

Variability of Familial Risk of Alzheimer Disease Across the Late Life Span

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Context: The role of genetic factors in Alzheimer disease (AD) varies across the late life span, complicating efforts to quantify the risk of AD for relatives of probands with AD.

Objectives: To visualize the changing levels of familial risk according to proband onset age and the age of the at-risk relative and to determine the familiarity of age at onset in AD.

Design: A retrospective, informant-based family study.

Setting, Patients, and Other Participants: Siblings and parents of probands with AD (relatives=4687; probands=904), ascertained at geriatric clinic and nursing home settings, and of elderly probands without dementia (relatives=7649; probands=1525) who were spouses of probands, participants at senior centers, or nursing home residents without dementia.

Main Outcome Measures: Informant-based assessments of AD in the relatives were used to generate 3-dimensional surfaces representing the patterns of risk of AD across the late life span depending on the specific onset age of the proband with AD (or assessment age of the

elderly proband without dementia). We then constructed a 3-dimensional, age-specific, 10-year hazard rate ratio (HRR) surface representing the relative risk of AD in relatives of probands with AD with smoothly shifting levels of onset age compared with relatives of elderly probands without dementia.

Results: The HRR surface peaked (HRR, 13.0) for younger sexagenarian relatives related to probands with AD with onset age in their early 60s. The HRRs dropped sharply both as the proband age at onset and the age of the relative increased. For relatives aged in their late 80s, the HRR fell lower than 2.0 regardless of proband onset age and their lower-limit 95% confidence intervals were less than 1.0.

Conclusions: The role of genetic risk factors decreases with increasing onset age of the proband with AD regardless of the age of the relatives themselves. The familiarity of onset age is greatly reduced at later ages. The role of environmental risk factors in AD likely increases with onset age.

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NUMEROUS REPORTS INDICATE that first-degree relatives of patients with Alzheimer disease (AD) have an increased risk for this disease.¹ However, the variable role of genetic factors in AD complicates efforts to quantify the risk to relatives. A small fraction of AD cases have an autosomal dominant mendelian variant associated with very early onset.² The risk of AD arising after around age 60 years is influenced by the apolipoprotein E (*APOE*) genotype where the $\epsilon 4$ allele increases the risk of AD compared with the more common $\epsilon 3$ allele.³ While a major risk factor, the *APOE* $\epsilon 4$ allele does not explain all or perhaps even most of the familial aggregation in AD^{2,4}; other unidentified or un-

confirmed genes likely also affect the level of risk of AD as well as nongenetic factors.^{2,4,5} Also, studies dichotomizing probands with AD at certain onset-age cut points (eg, age 70 or 85 years) have shown that relatives of probands with earlier onset face a greater risk of AD than relatives of probands with later onset.⁶⁻⁸ Finally, even as the absolute risk of AD increases with age, the relative risk in family members of probands with AD is highest at early ages and decreases with increasing age.⁸ Thus, no single relative risk statistic or one cumulative risk curve is uniformly appropriate for risk estimation for all relatives of probands with AD.

More specific risk estimation requires a comprehensive investigation of a large proband sample in which the varying ef-

fects of proband onset age and the age of the at-risk relatives can be conjointly examined. (Even greater accuracy would be achieved through stratifying by *APOE* genotype, but this is typically unavailable for clinical purposes or genetic counseling⁹⁻¹² and the sample requirements would be many times multiplied.) Rather than using a single arbitrary age cut point, the potentially complex relationship between onset age of the proband and age of the relative would be more fully revealed by displaying the changing levels of relative risk as these 2 parameters vary.

Beyond risk assessment, such an approach might help determine whether age at onset in AD is itself an independently heritable trait and, if so, whether this holds across the late life span. This possibility is especially pertinent since the *APOE* gene has been suggested to be a determinant more of AD onset age than overall disease liability (ie, associated less with whether than when AD arises).¹³⁻¹⁵ For overall familial risk, determining whether onset age is a heritable trait is not straightforward. For example, correlating onset ages of multiple cases within families (ie, numerator data) fails to consider the changing base rates of disease at different ages and ignores simplex families. A better alternative approach would involve examining whether, across the broad range of proband onset ages, the peak levels of increased relative risk occur at approximately corresponding ages in the at-risk relatives. This approach incorporates the increasing risk associated with age and allows for variability of risk in relatives of probands with AD characterized by onset age.

In the present study, we used informant-based cognitive assessments of relatives of probands with AD and elderly probands without dementia to generate 3-dimensional surfaces representing the patterns of risk (using age interval-specific hazard rates) of AD over the late life span depending on the onset age of the proband with AD (or age at assessment in the elderly probands without dementia). This allowed us to measure the relative risk to family members of probands with AD, using hazard rate ratios (HRR), across smoothly shifting levels of proband age onset compared with relatives of elderly probands without dementia.

METHODS

ASCERTAINMENT OF PROBANDS WITH AD AND ELDERLY PROBANDS WITHOUT DEMENTIA

A detailed description of the recruitment and diagnostic procedures has been described elsewhere.⁸ Briefly, since 1984, concurrent family data collection of both probands with AD and elderly probands without dementia has been conducted using uniform procedures either directly by or supervised by 1 of us (J.M.S.). To provide a wide range of onset ages of probands with AD, probands with AD were ascertained from both clinic (which tends to include more earlier-onset AD) and nursing home (which tends to include more later-onset AD) settings. Probands with at least 1 knowledgeable family informant (>90% of prospective probands) and a clinical diagnosis of AD (n=904) were ascertained from consecutively admitted individuals to the Jewish Home and Hospital, Manhattan and Bronx, NY, (n=266) and consecutively admitted patients in memory disorders clinics associated with the Mount Sinai Alzheimer's Dis-

ease Research Center, New York, NY (n=638). Diagnosis of AD followed *International Classification of Diseases, Ninth Revision (ICD-9)* or the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations' (NINCDS-ADRDA) criteria for probable AD.¹⁶ Combining the probands with AD in this way posed the possibility of a family history status bias associated with the use of different proband diagnostic criteria (NINCDS-ADRDA vs *ICD-9*) and different proband sources (clinic vs nursing home). However, a recent investigation¹⁷ found the familial risk of AD to be identical (relative risk, 1.0) between probands with AD diagnosed by NINCDS-ADRDA vs *ICD-9* criteria. In addition, the cumulative risk curves in relatives of clinic-based and nursing home-based probands with AD were wholly indistinguishable when probands were matched by age at onset. These results justified combining the proband samples. Agreement on age at onset, defined for probands with AD and affected 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 1 and a half years (test-retest reliability) has been found to be very good (both intraclass correlations, 0.91).^{18,19}

Elderly probands without dementia (n=1525) were recruited from: (1) spouses of Mount Sinai Alzheimer's Disease Research Center probands (n=583); (2) spouses of Jewish Home and Hospital residents with and without dementia (n=371); (3) temporary (rehabilitation) residents without dementia at the Jewish Home and Hospital (n=145); and (4) participants in New York City-sponsored senior centers (n=426).²⁰ In all cases, these elderly probands were required to be functional in the community (although physical impairments might be present), to have no subjective memory complaints, and to be able to provide comprehensive, detailed histories regarding themselves, their family of origin, and their spouse (if married). Other details describing the ascertainment of our sample without dementia have been published previously.^{8,20-22} Using a subset of the current sample, the cumulative risk curve for AD in relatives of senior-center participants and that of other elderly probands without dementia were highly similar.²² Finally, we reran these analyses using the present data set and again found very similar risk curves (log rank, 0.04; *P*>.80), justifying the joining of these probands without dementia.

ASSESSMENT OF RELATIVES

The siblings and parents of the probands with AD and elderly probands without dementia were identified by telephone or in person with 1 or more family informants. The Alzheimer's Disease Risk Questionnaire²³ was used to assess birth year, sex, current age (if alive), or age at and cause of death (if not) for each relative. The Alzheimer's Disease Risk Questionnaire was also used to screen for dementia, cognitive impairment, or memory loss of any type, and if suggested, the Dementia Questionnaire¹⁸ was administered. The 50-item Dementia Questionnaire was used to determine whether a dementia was present and, if so, its specific type and age at onset. Alzheimer disease was diagnosed according to previously published criteria¹⁹ similar to *DSM-IV* criteria for dementia of the Alzheimer type²⁴ but modified for informant-based assessment. For AD, this method has had very good interinformant¹⁸ and test-retest¹⁹ reliability. Furthermore, in both our hands and others, the Dementia Questionnaire has shown excellent sensitivity and specificity for identifying dementias ascertained through direct clinical and neuropathological diagnoses.²⁵⁻²⁷ All protocols used were approved by the Mount Sinai institutional review board and the Jewish Home and Hospital, and informed consent was obtained.

Table. Characteristics of Probands with Alzheimer Disease (AD) and Elderly Probands Without Dementia and Their Parents and Siblings

Group	Probands				Parents and Siblings				
	Sample Size	Age, y, Mean (SD)	No. (%) of Women	AD Age at Onset, y, Mean (SD)	Sample Size	Age, y, Mean (SD)	No. (%) of Women	No. of AD Cases	AD Age at Onset, y, Mean (SD)
Probands with AD	904	78 (11)	594 (66)	73 (11)	4687	69 (17)	2438 (52)	393	74 (11)
Elderly probands without dementia	1525	74 (11)	857 (56)	NA	7649	68 (20)	3787 (50)	223	78 (10)

Abbreviation: NA, not applicable.

STATISTICS

We used survival analysis, specifically the actuarial life table method, for the primary statistical procedures.²⁸ This method has typically been used to generate cumulative risk curves and, less frequently, associated age-specific hazard rates and to compare different groups (eg, in relatives of probands with AD vs probands without dementia or relatives of probands with early-onset vs late-onset AD) using hypothesis testing.^{6,8,29,30} In the present study, we used survival analysis in a novel way (ie, to visually examine the risk of AD in first-degree relatives of probands with AD associated with the conjoint, continuous effects of onset age of the proband with AD and the age of the relatives themselves). For this purpose, we constructed 3-dimensional surface plots to provide a smooth graphic representation of the changing pattern of the medium-term (10-year) risk of AD in relatives of probands with AD and relatives of elderly probands without dementia over time and across probands with different onset ages (probands with AD) or ages at assessment (elderly probands without dementia). The kernel statistic for this study was the age interval-specific hazard rates (ie, the per-year risk of disease an individual faces in an age interval given that he or she is alive and at risk at its start). Thus, a single hazard rate statistic is the proportion of cases identified within a given age interval divided by the number of person-years in at-risk relatives living to at least the start of the interval and adjusting for the censorship during the interval.

For probands with AD, we defined groups of probands by whether their onset of AD fell within a specified age range. Similarly, groups of elderly probands without dementia were created according to whether their age at assessment fell within a specified age range. We used 30 different 15-year age ranges from age 53 to 97 years to obtain sufficiently large groups of probands with AD and elderly probands without dementia across the late life span. Each of these proband groups differed from the adjacent groups by a 1-year shift in age range. Thus, for probands with AD, the first group included those with onset between ages 53 and 67 years (median age at onset, 60 years). The second, overlapping, group included those with onset between ages 54 and 68 years (median age, 61 years), the third included those with onset between ages 55 and 69 years (median age, 62 years), and so on until the last group of probands with AD was defined with onsets between ages 83 and 97 years (median age, 90 years). We used the same procedure on the elderly probands without dementia with their age at the time of assessment (15-year intervals shifting, year by year, over the same span of years). The shifting groups of probands created by this procedure were obviously highly overlapping. However, our intent was not to obtain independent estimates of risk and then test the differences between AD groups or between groups of probands with AD and elderly probands without dementia; such testing here would not be appropriate. Instead, our aim was to visually represent the changing levels of medium-

term risk in groups of elderly probands as the onset age gradually increases in probands with AD.

In addition, for each of the overlapping proband groups created, we calculated the 10-year, age-specific hazard rates of the relatives of each group of probands with AD and elderly probands without dementia for every year from age 60 to 90 years. The large number of relatives assessed permitted the use of a 10-year interval for the age-specific hazard rates (as opposed to the 15-year intervals we used to group the probands). Hence, at age 60 years, for each of the overlapping probands with AD (and for the elderly probands without dementia), we calculated the 10-year hazard rate for their associated first-degree relatives (ie, an estimate of their per-year risk of AD between ages 60 and 69 years). Then we did the same at age 61 years, calculating the per-year risk between ages 61 and 70 years. In a given proband group, the change from 1 year to the next would reflect the effect of both dropping the first year in the earlier estimate and adding the next year beyond the earlier estimate. Again, such estimates will be highly overlapping and not appropriate for statistical testing one against another. However, a visual display of these rates would show the gradual change of the medium-term risk over the late life span in a given group of relatives. At the same time, scanning across the proband groupings would show the shifting levels of risk in groups of elderly probands without dementia defined by their relationships to probands with AD with gradually shifting onset ages. In this way, the patterns of risk that emerged would help reveal novel aspects of the complex relationship between proband onset age and the age of at-risk relatives.

We calculated HRRs for relatives in the groups of probands with AD using relatives of the elderly probands without dementia as the reference group. The HRR statistic is the hazard rate from one group (here, the relatives of probands with AD with a given range of age at onsets) over that of the reference group. Similar to a relative risk, the HRR is a measure of the extent to which, at a given age interval, the hazard rate is increased ($HRR > 1.0$) or decreased ($HRR < 1.0$) over the hazard rate in the reference group. The data analysis and associated data plots relied on a program written with S-Plus⁶³¹ developed by 2 of the authors (J.M.S. and G.C.) (available on request).

RESULTS

We assessed 4687 siblings and parents of probands with AD and 7649 siblings and parents of elderly probands without dementia. Demographic characteristics of these 2 samples are presented in the **Table**. The number of person-years among at-risk relatives used to calculate age-specific hazard rates varied according to both onset age of probands with AD (or age at assessment of elderly probands without dementia) and the age of the at-risk rela-

tives (or, for relatives who developed dementia, their age at onset). The contour plots in **Figure 1** present person-years of at-risk relatives of probands with AD and elderly probands without dementia. To be consistent with all subsequent Figures, the x-axes showing increasing age of the relatives run from right to left. Similarly, the y-axes showing increasing onset or assessment age of the probands run from top to bottom. Scanning from right to left, each contour represents a decrement of 500 person-years. Thus, for example, there were approximately 13 500 person-years to assess the 10-year hazard rate from age 65 years among at-risk relatives of probands with AD with a median onset age of 75 years and for relatives of elderly probands without dementia, at the same coordinates, there were approximately 23 000 person-years.

Figure 2 is a 3-dimensional surface plot showing the hazard rates of AD in relatives of probands with AD and, separately, elderly probands without dementia by relative age (x-axis) and by onset age of probands with AD (y-axis) (Figure 2A) or assessment age of elderly probands without dementia (y-axis) (Figure 2B). The z-axis in each plot represents the age-specific, 10-year hazard rate of AD in the relatives of the respective proband groups. Among the relatives of the probands with AD, the rates of AD were zero or very low at early ages across all onset ages of probands with AD. As expected, as the age of the at-risk relatives increased, these rates rose substantially. For relatives of probands with AD with earlier onset ages, however, the rise in hazard rates began earlier, increased more sharply, and reached a higher level than relatives of probands with AD with progressively later onset ages. Figure 2 shows that the 10-year hazard rates for the relatives of the probands with earlier-onset AD peak in the late 70s (indicating highest incidence rates from around age 75 to 85 years), the relatives of the probands with later-onset AD show their peak 10-year hazard rates later, after age 80 years (indicating peak rates from the early 80s to the mid 90s). As expected, the relatives of the elderly probands without dementia also showed increasing 10-year hazard rates with increasing age, but compared with the relatives of probands with AD these rates rose later, did not rise as high, and, while some downward sloping was evident across ages of elderly probands without dementia, they were generally more uniform across the y-axis.

We then assessed the 10-year HRR for the relatives of the probands with AD (**Figure 3**). We chose one 15-year band of elderly probands without dementia (age range, 75-89 years; median age, 82 years) as the reference group. In this group, there were 22 695 person-years available for analysis at age 60 years, 15 070 at age 70 years, 6420 at age 80 years, and 1225 at age 90 years. Hence, all the hazard rates of AD in relatives of probands with AD represented by the surface in Figure 2A were divided by the hazard rates for this single group of relatives of elderly probands without dementia. By holding the reference group constant, variations in HRRs were more easily interpreted. As depicted in Figure 3, the highest HRRs were observed in the youngest relatives (approximately ages 60-63 years) of probands with AD with the earliest onset ages (also approximately ages 60-63 years). From this peak, the HRRs diminished across the

x-axis, across the y-axis, and diagonally across the surface.

Each set of coordinates in Figure 3 represents an HRR and has an associated 95% confidence interval, a function both of the effect size and the size of the sample (which diminishes with increasing age and, hence, increases the uncertainty of the estimate). We calculated the 95% confidence intervals for all the HRRs shown in Figure 3. **Figure 4** is a contour plot of the lower limit of these confidence intervals from less than 0.8 to greater than 2.5. The overall pattern is roughly similar to the HRR values, highest for younger relatives of probands with earlier-onset AD and generally lower in all directions as age in relatives and ages at onset in probands with AD increase. The lower limit confidence intervals did not exceed 1.0 after ages in the early 80s for either the age of relatives or the median onset age of probands with AD.

COMMENT

We used a novel approach to graphically represent the shifting levels of risk of AD in relatives of probands with AD and elderly probands without dementia as onset age of probands with AD (or assessment age in elderly probands without dementia) and the age of a specific relative varies. The risk of AD to relatives of probands with AD not only increases with increasing age at least until the age mid to late 80s, it also varies with the age at onset of the proband with AD, decreasing as the onset age of the proband with AD increases. The 10-year, age-specific hazard rate estimates thus use both smoothly shifting proband onset age and the age of a given relative, providing improved estimation of the risk of illness for first-degree relatives of probands with AD over those without making onset distinctions or using arbitrary dichotomies. These calculations permitted the construction of an HRR surface plot, which revealed the variability of familial risk of AD depending on the onset age of the proband as well as the age of the relative. In addition, the surface observed was influenced by the use of elderly probands without dementia aged 75 to 89 years who, by virtue of their age and dementia-free status, may be less likely to carry genetic risk factors, such as APOE e4, for AD (and perhaps more likely to have genetically influenced increased longevity). A younger reference group, with greater likelihood of genetic liability for AD, would likely reduce to some extent the heights observed on the HRR surface.

The HRR surface helps to evaluate several competing hypotheses regarding familial aggregation in later-onset (≥ 60 years) AD. One hypothesis regarding the influence of genetic risk factors in AD is that, with the obvious exception of the very early-onset (typically < 55 years), mendelian-transmitted AD, they are essentially uniform across late life.³² If this were so, then the HRRs would not vary by onset age of the proband with AD or relative age. On a 3-dimensional plot, a surface representing the HRRs for different proband onset ages and relative ages would tend to be flat. A second hypothesis is that the onset age of AD itself is a familial trait across the late life span. Under this hypothesis, HRRs would be highest approximately around the point where the

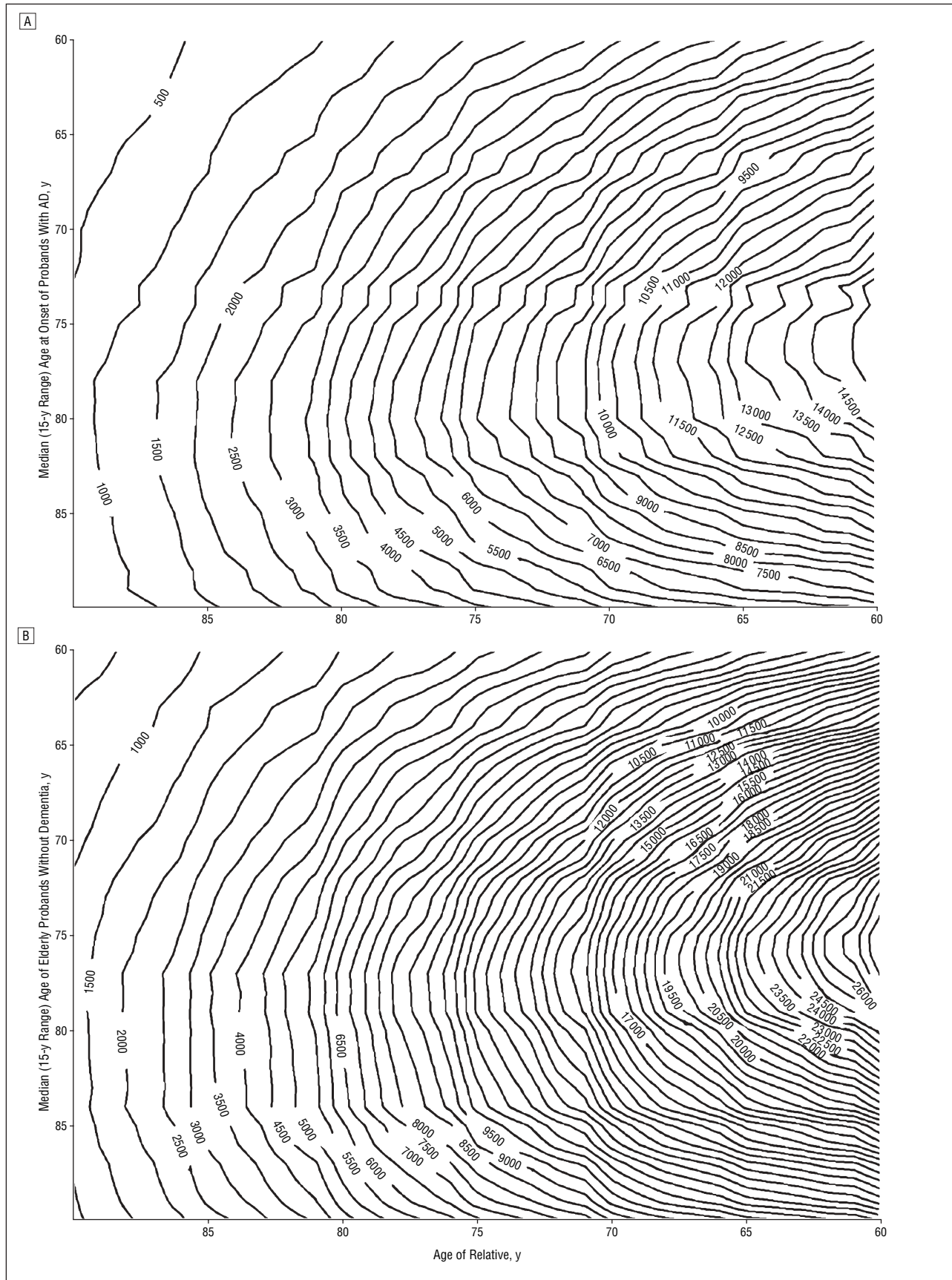


Figure 1. The numbers of person-years (in increments of 500) for relatives of probands with Alzheimer disease (AD) (A) and elderly probands without dementia (B) by the age of the relatives (the x-axis) and the age at onset (probands with AD) or age at interview (elderly probands without dementia) of the probands (y-axis). For consistency with subsequent figures, ages descend from left to right on the x-axis and from top to bottom on the y-axis.

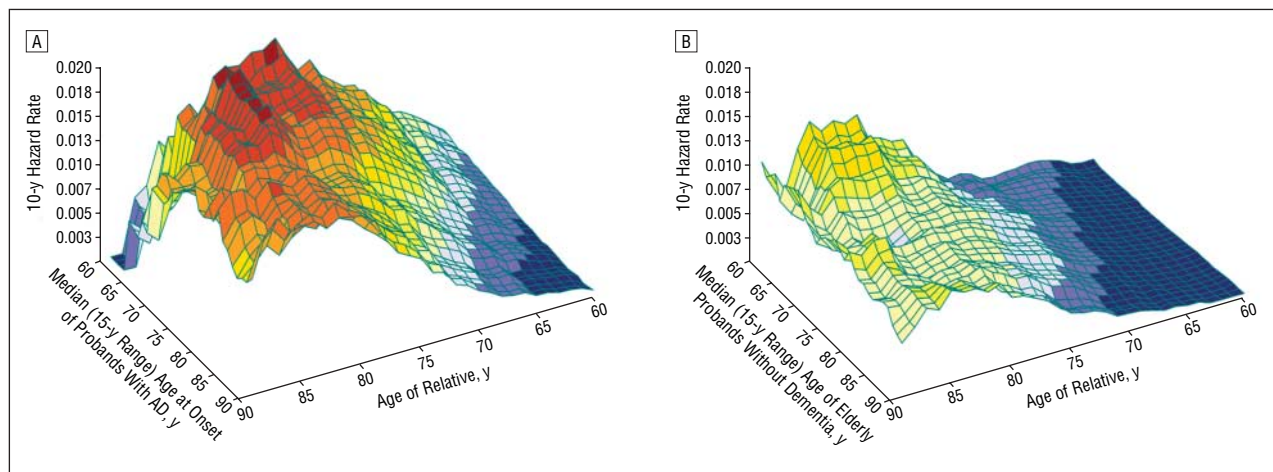


Figure 2. The 10-year hazard rates of Alzheimer disease (AD) (z-axis) in relatives of probands with AD (A) and elderly probands without dementia (B) by relative age (x-axis) and the age at onset (probands with AD) or age at interview (elderly probands without dementia) of the probands (y-axis).

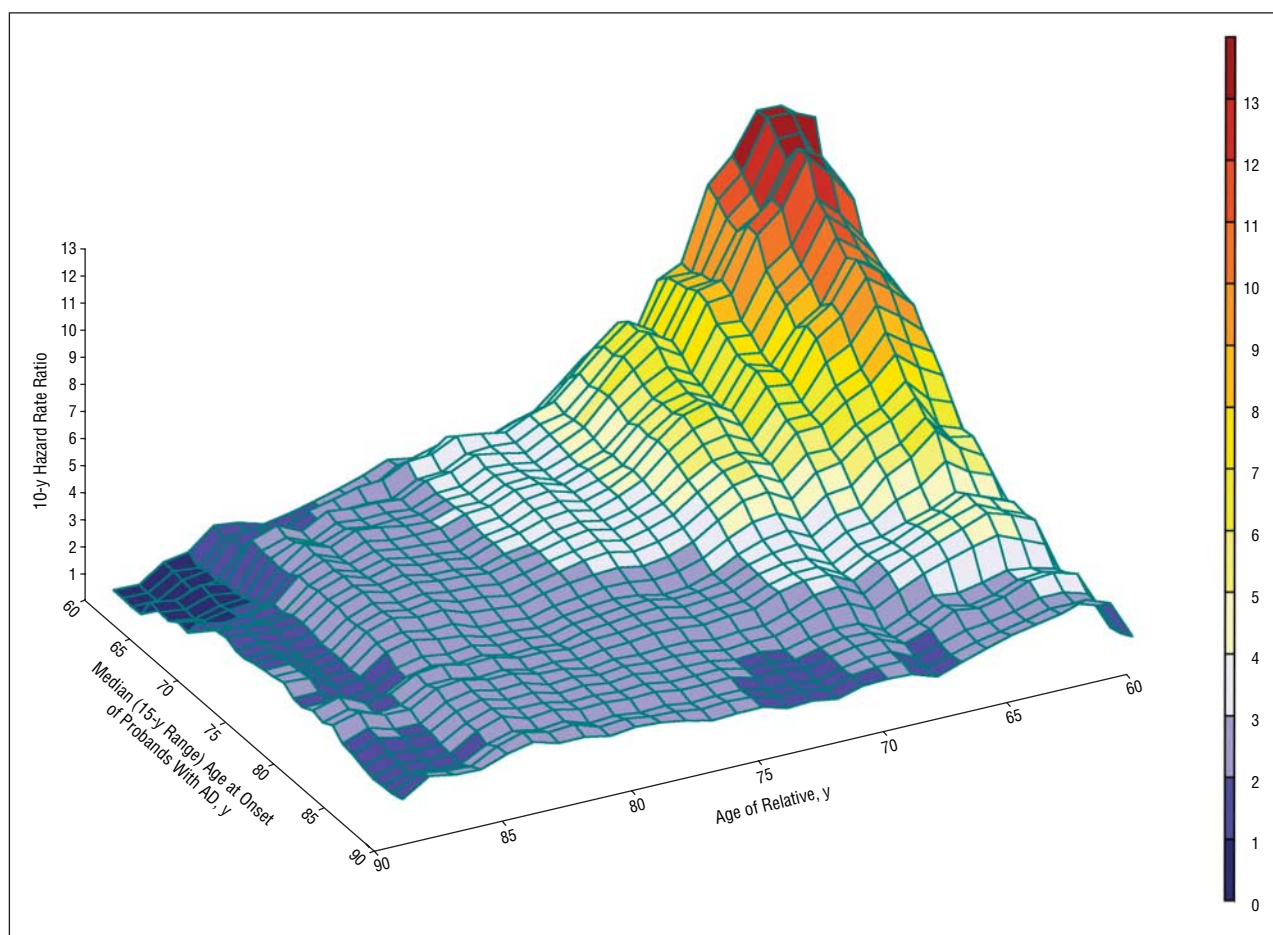


Figure 3. The 10-year hazard rate ratio of Alzheimer disease (AD) (z-axis) in relatives of probands with AD against the reference group, relatives of elderly probands without dementia aged 75 to 89 years (median age, 82), by relative age (x-axis) and the onset age of the probands with AD (y-axis).

proband onset age and the age of relatives coincide. On a surface plot, this would create a diagonal ridge running approximately from the proband with early-onset AD/younger relative age corner to the proband with late-onset AD/older relative age corner. As the base rate in the reference group increases with age, the n-fold increase in the HRR for relatives of probands with AD may

be subject to a ceiling effect. Even so, under the hypothesis that onset age is a heritable trait across the late life span, a diagonal ridge (or bulge) on the HRR surface plot would still be evident, albeit with a declining slope.

The HRR surface supports neither of these 2 hypotheses; the surface is neither flat nor is any ridge present across the full diagonal. Instead, the plot shows a ridge

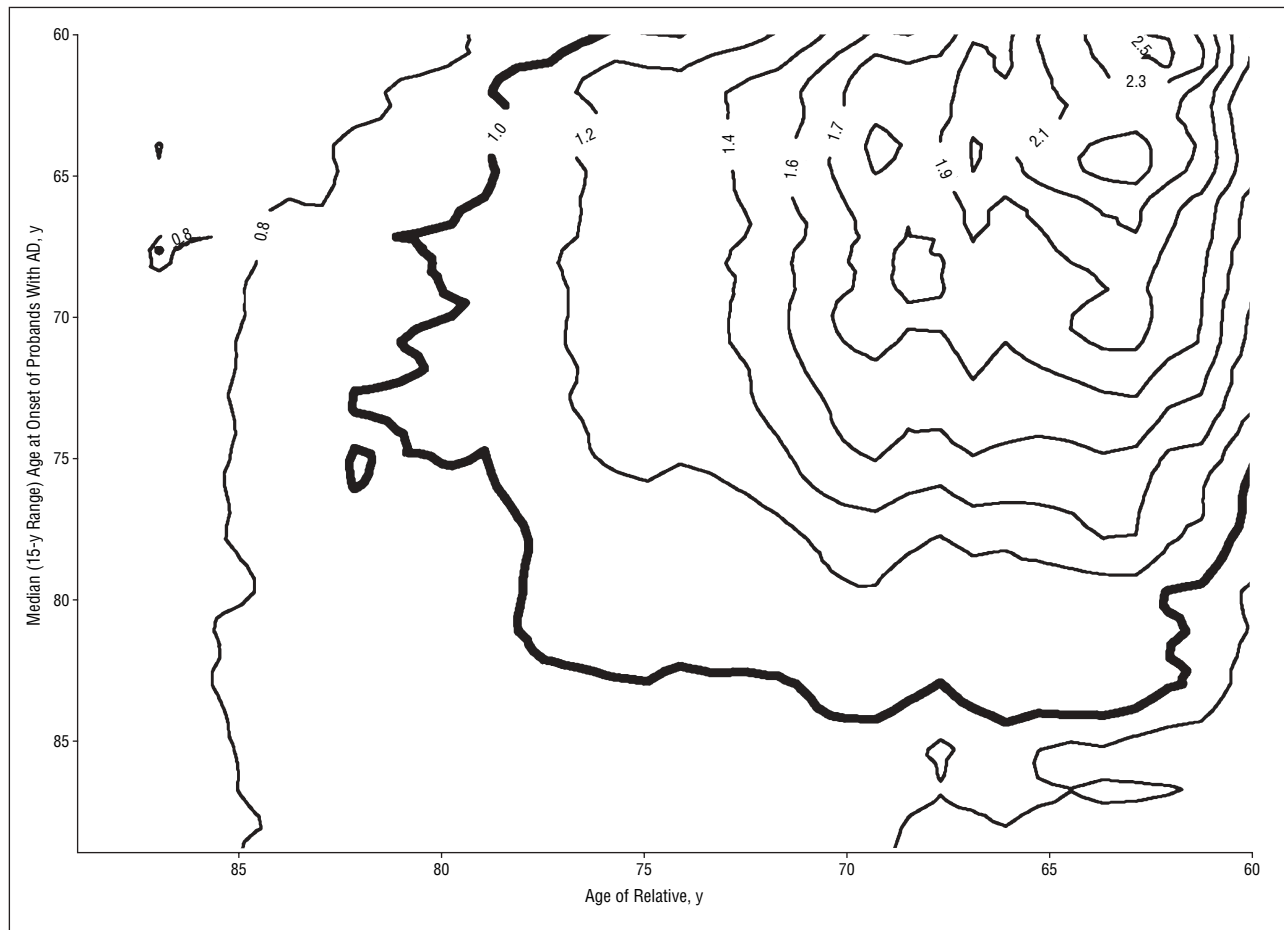


Figure 4. The lower limit of the 95% confidence intervals for the associated hazard rate ratios (Figure 3) by the age of the relatives (x-axis) and the age at onset of the probands with Alzheimer disease (AD) (y-axis).

running straight along the lines of the younger sexagenarian relatives (approximately between ages 61-63 years, inclusive). This ridge has a distinct peak at the early 60s proband onset age/early 60s relative age corner and then slopes downward with increasing proband onset age. Also from this peak and the higher portions of the ridge (ie, earlier proband onset ages) there is a steep slope as the age of relatives increases to the early 70s. The flattest and lowest section is in the quadrant for older (≥ 70 years) relatives of probands with later onset (≥ 75 years). For all of these relatives, the lower 95% confidence intervals fell lower than 1.0 after the early 80s. It is possible that with a larger sample of very old relatives more of the lower-limit confidence intervals associated with these HRRs would have been greater than 1.0, but it is the observed pattern of risk observed herein that is most telling. The decreasing HRRs with increasing age of the relatives, of course, refer to decreasing relative risks. Relatives of probands with AD still face an increasing risk of AD with increasing age (at least until the oldest age ranges). However, the rate of growth among the relatives of the probands with AD becomes comparable with the risk of AD among elderly probands without dementia with increasing age. These data thus support a third hypothesis, that genetic risk factors for AD primarily affect the expression of AD at onset ages in the seventh and, to a lesser extent, the eighth decade. Regardless of the age at

onset of the proband with AD, however, familial/genetic risk factors explain much less of the occurrence of AD arising among the oldest old, when AD incidence is highest.

Until relatively recently, there was little evidence available supporting the widely held assumption that genetic risk factors have a diminished role in later-onset AD compared with clinically identified early-onset AD. A recent twin study, for example, failed to detect differences in heritability of incident AD at younger and older ages,³³ but the sample was small (reducing power), and only the heritability estimate for the younger twin pairs was significant.³⁴ Also, in earlier family history studies using the conventional but arbitrary onset age of 65 years to divide early-onset from late-onset probands, no differences in familial aggregation were identified.^{6,7,35-38} However, as familial investigations used larger samples and considered age-specific HRRs or alternative proband onset ages to define early vs late onset, compelling evidence suggesting decreasing influence of genetic risk with increasing age began to accrue.^{6-8,22} The sole definitive genetic risk factor for AD, *APOE*, is most potent primarily prior to age 70 or 75 years and has little to no impact in late life^{3,39-47} and may affect the age at onset of AD more than overall lifetime susceptibility.¹³⁻¹⁵

The HRR surface plot can be used to estimate the medium-term (10-year) relative risk of AD that is associ-

ated with a first-degree relationship with someone with AD. For example, a 67-year-old woman may be concerned about the level of increased risk she faces because her father developed AD at age 75 years. Using the HRR plot, one can find an optimized estimate of her present 10-year HRR by determining the z coordinate at the intersection of her own age, 67 years (the x-axis), and her father's onset age, 75 years (the y-axis). Thus, this woman faces an approximately 8-fold increased risk of AD over the next 10 years compared with family members of elderly probands with dementia between 75 and 89 years of age (the reference group used to derive the HRRs). In contrast, the optimized estimate for another 67-year-old woman whose mother developed AD at age 84 years faces an approximately 3-fold increased risk over the next 10 years compared with the same reference group. Comparisons such as these are facilitated by our decision to use a single subgroup of relatives of elderly probands without dementia (age at assessment, 75-89 years; median age, 82 years) as a reference group to calculate the HRRs for the relatives of the probands with AD. While it must be stressed that these HRRs are approximations only, they nevertheless improve on the use of a single relative risk statistic for family members of all probands with AD and at all ages.

Limitations of this study include our inability to directly verify the cognitive status of the relatives and the possibility that, perhaps especially at very old ages, new cases of AD may be misclassified as unaffected through our informant-based methods and rates of censorship will increase. Similarly, in the absence of neuropathological confirmation, proband classification is vulnerable to error. Concerning relatives, like most familial aggregation studies of very late-onset disorders, those of greatest interest would have been missed under the usually desirable direct family study approach because most affected relatives had already died along with most of the oldest relatives. Furthermore, studies of the family history method show good reliability and good agreement for both relatives of probands with AD and elderly probands without dementia and classification agrees well with independently derived clinical assessments and neuropathologically derived diagnoses.^{18,19,25-27} Consistent with accurate classification of the elderly probands without dementia, the patterns of rate ratio obtained in their relatives were found to be comparable with those in US population-based incidence studies (comparison data not shown). Finally, the observed patterns of familial risk in this study do not depend on the precise numbers of those with and without dementia identified among the relatives but on relative differences among the groupings of relatives of probands with AD and elderly probands without dementia. Provided such occasional errors are not disproportionately associated with 1 group, given the large sample sizes used, the overall patterns of risk are likely to be robust.

The results provide evidence that in relatives of probands with AD the role of genetic risk factors steadily decreases with increased age and as the onset age of the proband with AD increases. By genetic risk factors, we mean alleles for genes associated with an increased risk compared with the most common alleles. Our results do not

suggest that genetics per se play no role in later-onset AD. Rather, they suggest that liability alleles involved in the pathophysiologic features of very late-onset AD may be so ubiquitous, perhaps even monomorphic, that no differences in risk can be discerned between relatives of probands with AD and elderly probands without dementia. Identifying such genes may ultimately depend on studying families of cognitively successful, very elderly individuals (ie, studying atypical families who may carry rare genetic protective factors). With respect to nongenetic factors associated with AD, because there is still variability at any given late age among those who develop AD and those who don't, studying elderly probands without dementia showing the HRR levels closest to 1.0 may be an especially ideal target for identifying environmental AD risk factors; the present results suggest that such factors are likely to have a disproportionately strong role in very old age.

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REFERENCES

1. Hendrie HC. Epidemiology of dementia and Alzheimer's disease. *Am J Geriatr Psychiatry*. 1998;6:S3-18.
2. Tanzi RE, Bertram L. New frontiers in Alzheimer's disease genetics. *Neuron*. 2001; 32:181-184.
3. 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.
4. Li G, Silverman JM, Altstiel LD, Haroutunian V, Perl DP, Purohit D, Birstein S, Lantz M, Mohs RC, Davis KL. Apolipoprotein E-epsilon 4 allele and familial risk in Alzheimer's disease. *Genet Epidemiol*. 1996;13:285-298.
5. Papassotiropoulos A, Streffer JR, Tzolaki M, Schmid S, Thal D, Nicosia F, Iakovidou V, Maddalena A, Lutjohann D, Ghebremedhin E, Hegi T, Pasch T, Traxler M, Bruhl A, Benussi L, Binetti G, Braak H, Nitsch RM, Hock C. Increased brain beta-amyloid load, phosphorylated tau, and risk of Alzheimer disease associated with an intronic CYP46 polymorphism. *Arch Neurol*. 2003;60:29-35.
6. 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.
7. 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.
8. Silverman JM, Smith CJ, Marin DB, Mohs RC, Propper CB. Familial patterns of risk in very late-onset Alzheimer disease. *Arch Gen Psychiatry*. 2003;60:190-197.
9. Statement on use of apolipoprotein E testing for Alzheimer disease: American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer disease. *JAMA*. 1995;274:1627-1629.
10. Farlow MR. Alzheimer's disease: clinical implications of the apolipoprotein E genotype. *Neurology*. 1997;48:S30-S34.

11. Relkin NR, Kwon YJ, Tsai J, Gandy S. The National Institute on Aging/Alzheimer's Association recommendations on the application of apolipoprotein E genotyping to Alzheimer's disease. *Ann N Y Acad Sci.* 1996;802:149-176.
12. McConnell LM, Koehn BA, Greely HT, Raffin TA. Genetic testing and Alzheimer disease: has the time come? Alzheimer Disease Working Group of the Stanford Program in Genomics, Ethics & Society. *Nat Med.* 1998;4:757-759.
13. Bennett C, Crawford F, Osborne A, Diaz P, Hoyne J, Lopez R, Roques P, Duara R, Rossor M, Mullan M. Evidence that the APO E locus influences rate of disease progression in late onset familial Alzheimer's disease but is not causative. *Am J Med Genet.* 1995;60:1-6.
14. 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.
15. Khachaturian AS, Corcoran CD, Mayer LS, Zandi PP, Breitner JC. Apolipoprotein E epsilon4 count affects age at onset of Alzheimer disease, but not lifetime susceptibility: the Cache County Study. *Arch Gen Psychiatry.* 2004;61:518-524.
16. 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.
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. 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.
19. 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.
20. 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.
21. 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.
22. 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 [see comments]. *Arch Gen Psychiatry.* 1994;51:577-586.
23. Breitner JC, Folstein MF. Familial Alzheimer's disease: a prevalent disorder with specific clinical features. *Psychol Med.* 1984;14:63-80.
24. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.* Washington, DC: American Psychiatric Association; 1994.
25. Ellis RJ, Jan K, Kwas C, Koller WC, Lyons KE, Jeste DV, Hansen LA, Thal LJ. Diagnostic validity of the dementia questionnaire for Alzheimer disease. *Arch Neurol.* 1998;55:360-365.
26. Kwas C, Segal J, Stewart WF, Corrado M, Thal L. A validation study of the Dementia Questionnaire. *Arch Neurol.* 1994;51:901-906.
27. 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.
28. Klein JP, Moeschberger ML. *Survival Analysis: Techniques for Censored and Truncated Data.* New York, NY: Springer-Verlag; 1997.
29. Heun R, Papassotiropoulos A, Jessen F, Maier W, Breitner JC. A family study of Alzheimer disease and early- and late-onset depression in elderly patients. *Arch Gen Psychiatry.* 2001;58:190-196.
30. Li G, Silverman JM, Mohs RC. Clinical genetic studies of Alzheimer's disease. *Psychiatr Clin North Am.* 1991;14:267-286.
31. *S-Plus 6 for Windows.* Seattle, Wash: Insightful Corp; 2002.
32. Ashford JW, Mortimer JA. Non-familial Alzheimer's disease is mainly due to genetic factors. *J Alzheimers Dis.* 2002;4:169-177.
33. Pedersen NL, Gatz M, Berg S, Johansson B. How heritable is Alzheimer's disease late in life? findings from Swedish twins. *Ann Neurol.* 2004;55:180-185.
34. Silverman JM. Comment on news and primary papers: Swedish twins suggest environment trumps genes in late-onset AD [Alzheimer Research Forum Web site]. December 19, 2003. Available at: <http://www.alzforum.org/new/detailprint.asp?id=934>. Accessed January 6, 2004.
35. Breitner JC, Silverman JM, Mohs RC, Davis KL. Familial aggregation in Alzheimer's disease: comparison of risk among relatives of early- and late-onset cases, and among male and female relatives in successive generations. *Neurology.* 1988;38:207-212.
36. 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), Part 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.
37. Huff FJ, Auerbach J, Chakravarti A, Boller F. Risk of dementia in relatives of patients with Alzheimer's disease. *Neurology.* 1988;38:786-790.
38. Farrer LA, O'Sullivan DM, Cupples LA, Growdon JH, Myers RH. Assessment of genetic risk for Alzheimer's disease among first-degree relatives. *Ann Neurol.* 1989;25:485-493.
39. Scacchi R, De BL, Mantuano E, Donini LM, Vilardo T, Corbo RM. Apolipoprotein 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.
40. 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.
41. 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. *Dementia.* 1996;7:251-255.
42. Graff-Radford NR, Green RC, Go RC, Hutton ML, Edeki T, Bachman D, Adamson JL, Griffith P, Willis FB, Williams M, Hipps Y, Haines JL, Cupples LA, Farrer LA. Association between apolipoprotein E genotype and Alzheimer disease in African American subjects. *Arch Neurol.* 2002;59:594-600.
43. Juva K, Verkkoniemi A, Viramo P, Polvikoski T, Kainulainen K, Kontula K, Sulkava R. APOE epsilon4 does not predict mortality, cognitive decline, or dementia in the oldest old. *Neurology.* 2000;54:412-415.
44. Frisoni GB, Manfredi M, Geroldi C, Binetti G, Zanetti O, Bianchetti A, Trabucchi M. The prevalence of apoE-epsilon4 in Alzheimer's disease is age dependent. *J Neurol Neurosurg Psychiatry.* 1998;65:103-106.
45. 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.
46. 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.
47. Skoog I, Hesse C, Fredman P, Andreasson LA, Palmertz B, Blennow K. Apolipoprotein E in cerebrospinal fluid in 85-year-old subjects: relation to dementia, apolipoprotein E polymorphism, cerebral atrophy, and white matter lesions. *Arch Neurol.* 1997;54:267-272.