municative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD³² were used at the ADRC, and the *International Classification of Diseases, Ninth Revision* criteria were primarily used at the JHH (however, a subset of probands at the JHH received a diagnosis by means of NINCDS-ADRDA criteria). The possibility of a family history status bias associated with the use of different proband diagnostic criteria and different sources of ascertainment was a major focus in a previously published study.¹⁷ First, within the JHH sample, we compared the use of the 2 different diagnostic systems and found the familial risk for AD to be identical (relative risk, 1.0). Second, cumulative risk curves in the relatives of clinic (ADRC)-and nursing home (JHH)-based AD probands were wholly indistinguishable when probands were matched by age at onset. Because we found no evidence of a bias associated with family history ascertainment, we combined the JHH and ADRC samples.

The AD probands were then divided between those with onset at 85 years or older (VLOAD group) and those with onset at younger than 85 years. The onset age of 85 years was used as a cutoff because, compared with earlier ages, AD incidence is strongly higher after 85 years, comparable data are sparse after 90 years of age,³³ and this cutoff age provided sufficiently large groups of relatives for meaningful comparisons through most of the human life span. Agreement on age at onset, defined for probands and relatives as the age when the first definite symptom was recognized, between 2 independent family informants (interinformant reliability) and between independent interviews (and interviewers) separated by at least 1½ years (test-retest reliability) were previously found to be very good (intraclass correlation, 0.91).^{34,35}

NONDEMENTED ELDERLY PROBANDS

Family histories were collected from 1474 elderly nondemented probands. These subjects were recruited from (1) the nondemented spouses of ADRC patients, including the spouses of the AD probands and of patients with other disorders (n=583); (2) the nondemented spouses of demented and nondemented JHH residents (n=330); (3) nondemented residents at the JHH (n=135); and (4) Jewish and Italian participants in New York City-sponsored senior centers (n=426).³⁶ The family history of the spouses of demented probands was routinely collected, although we excluded spouses with possible evidence of a memory problem or dementia. The senior center participants were ascertained with the cooperation of the New York City Department for the Aging and the individual administrations of participating centers. Nondemented elderly probands were recruited from each center following uniform procedures described in detail elsewhere,³⁶ in which participants were asked to complete a health survey about themselves and their family without mentioning dementia, AD, or memory problems at the time of initial recruitment and which included health-related questions in other areas. Although the probands in the latter 3 groups were more ethnically homogeneous than the first, the cumulative risk curves for AD in their relatives have been found to be almost identical,³⁷ justifying their inclusion in a single, nondemented proband group. These index cases were determined to be free of dementia by means of the Alzheimer's Disease Risk Questionnaire³⁸ and the Dementia Questionnaire (DQ),³⁴ administered to 1 or 2 family informants. Nondemented index cases 90 years or older were excluded because these individuals have markedly reduced familial aggregation of AD, even when compared with nondemented probands aged 85 to 89 years, whereas younger nondemented elderly probands, subdivided by age (ie, 60-74 vs 75-89 years), showed comparable levels of risk.³⁷

Table 1. Demographic and Disease Characteristics of VLOAD and Earlier-Onset AD Probands and Nondemented Elderly Subjects and Their Parents and Siblings*

Proband Group	Probands			Parents and Siblings			
	No.	Mean (SD) Age at Onset, y	Mean (SD) Age, y	No. (%) Female†	No.	Mean (SD) Age, y‡	No. (%) Female§
VLOAD	144	89 (4)	93 (4)	116 (81)	809	72 (19)	411 (51)
Earlier-onset AD	793	70 (9)	76 (10)	496 (63)	4235	68 (17)	2144 (51)
Nondemented elderly	1493	...	73 (10)	802 (54)	7646	68 (18)	3776 (49)

Abbreviations: AD, Alzheimer disease; VLOAD, very late-onset AD.

*Proband groups are described in the "AD Probands" and "Nondemented Elderly" subsections of the "Methods" section.

† $\chi^2 = 48.07$; $P < .001$.

‡ $F_{2,11626} = 18.87$; $P < .001$.

§ $\chi^2 = 1.94$; $P = .19$.

ASSESSMENT OF RELATIVES

The proband's first-degree relatives were identified through interviews usually conducted by telephone with 1 or more family informants. Using the Alzheimer's Disease Risk Questionnaire,³⁸ we assessed the birth year, sex, and current age (if alive) or age at and cause of death for each relative. The Alzheimer's Disease Risk Questionnaire was then used to screen for dementia, cognitive impairment, or memory loss of any type. We administered the DQ³⁴ when any of these were suggested. The 50-item DQ focuses on whether a dementia is present and, if so, determines its specific type and age at onset. Relatives were classified as having AD if they fulfilled previously published criteria³⁵ similar to DSM-IV criteria for dementia of the Alzheimer type³⁹ but designed for informant-based assessment. For AD, this method has had very good interinformant³⁴ and test-retest³⁵ reliability. An independent group found that the DQ has excellent sensitivity and specificity for identifying dementias ascertained through direct clinical assessment.⁴⁰ In addition, at our center, in a series of deceased elderly subjects who underwent autopsy, informant-based DQ diagnoses were compared with results of independent neuropathological examinations; for AD, the DQ was found to be only slightly less sensitive than direct clinical assessment, and its specificity was virtually at the same level.⁴¹ Only the parents and siblings of the probands were included. Offspring were excluded because the spouses of AD probands were frequently included among the nondemented elderly comparison group and, hence, such offspring would be categorized in 2 different groups. In any case, most of the offspring were too young to be at risk for AD and their exclusion did not affect the results. In addition, we compared familial aggregation in the families of AD probands in which the spouses served or did not serve as an informant while controlling for proband onset. We found no significant differences in the cumulative risk curves. All protocols used were approved by the Mount Sinai Institutional Review Board, and informed consent was obtained.

STATISTICS

Survival analysis was used to examine the cumulative risk for AD. We used the actuarial life-table method as implemented by SPSS software (release 10.0.5; SPSS Inc, Chicago, Ill), with 1-year intervals to generate risk curves for AD in groups of relatives and compare curves in different groups while controlling for differences in age structure. As described more fully elsewhere,¹⁰ in contrast to the Kaplan-Meier method, the actuarial method includes an estimation of within-interval censorship that, when the interval is minimized, likely improves the risk estimate. We used the Wilcoxon-Gehan (W) statistic⁴² to test the difference between curves.

Hazard rate ratios were calculated for relatives in both AD proband groups using 5-year age intervals, with the relatives of the nondemented elderly probands serving as the reference group. This statistic uses the age interval-specific hazard rate, ie, the per-year risk for AD that an individual faces during a given age interval, given that he or she is alive and at risk at its start. The hazard rate ratio, then, is a measure of the extent to which, at a given age interval, the hazard rate is increased (hazard rate ratio, >1.0) or decreased (hazard rate ratio, <1.0) over the hazard rate in the reference group. Examining hazard rate ratios across age intervals helps reveal whether an overall difference in risk curves derives from proportionately similar levels of increased risk across the late life span or is disproportionately driven by hazard rates at particular ages.

RESULTS

SAMPLE CHARACTERISTICS

The number and characteristics of the 3 proband groups are shown in **Table 1**. By definition, proband age at onset differed between the 2 AD groups, leading also to a difference in their age at assessment. Although probands were more frequently women than men in all groups, the extent to which they predominated varied significantly. This finding was consistent with the increased longevity and greater prevalence of VLOAD in women.⁴³ Also in Table 1, the number and characteristics of the 3 groups of parents and siblings are presented. As expected, the ages of these relatives were significantly different between the groups, but no difference was seen in the sex distribution.

CUMULATIVE RISK

Cumulative risk curves (with SEs) were constructed for the relatives in each of the 3 proband groups (**Figure 1**). In the relatives of the earlier-onset AD proband group, the risk for AD first exceeded 2% at 65 years of age and 10% at 77 years of age. By 85, 90, and 95 years of age, the cumulative risk for AD in this group was 22.1% ± 1.3%, 26.5% ± 1.7%, and 30.6% ± 2.3%, respectively. Beyond 95 years of age, there were only 42.5 relatives at risk, reducing the reliability of the estimate to unacceptable levels. In the relatives of the VLOAD proband group, the cumulative risk first exceeded 2% at 71 years of age (6

years later than in the relatives of the earlier-onset AD proband group) and 10% by 87 years of age (10 years later). At 85, 90, and 95 years of age, the cumulative risk for AD was $8.8\% \pm 1.7\%$, $16.7\% \pm 2.8\%$, and $30.7\% \pm 6.9\%$, respectively. By 92 years of age, however, the number of at-risk relatives dropped below 50 and was only 17 at 95 years of age. In relatives of nondemented elderly, the risk for AD first exceeded 2% by 72 years of age and 10% at 88 years of age. At the landmark ages of 85, 90, and 95 years, the cumulative risk reached $8.2\% \pm 0.7\%$, $11.7\% \pm 1.0\%$, and $19.0\% \pm 2.2\%$, respectively. At 95 years of age, 118.5 relatives were still at risk in this group.

The risk curve associated with the relatives of the earlier-onset AD probands was significantly different than the curves of the relatives of the VLOAD probands ($W=28.63$; $P<.001$) and the relatives of the nondemented elderly ($W=198.45$; $P<.001$). In contrast, the latter 2 curves were almost identical until approximately 87 years of age, when the risk to relatives of VLOAD probands began to rise more sharply. We detected no significant differences between these 2 curves ($W=2.08$; $P=.10$). We then restricted the nondemented elderly probands to those aged 85 to 89 years ($n=155$; relatives, $n=942$) and the VLOAD group to those with onset before 90 years of age ($n=94$; relatives, $n=699$). In this way, we excluded nondemented elderly probands who were not yet at risk for VLOAD and VLOAD probands with onset ages beyond those of any of the nondemented elderly probands. The close similarity between the 2 curves through most of the late life span and their divergence in the middle to late ninth decade of life persisted using these more restricted samples. The pairwise statistical comparison of all 3 curves remained at the same levels of statistical significance (data not shown).

Because the VLOAD group was older, their parents had been dead longer than in the other 2 groups. This raised the possibility of differential reliability of the parental diagnostic classifications, which in turn might explain the reduced risk observed in the VLOAD group. Hence, we restricted the sample of relatives to siblings alone. Unlike the parents, a proportion of the siblings were still alive at assessment time, and most of those who had died had done so more recently. In addition, we found among deceased siblings no differences between groups in the interval from death to the time of assessment ($F_{2,2932}=0.51$; $P=.60$). The cumulative risk curves using siblings alone were essentially unchanged, and none of the statistical findings differed from those that used the entire sample. However, since a larger proportion of siblings in the VLOAD group were dead (79.5%) compared with those of the other 2 groups (earlier-onset AD, 47.8%; nondemented elderly, 52.8%; $\chi^2_2=173.4$; $P<.001$), we compared the risk for AD between groups using siblings alone while stratifying by living status. Again, the risk curves looked very similar to those observed with the full sample, and their statistical comparisons were unchanged. These results led us to retain the full sample of relatives for the subsequent analyses.

HAZARD RATE RATIOS

We next calculated the 5-year hazard rates of AD (**Table 2**) and examined the patterns of hazard rate ra-

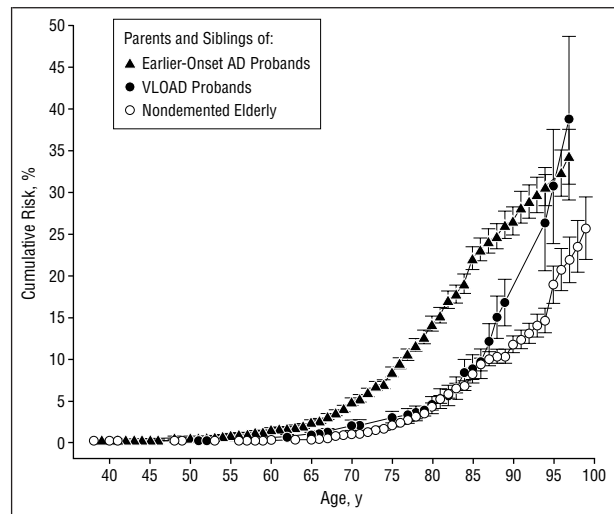


Figure 1. Cumulative risk for Alzheimer disease (AD) in parents and siblings of earlier-onset AD probands (onset age, <85 years), very late-onset AD (VLOAD) probands (onset age, ≥ 85 years), and nondemented elderly subjects (reference group).

tios in relatives of each of the 2 AD proband groups using the relatives of the nondemented elderly as a reference group (**Figure 2**). For the relatives of the earlier-onset AD probands, with the exception of the group aged 90 to 94 years, significantly higher hazard rates were observed compared with the relatives of nondemented elderly probands (Table 2). In contrast, for the relatives of the VLOAD, none of the hazard rates were significantly different.

For the 9 successive age intervals ranging from 50 to 54 years to 90 to 94 years among the earlier-onset AD probands, the 9 hazard rate ratios were 19.71, 6.35, 5.21, 4.06, 3.85, 3.43, 2.23, 2.21, and 1.17. Thus, the ratios dropped with successive age intervals. The lower 95% confidence intervals for 6 of the first 7 hazard rate ratios were equal to or greater than 1.0 (Figure 2; the exception was the group aged 55-59 years, with the lower 95% confidence limit of 0.91). In contrast, the hazard rate ratios for the relatives of the VLOAD probands exceeded 1.50 at only 3 age intervals. Two of these 3 were the earliest intervals examined (ages 50-54 years: hazard rate ratio, 9.56; ages 55-59 years: hazard rate ratio, 2.39), but in both cases, a single AD case was identified in the relatives of the VLOAD probands (Table 2). The third age interval constituted ages 85 to 89 years (hazard rate ratio, 1.95) and included 12 AD cases in the VLOAD group. However, no hazard rate ratio for the VLOAD group had a lower 95% confidence limit excluding 1.0 (Figure 2).

RISK USING OTHER PROBAND ONSET CUTOFFS

Familial aggregation of AD was also investigated by successively redividing the entire AD proband group and using lower age cutoffs at 5-year intervals as young as 60 years. **Table 3** shows comparisons of the risk curve in the original groups and for each redivision of the relatives. All pairwise comparisons of cumulative risk curves in the redivided relatives of AD probands and the nondemented elderly subjects were significant.

Table 2. Relatives at Risk in the VLOAD, Earlier-Onset AD, and Nondemented Elderly Proband Groups*

Age Interval, y	VLOAD Proband Group				Earlier-Onset AD Proband Group				Nondemented Elderly Proband Group			
	No. of Relatives at Risk	Person-years	No. of AD Cases	Hazard Rate (SE), %†	No. of Relatives at Risk	Person-years	No. of AD Cases	Hazard Rate (SE), %	No. of Relatives at Risk	Person-years	No. of AD Cases	Hazard Rate (SE), %
50-54	615.0	3072.5	1	0.033 (0.033)	3287.5	16410.5	11	0.067 (0.020)‡	5919.5	29595.0	1	0.003 (0.003)
55-59	582.0	2907.5	1	0.034 (0.034)	3067.5	15302.5	14	0.092 (0.020)‡	5544.5	27712.5	4	0.014 (0.007)
60-64	540.5	2700.0	1	0.037 (0.037)	2751.0	13705.0	20	0.146 (0.033)§	4997.5	24970.0	7	0.028 (0.011)
65-69	486.5	2425.0	3	0.124 (0.071)	2326.0	11507.5	49	0.426 (0.061)§	4206.5	20977.5	22	0.104 (0.022)
70-74	419.0	2085.0	4	0.192 (0.096)	1800.0	8962.5	55	0.621 (0.084)§	3238.0	16125.0	26	0.161 (0.032)
75-79	341.5	1695.0	5	0.295 (0.132)	1240.0	6007.5	77	1.282 (0.146)§	2268.0	11235.0	42	0.374 (0.058)
80-84	252.0	1230.0	12	0.976 (0.282)	719.0	3462.5	53	1.531 (0.210)§	1394.5	6855.0	47	0.686 (0.100)
85-89	145.5	697.5	12	1.720 (0.496)	343.5	1637.5	32	1.954 (0.345)‡	693.5	3392.5	30	0.884 (0.161)
90-94	54.5	265.0	3	1.132 (0.653)	117.5	570.0	7	1.228 (0.464)	254.5	1240.0	13	1.048 (0.291)

Abbreviations are explained in the first footnote to Table 1.

*For the hazard rate calculation, person-years indicates the number of years in the interval (ie, 5) multiplied by the number of at-risk relatives reduced by half the number of cases identified in the interval. Proband groups are described in the "AD Probands" and "Nondemented Elderly Probands" subsections of the "Methods" section.

†No significant differences were found in the comparison with relatives of the nondemented elderly group.

‡ $P < .005$ compared with the relatives of the nondemented elderly group.

§ $P < .001$ compared with the relatives of the nondemented elderly group.

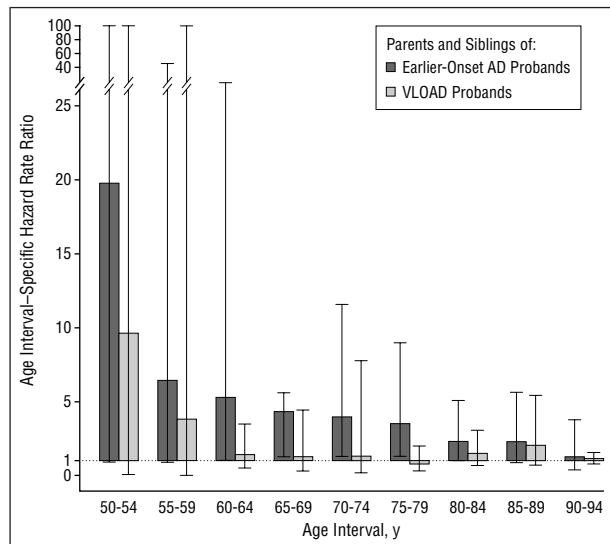


Figure 2. Five-year age interval-specific hazard rate ratios for parents and siblings of earlier-onset AD and VLOAD probands, with the parents and siblings of nondemented elderly subjects as the reference group. Abbreviations and proband groups are explained in the legend to Figure 1.

COMMENT

At least until the middle to late ninth decade of life, the risk for AD among the parents and siblings of VLOAD probands was significantly lower than among the parents and siblings of earlier-onset AD probands and did not significantly differ from that of the parents and siblings of the nondemented elderly group. Indeed, until 87 years of age, the risks for AD in the relatives of the VLOAD and nondemented elderly groups were essentially identical. In addition, these results were unchanged when the VLOAD and nondemented elderly probands were restricted to strengthen the disease distinction between the samples, and when the sample was restricted to siblings alone, whether compared unstratified or stratified by whether they

were alive at assessment. To our knowledge, no previous study of AD familial aggregation has included a comparably sized number of VLOAD probands, and no study of any size has examined the risk for AD in the relatives of VLOAD probands alone. The present results suggest that, at least through 87 years of age, the risk for AD in the first-degree relatives of VLOAD probands is no greater than that among the relatives of nondemented elderly subjects. This underscores the need for physicians, genetic counselors, and other professionals working with the family members of patients with AD who are concerned about their own risk to assess the presence of AD among family members and their ages at onset.

A second line of evidence suggests that genetic risk factors that operate at earlier ages have a greatly reduced role in the expression of VLOAD. This conclusion emerges from the pattern of age interval-specific hazard rate ratios in the relatives of the AD probands with an onset before 85 years of age. Although the overall incidence of AD increased with age among the relatives of AD probands, the diminishing hazard rate ratios during a 45-year span illustrate the decreasing levels of increased risk associated with a biological relationship with an AD proband with onset before 85 years of age. In other words, first-degree relatives of AD probands with onset before 85 years of age have a greater risk for AD than do those with no such relative, but the extent of the increased risk decreases with age and may dissolve entirely by very late life. This pattern of risk was previously observed in an overlapping but much smaller sample—about one quarter as large—of earlier-onset AD probands.¹⁰ Although DNA was not available in sufficient numbers of probands to specifically examine the role of APOE in the present sample, the results are also broadly consistent with those studies that find diminishing influence of APOE- $\epsilon 4$ on AD in very late life.^{27-30,44-47} Our findings suggest that in counseling family members of earlier-onset AD probands, the age of the concerned relative has bearing on the extent of the increased risk that person faces.

Table 3. Differences of Cumulative Risk Curves Using Alternative Proband Age at Onset Cutoffs*

	No. of Relatives	Cumulative Risk (SE) at 85 Years of Age, %	W Statistic (P Value)		
			Later- vs Earlier-Onset AD	Late-Onset AD vs Nondemented Subjects	Earlier-Onset AD vs Nondemented Subjects
Proband group (onset age, y)					
VLOAD (≥85)	809	8.8 (1.7)	28.63 (<.001)	2.08 (.10)	198.45 (<.001)
Earlier-onset AD (<85)	4235	22.1 (1.3)			
Nondemented elderly	7646	8.2 (0.7)			
Onset age, y					
≥80	1570	11.6 (1.4)	62.69 (<.001)	4.9 (.05)	236.1 (<.001)
<80	3474	24.2 (1.6)			
≥75	2467	13.7 (1.2)	69.41 (<.001)	28.54 (<.001)	258.48 (<.001)
<75	2577	27.3 (2.0)			
≥70	3284	15.7 (1.2)	74.54 (<.001)	57.50 (<.001)	275.84 (<.001)
<70	1760	29.2 (2.5)			
≥65	3940	18.0 (1.2)	57.19 (<.001)	94.28 (<.001)	245.69 (<.001)
<65	1104	25.0 (2.9)			
≥60	4431	18.3 (1.1)	62.33 (<.001)	112.52 (<.001)	256.52 (<.001)
<60	613	28.7 (4.1)			

Abbreviation: W statistic, Wilcoxon-Gehan statistic. Other abbreviations are explained in the first footnote to Table 1.

*Comparisons are provided for comparison with alternative cutoffs for onset age. Proband groups are described in the "AD Probands" and "Nondemented Elderly Probands" subsections of the "Methods" section.

Implications also exist for future studies of familial aggregation of AD using survival analysis techniques such as a Cox regression model. The different patterns of risk observed in the relatives of VLOAD and earlier-onset AD probands are a clear example of nonproportional hazards. Therefore, we cannot compare risk across the life span in a Cox regression model without considering this nonproportionality in the model.

The use of alternative cutoff onset ages from 60 to 80 years showed significantly lower cumulative risk curves in the relatives of the later-onset AD proband group compared with the earlier-onset group. However, unlike the VLOAD group, for each of the lower cutoff ages used, the familial aggregation of the later- and earlier-onset AD proband groups was significantly greater than that among the nondemented elderly. Although these results further support the inverse relationship between familial aggregation and age at onset, they also support a continuing role for genetic risk factors at least up to the middle of the ninth decade of life.

Collectively, these results indicate that relatives of VLOAD probands are not at increased risk for earlier-onset AD, and relatives of earlier-onset AD are not at increased risk for VLOAD. We also observed a rise very late in life in the cumulative risk for the relatives of the VLOAD group beyond that of the relatives of the nondemented elderly group to a level, by the middle to late 90s, that was slightly higher than that for the relatives of the earlier-onset AD probands. Might both findings be explained by positing onset as a familial trait? First, even in these large groups of relatives, the number of relatives in the AD groups was modest beyond 90 years of age, so that divergences in the survival curves at these ages may be due to increased instability of the estimate. Second, better than risk curves, which reflect the extent of previous and current age-adjusted rates of illness, the hazard rate ratio more precisely reveals differences in relative risk between groups

at specific ages. In fact, the hazard rate ratio did not appreciably rise, or rose only relatively modestly (in those aged 85-89 years), compared with relatives of the nondemented elderly group. More to the point, the ratios were very similar or even slightly reduced compared with those seen in the earlier-onset AD group of relatives. Calculating hazard rate ratios for VLOAD group using the earlier-onset AD group as the reference (rather than the nondemented controls) gives ratios that are all less than 1.0, ie, 0.64, 0.88, and 0.92 for those aged 80 to 84, 85 to 89, and 90 to 94 years, respectively. Hence, at approximately the ages when the VLOAD probands have had their own onset of disease, their relatives show no increased risk for AD compared with the relatives of earlier-onset AD probands. Thus, rather than familiarity of onset, the overall difference in patterns of risk between these 2 groups suggests that their familial etiologic underpinnings are different.

Reliance on family informants for information about relatives is a limitation of this study. However, since most affected relatives are usually dead at the time of study (and many others may be otherwise unavailable), the usually desirable direct family study approach would fail to ascertain most relatives of greatest interest. Furthermore, studies of the family history method conducted here and by others have found good reliability^{34,35} and good agreement with independently derived clinical assessments⁴⁰ and neuropathologically derived diagnoses.⁴¹ Nevertheless, as the validity studies have dealt primarily with living or relatively recently deceased individuals, the validity of an AD classification in long-dead relatives remains uncertain. Another methodological concern is the possibility of age-associated diagnostic misclassification. If the likelihood of misdiagnosing AD increases with the age of the subject, then the VLOAD group may have less familial aggregation because it represents less pure AD than the earlier-onset AD probands. An unbiased series

of probands with neuropathologically diagnosed AD constitutes an ideal group. In practice, however, a sufficiently large sample would be very difficult to ascertain, and avoidance of the influence of family history status on the family decision for autopsy (an influence that may itself be associated with onset age) would be unlikely. A third limitation is that the proband and reference groups were not ascertained through population-based sampling methods, which makes unclear how our samples might differ from the population from which they arose.

The results of the present study do not lead to the conclusion that genetic factors in VLOAD are entirely absent. The force of natural selection for genes with deleterious very late-life effects, ie, long after reproductive ages, may be extremely limited or entirely absent. Thus, liability genes for VLOAD, for example, may be ubiquitous or even monomorphic throughout the general population. This possibility would reduce or remove familial risk differences between AD and non-AD proband groups. Hence, although predisposing genes are likely in VLOAD, they may be difficult to discern in traditional disease-focused molecular genetic studies because of their presumptive ubiquity. The occasional protective variants that may have arisen over time may remain rare because late-life beneficial effects possess little if any selective advantage, although they would be more likely found in the nondemented oldest old subjects.³⁷

Although a role for genetics almost certainly persists for VLOAD, the difference in familiarity between earlier-onset AD and VLOAD has implications for efforts to identify other risk and protective factors associated with AD. After increased age, no AD risk factors have been identified with the certainty of family history status or APOE genotype.²⁵ Most efforts to identify nongenetic risk factors, however, have used AD samples with relatively early onset ages, when genetic risk factors are unambiguously powerful. The present results suggest that a focus on VLOAD may identify a group that has different etiologic underpinnings than the group with earlier-onset AD and in which environmental factors may play a larger role. Such a sample may provide greater power to detect environmental factors.

Submitted for publication October 19, 2001; final revision received June 4, 2002; accepted June 6, 2002.

This study was supported by grants AG-02219 and AG-05138 from the National Institute of Aging, Bethesda, Md, and by the New York Community Trust, New York.

We thank Joshua Judin for the database assistance.

Corresponding author: Jeremy M. Silverman, PhD, Department of Psychiatry, Box 1230, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029 (e-mail: jeremy.silverman@mssm.edu).

REFERENCES

1. Hebert LE, Scherr PA, Beckett LA, Albert MS, Pilgrim DM, Chown MJ, Funkstein HH, Evans DA. Age-specific incidence of Alzheimer's disease in a community population. *JAMA*. 1995;273:1354-1359.
2. Bachman DL, Wolf PA, Linn RT, Knoefel JE, Cobb JL, Belanger AJ, White LR, D'Agostino RB. Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. *Neurology*. 1993;43(3, pt 1):515-519.
3. Gao S, Hendrie HC, Hall KS, Hui S. The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. *Arch Gen Psychiatry*. 1998;55:809-815.
4. Kranczer S. Record high U.S. life expectancy. *Stat Bull Metrop Insur Co*. 1997;78:2-8.
5. Kranczer S. Banner year for U.S. longevity. *Stat Bull Metrop Insur Co*. 1998;79:8-14.
6. Kranczer S. Continued United States longevity increases. *Stat Bull Metrop Insur Co*. 1999;80:20-27.
7. US Bureau of the Census. *The Elderly of Today and Tomorrow: Current Population Reports, Special Studies, P23-190, 65+ in the United States*. Washington, DC: US Government Printing Office; 1996:7-1-7-2.
8. Li G, Silverman JM, Mohs RC. Clinical genetic studies of Alzheimer's disease. *Psychiatr Clin North Am*. 1991;14:267-286.
9. Mayeux R, Sano M, Chen J, Tatemichi T, Stern Y. Risk of dementia in first-degree relatives of patients with Alzheimer's disease and related disorders. *Arch Neurol*. 1991;48:269-273.
10. Silverman JM, Li G, Zaccario ML, Smith CJ, Schmeidler J, Mohs RC, Davis KL. Patterns of risk in first-degree relatives of patients with Alzheimer's disease. *Arch Gen Psychiatry*. 1994;51:577-586.
11. Silverman JM, Raiford K, Edland S, Fillenbaum G, Morris JC, Clark CM, Kukull W, Heyman A. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). VI: family history assessment: a multicenter study of first-degree relatives of Alzheimer's disease probands and nondemented spouse controls. *Neurology*. 1994;44:1253-1259.
12. Lautenschlager NT, Cupples LA, Rao VS, Auerbach SA, Becker R, Burke J, Chui H, Duara R, Foley EJ, Glatt SL, Green RC, Jones R, Karlinsky H, Kukull WA, Kurz A, Larson EB, Martelli K, Sadovnick AD, Volicer L, Waring SC, Growdon JH, Farrer LA. Risk of dementia of Alzheimer's disease patients in the MIRAGE study: what is in store for the oldest old? *Neurology*. 1996;46:641-650.
13. Hirst C, Sadovnick AD. Familial risks for Alzheimer disease from a population-based series. *Genet Epidemiol*. 1994;11:365-374.
14. Korten AE, Jorm AF, Henderson AS, Broe GA, Creasey H, McCusker E. Assessing the risk of Alzheimer's disease in first-degree relatives of Alzheimer's disease cases. *Psychol Med*. 1993;23:915-923.
15. Wu Z, Kinslow C, Pettigrew KD, Rapoport SI, Schapiro MB. Role of familial factors in late-onset Alzheimer disease as a function of age. *Alzheimer Dis Assoc Disord*. 1998;12:190-197.
16. Li G, Silverman JM, Smith CJ, Zaccario ML, Schmeidler J, Mohs RC, Davis KL. Age at onset and familial risk in Alzheimer's disease. *Am J Psychiatry*. 1995;152:424-430.
17. Silverman JM, Smith CJ, Marin DB, Schmeidler J, Birstein S, Lantz M, Davis KL, Mohs RC. Has familial aggregation in Alzheimer's disease been over-estimated? *Int J Geriatr Psychiatry*. 2000;15:631-637.
18. Cruts M, Van Broeckhoven C. Molecular genetics of Alzheimer's disease. *Ann Med*. 1998;30:560-565.
19. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261:921-923.
20. Warwick DE, Payami H, Nemens EJ, Nochlin D, Bird TD, Schellenberg GD, Wijsman EM. The number of trait loci in late-onset Alzheimer disease. *Am J Hum Genet*. 2000;66:196-204.
21. Li G, Silverman JM, Altstiel LD, Haroutunian V, Perl DP, Purohit D, Birstein S, Lantz M, Mohs RC, Davis KL. Apolipoprotein E-ε4 allele and familial risk in Alzheimer's disease. *Genet Epidemiol*. 1996;13:285-298.
22. Price DL, Tanzi RE, Borchelt DR, Sisodia SS. Alzheimer's disease: genetic studies and transgenic models. *Annu Rev Genet*. 1998;32:461-493.
23. Gatz M, Pedersen NL, Berg S, Johansson B, Johansson K, Mortimer JA, Posner SF, Viitanen M, Winblad B, Ahlborn A. Heritability for Alzheimer's disease: the study of dementia in Swedish twins. *J Gerontol A Biol Sci Med Sci*. 1997;52:M117-M125.
24. Raiha I, Kaprio J, Koskenvuo M, Rajala T, Sourander L. Alzheimer's disease in Finnish twins. *Lancet*. 1996;347:573-578.
25. Hendrie HC. Epidemiology of dementia and Alzheimer's disease. *Am J Geriatr Psychiatry*. 1998;6(suppl):S3-S18.
26. Tol J, Roks G, Slioter AJ, van Duijn CM. Genetic and environmental factors in Alzheimer's disease. *Rev Neurol (Paris)*. 1999;155(suppl 4):S10-S16.
27. Blacker D, Haines JL, Terwedow H, Go RCP, Harrell LE, Perry RT, Bassett SS, Chase GA, Meyers D, Albert MS, Tanzi R. ApoE-4 and age at onset of Alzheimer's disease. *Neurology*. 1997;48:139-147.
28. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer's disease: a meta-analysis. *JAMA*. 1997;278:1349-1356.
29. Scacchi R, De Bernardini L, Mantuano E, Donini LM, Vilardo T, Corbo RM. Apo-

- lipoprotein E (APOE) allele frequencies in late-onset sporadic Alzheimer's disease (AD), mixed dementia and vascular dementia: lack of association of $\epsilon 4$ allele with AD in Italian octogenarian patients. *Neurosci Lett*. 1995;201:231-234.
30. Murman DL, Foster NL, Kilgore SP, McDonagh CA, Fink JK. Apolipoprotein E and Alzheimer's disease: strength of association is related to age at onset. *Dement Geriatr Cogn Disord*. 1996;7:251-255.
 31. Polvikoski T, Sulkava R, Myllykangas L, Notkola IL, Niinisto L, Verkkoniemi A, Kainulainen K, Kontula K, Perez-Tur J, Hardy J, Haltia M. Prevalence of Alzheimer's disease in very elderly people: a prospective neuropathological study. *Neurology*. 2001;56:1690-1696.
 32. McKhann G, Drachman D, Folstein MF, Katzman R, Price D, Stadlen E. Report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34:939-944.
 33. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. *Neurology*. 1998;51:728-733.
 34. Silverman JM, Breitner JC, Mohs RC, Davis KL. Reliability of the family history method in genetic studies of Alzheimer's disease and related dementias. *Am J Psychiatry*. 1986;143:1279-1282.
 35. Silverman JM, Keefe RS, Mohs RC, Davis KL. A study of the reliability of the family history method in genetic studies of Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1989;3:218-223.
 36. Silverman JM, Li G, Scheer S, Wang ZX, Sotolongo C, Somary K, Mohs RC. A cross-cultural family history study of primary progressive dementia in relatives of nondemented elderly Chinese, Italians, Jews and Puerto Ricans. *Acta Psychiatr Scand*. 1992;85:211-217.
 37. Silverman JM, Smith CJ, Marin DB, Birstein S, Mare M, Mohs RC, Davis KL. Identifying families with likely genetic protective factors against Alzheimer disease. *Am J Hum Genet*. 1999;64:832-838.
 38. Breitner JCS, Folstein MF. Familial Alzheimer's disease: a prevalent disorder with specific clinical features. *Psychol Med*. 1984;14:63-80.
 39. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*. Washington, DC: American Psychiatric Association; 1994.
 40. Kawas C, Segal J, Stewart WF, Corrado M, Thal L. A validation study of the Dementia Questionnaire. *Arch Neurol*. 1994;51:901-906.
 41. Li G, Aryan M, Silverman JM, Haroutunian V, Perl DP, Birstein S, Lantz M, Marin DB, Mohs RC, Davis KL. The validity of the family history method for identifying Alzheimer disease. *Arch Neurol*. 1997;54:634-640.
 42. Klein JP, Moeschberger ML. *Survival Analysis: Techniques for Censored and Truncated Data*. New York, NY: Springer-Verlag NY Inc; 1997.
 43. Hebert LE, Scherr PA, McCann JJ, Beckett LA, Evans DA. Is the risk of developing Alzheimer's disease greater for women than for men? *Am J Epidemiol*. 2001;153:132-136.
 44. Corder EH, Lannfelt L, Viitanen M, Corder LS, Manton KG, Winblad B, Basun H. Apolipoprotein E genotype determines survival in the oldest old (85 years or older) who have good cognition. *Arch Neurol*. 1996;53:418-422.
 45. Asada T, Yamagata Z, Kinoshita T, Kinoshita A, Kariya T, Asaka A, Kakuma T. Prevalence of dementia and distribution of ApoE alleles in Japanese centenarians: an almost-complete survey in Yamanashi Prefecture, Japan. *J Am Geriatr Soc*. 1996;44:151-155.
 46. Sobel E, Louhija J, Sulkava R, Davanipour Z, Kontula K, Miettinen H, Tikkanen M, Kainulainen K, Tilvis R. Lack of association of apolipoprotein E allele $\epsilon 4$ with late-onset Alzheimer's disease among Finnish centenarians. *Neurology*. 1995;45:903-907.
 47. Meyer MR, Tschanz JT, Norton MC, Welsh-Bohmer KA, Steffens DC, Wyse BW, Breitner JC. APOE genotype predicts when—not whether—one is predisposed to develop Alzheimer disease [letter]. *Nat Genet*. 1998;19:321-322.

Correction



Error With Figure. The Cover figure for the December issue of the ARCHIVES, in addition to the thumbnail figure that follows (*Arch Gen Psychiatry*. 2002;59:1083-1084) is reversed in orientation. Please see the **Figure** herein to see the image as it should have appeared.