

Familial Aggregation of Alzheimer Disease Among Whites, African Americans, and Caribbean Hispanics in Northern Manhattan

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Background: Alzheimer disease (AD) aggregates in families.

Objective: To compare the familial aggregation and lifetime risk of AD to the age of 90 years in the first-degree relatives of patients with AD and unrelated controls among Caribbean Hispanics, African Americans, and whites in Washington Heights, Manhattan, New York, NY.

Methods: Family history of AD and demographic information were obtained from informants of 435 patients with probable or possible AD concerning 1577 siblings and parents and from 1094 controls without dementia concerning 3952 siblings and parents.

Results: Lifetime risk of AD to the age of 90 years was 25.9% in relatives of patients and 19.1% in relatives of

controls. Rate ratio (RR) for AD in relatives of patients compared with relatives of controls was 1.5 overall (95% confidence interval [CI], 1.2-1.9), and was greater for siblings (RR, 1.8; 95% CI, 1.2-2.5) than for parents (RR, 1.2; 95% CI, 0.9-1.8). Within ethnic groups, RR for AD among relatives was significantly elevated in whites (RR, 2.0; 95% CI, 1.2-3.3) and Hispanics (RR, 1.5; 95% CI, 1.1-2.1), but the difference did not reach statistical significance in African Americans (RR, 1.4; 95% CI, 0.7-2.7). Risk of AD was greater among relatives who were women compared with men (RR, 1.5; 95% CI, 1.2-1.9).

Conclusions: Familial aggregation of AD was increased among families of patients compared with those of controls in all 3 ethnic groups. Risk of AD was highest among siblings and women relatives.

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ALZHEIMER DISEASE (AD) aggregates in the families of patients with both early- and late-onset disease.^{1,2} Genetic or environmental factors such as collective exposure to occupational hazards or viral or other infections may explain familial aggregation of AD.³⁻⁵ Mutations in 3 genes on chromosomes 1, 14, and 21 result in an autosomal dominant form of AD with early onset.⁶⁻⁸ The $\epsilon 4$ isoform of the apolipoprotein E gene on chromosome 19 is also associated with increased risk for AD.^{9,10} However, the familial distribution of late-onset AD is seldom consistent with a simple mendelian model of inheritance.

Various studies¹¹⁻¹⁶ have evaluated familial aggregation of AD in both clinic- and population-based samples, and estimates of the lifetime risk of AD in first-degree relatives range widely, from 17% to 67%. Population-based studies¹⁷ are a more accurate reflection of familial aggregation of AD than clinic-based samples because the latter tend to be biased toward families with

multiple affected members. Although some large population studies such as the Canadian Study of Health and Aging¹⁸ and others^{19,20} have evaluated familial aggregation of AD predominantly in whites, familial aggregation of AD has not yet, to our knowledge, been investigated in a multi-ethnic urban population.

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We used the "reconstructed cohort" approach to investigate familial aggregation, estimating the cumulative risk of AD in first-degree relatives of patients with AD compared with first-degree relatives of controls without dementia. The alternative method is to compare the proportion of patients and controls with a family history of AD (ie, ≥ 1 affected relative). The reconstructed cohort method yields better power and allows control for the characteristics of relatives (eg, age, sex) that may influence the risk of AD.

PARTICIPANTS AND METHODS

POPULATION

Patients and controls were part of a community-based, epidemiologic study of aging and dementia in Manhattan. As previously described,^{24,25} a random sample of 50% of all persons older than 65 years, residing in the area and receiving Medicare, was obtained from the Health Care Finance Administration (HCFA). All persons were sent a letter from HCFA explaining that they had been selected to participate in a study of aging by investigators at Columbia University, New York, NY. Participation rate was 68% in the HCFA-based random sample and did not differ by ethnic group. The sample was enriched by participants from a previously established dementia registry, which included patients with AD and controls from the same community. A more detailed description of the dementia registry is provided elsewhere.²⁴ Recruitment in both the HCFA-based random sample (73.3%) and the dementia registry (26.7%) was carried out without regard to family history status, and participants were not aware of the goals of this particular study. All individuals provided informed consent for an ongoing longitudinal study on aging.

Ethnicity was classified by participants' self-reports as described previously²⁵ into white, African American, and Hispanic. Using the 1990 US Census questionnaire as a guide, participants were asked if they considered themselves white, black, or other, and then asked if they were Hispanic.²⁶ If Hispanic, the country in which they were born was queried. Most (84.2%) of those classified as Hispanic were of Caribbean origin, predominantly from the Dominican Republic, with the remainder from Mexico and Central America.

DIAGNOSIS IN PATIENTS AND CONTROLS

All patients and controls received structured neurologic and functional assessments by physicians, and a 1½-hour neuropsychological battery, encompassing memory, language, abstraction, and orientation subtests, administered by trained testers.²⁷ The diagnosis of probable or possible AD was made by a consensus group of neurologists and psychologists after review of these assessments, independent of family history. Controls were defined as participants without evidence of cognitive impairment on neuropsychological examination or a neurologic disorder. Patients were defined by National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria to be anyone with probable or possible AD,²⁸ including those with very mild AD (clinical dementia rating scale score of 0.5).²⁹

FAMILY HISTORY QUESTIONNAIRE AND DIAGNOSIS IN RELATIVES OF PATIENTS AND CONTROLS

After the consensus conference established the presence or absence of AD, informants for the patients, who were most often spouses, children, or siblings of patients, received a previously validated, structured family history interview over the telephone.²³ Controls were interviewed directly. Demographic characteristics for each first-degree relative were

collected. Screening questions for AD were "Did (does) this person have memory problems or AD?" and "Was (is) this person unable to care for himself/herself?" If either screening question was endorsed, the following questions were then asked:

1. Did the person have a gradual and progressive loss of memory?
2. Was the person confused and disoriented most of the time?
3. Did the person have difficulty recognizing family members?
4. Was the person seen by a physician for this condition? Was the diagnosis AD?
5. Was the person seen by a neurologist or a psychiatrist for this condition? Was the diagnosis AD?
6. Was there an autopsy indicating AD?

An algorithm was created to generate the final diagnosis of probable AD for each first-degree relative. If questions 1 through 3 were answered no, the relative was classified as unaffected. If only 1 of these questions was answered affirmatively, the relative was classified as doubtful and included in the analysis as unaffected. If at least 2 of the 3 questions were answered affirmatively or if the person had been diagnosed as having AD (questions 4-6), the relative was classified as affected.

DATA ANALYSIS

We used χ^2 analysis and the *t* test to evaluate differences in demographic characteristics between patients, controls, and their relatives. We excluded relatives whose current age or age at death was 29 years or younger, and all children of patients and controls. There were too few children 30 years or older to evaluate separately. We estimated the rate ratio (RR) for AD among first-degree relatives of patients and controls using a maximum likelihood-based survival analysis model with double censoring for missing information.²⁴ Left censoring was applied when a relative was known to have AD but the onset date was unknown (prevalent cases). Right censoring was applied when AD was never diagnosed in a relative, or when the relative died before diagnosis of AD. The current age or age of death of the relative, or the actual age at onset of AD as reported by the informant, was used when available.

This maximum likelihood method allowed the entire sample of relatives to be used to estimate the cumulative incidence and RR of AD in the first-degree relatives of patients vs relatives of controls.²⁴ The RR was also computed after adjusting for the independent effects of sex of proband and relative, ethnicity, relationship to proband (parent or sibling), and education of the proband as both a dichotomous (≤ 8 years or > 8 years) and a continuous variable. The median value for education in the population was 8 years.

We used the proband's educational value as an approximation for the relative's value because for many relatives this value was unknown by the informant. When the education variable was not missing in the relative, it correlated well with the proband's education (**Table 1**). In addition, in a prior study²³ of this population, the proband's educational level correlated highly with that of both the relative and the informant ($P < .001$).

Table 1. Demographic Features of Probands and Their Relatives*

| Feature | Controls | Patients With AD | P | Relatives of Controls | Relatives of Patients | P |
|-------------------------|----------|------------------|------|-----------------------|-----------------------|------|
| No. | 1094 | 435 | | 3952 | 1577 | |
| Age, mean (SD), y | 74 ± 6 | 79 ± 8 | .001 | 68.6 ± 15.5 | 69.8 ± 16.4 | .01 |
| Education, mean (SD), y | 9.7 ± 5 | 6.4 ± 4 | .001 | 8.6 ± 5 | 6.3 ± 5 | .001 |
| Sex, No. (%) | | | | | | |
| Male | 338 (31) | 109 (25) | .02 | 2054 (52) | 792 (50) | .20 |
| Female | 756 (69) | 326 (75) | | 1898 (48) | 785 (50) | |
| Ethnic group, No. (%) | | | | | | |
| White | 335 (31) | 57 (13) | .001 | 1147 (29) | 219 (14) | .001 |
| African American | 189 (17) | 112 (26) | | 687 (17) | 362 (23) | |
| Hispanic | 570 (52) | 266 (61) | | 2118 (54) | 996 (63) | |
| Relationship | | | | | | |
| Parent of proband | ... | ... | ... | 1943 (49) | 680 (43) | .001 |
| Sibling of proband | ... | ... | | 2009 (51) | 897 (57) | |

*AD indicates Alzheimer disease; ellipses, data not applicable.

We wished to assess the familial aggregation of AD in an urban population of whites, Caribbean Hispanics, and African Americans, and to compare the cumulative incidence of AD to the age of 90 years in relatives of patients and controls. We examined the influence of the proband's education and the relative's sex on the risk of AD in relatives of patients and controls because both have independent effects on risk for AD^{15,21,22} and may affect the accuracy of reporting of AD.²³

RESULTS

Among 9612 parents and siblings of patients with AD and controls with family history information, 4083 (42.5%) were excluded because they were 30 years or younger at the time the family history was obtained or had died at or before the age of 30 years. Thus, 5529 relatives were included in the analysis, 1577 (28.5%) of whom were relatives of 435 patients with AD (relatives per patient, 3.6), and 3952 (71.5%) were relatives of 1094 controls without dementia (relatives per control, 3.6) (Table 1). Of the relatives in the present study, 12.1% were aged 31 to 49 years, 12.6% were 50 to 59 years, 47.2% were 60 to 79 years, 19.5% were 80 to 89 years, and 8.7% were 90 years or older. White relatives were older than African American and Hispanic relatives among both controls (whites, 70 years; African Americans, 67 years; and Hispanics, 68 years; $P < .02$) and patients (whites, 72 years; African Americans, 67 years; and Hispanics, 70 years; $P = .003$).

Controls were younger than patients, more educated, and more likely to be male and white. Relatives of controls were also younger and more educated than relatives of patients but had equal proportions of men and women. Probands and their relatives had similar years of education (Table 1).

A higher proportion of relatives were parents in the control group (49.1%) than in the patient group (42.4%) (Table 1). Age (mean ± SD) at death for parents of patients was 71 ± 16 years, and for parents of controls, 70 ± 17 years. Age (mean ± SD) of death for siblings of patients was 68 ± 15 years, and for siblings of controls, 66 ± 14 years.

Adjusted and unadjusted RRs for the algorithm-derived diagnosis of AD in relatives given the proband's disease status (patient or control) and relative's sex are shown in **Table 2**. Overall adjusted RR for AD among relatives of patients compared with relatives of controls was 1.5 (95% confidence interval [CI], 1.2-1.9, $P = .001$). Female relatives were at higher risk for AD than were male relatives (RR, 1.5; 95% CI, 1.2-1.9, $P < .001$). The RR for AD in relatives of patients vs relatives of controls was elevated among whites (RR, 2.0; 95% CI, 1.2-3.3, $P = .003$) and Hispanics (RR, 1.5; 95% CI, 1.1-2.1, $P < .001$); among African Americans, the increased RR did not reach statistical significance (RR, 1.4; 95% CI, 0.7-2.7, $P = .36$) (Table 2). Adjusted RR was not affected by treating education as a continuous rather than a dichotomous variable.

Risk was increased 1.8-fold ($P = .004$) in siblings of patients compared with those of controls, but only 1.2-fold ($P = .19$) in parents of patients compared with parents of controls (**Table 3**). Among Hispanics, however, there was a 1.6-fold ($P = .04$) significantly increased risk among parents. The RR in siblings was greater in whites (3.8, $P < .001$) than in either African Americans (1.6, $P = .4$) or Hispanics (1.3, $P = .2$). In all 3 ethnic groups, RRs for AD in relatives of AD patients vs controls were similar in relatives of probands with 8 or more years of education and less than 8 years of education (Table 3).

Siblings of patients were at higher risk than those of controls at later years (ages 75-90 years) (**Figure 1**), whereas parents of patients were at higher risk than those of controls in earlier years (ages 65-80 years) (**Figure 2**). Cumulative incidence in relatives of patients was 1.9% by the age of 65 years, 5.8% by 75 years, 15.0% by 85 years, and 25.9% by 90 years. In relatives of controls, cumulative incidence was 2.7% by the age of 65 years, 4.4% by 75 years, 9.8% by 85 years, and 19.1% by 90 years.

Evaluating the data from the proband's perspective, 18.9% of patients with AD and 14.8% of controls reported a family history of AD in a parent or sibling (whites, 22.8% vs 18.5%; African American, 12.7% vs 10.4%; Hispanics, 20.8% vs 14.2%). Five percent of patients reported a family history in 2 or more first-degree relatives compared with 1.4% of the controls ($P < .001$).

Table 2. Proband's or Relative's Characteristics and Adjusted and Unadjusted Rate Ratios for AD in Relatives Stratified by Ethnic Group*

| Proband or Relative Characteristic | Total No. of Relatives | No. (%) With Probable AD | Unadjusted Rate Ratio (95% CI) | Adjusted Rate Ratio (95% CI) |
|------------------------------------|------------------------|--------------------------|--------------------------------|------------------------------|
| Overall | | | | |
| Relatives of patients | 1577 | 113 (7) | 1.4 (1.1-1.7) | 1.5 (1.2-1.9) |
| Relatives of controls | 3952 | 183 (5) | 1.0 (Reference) | 1.0 (Reference) |
| Female relatives | 2683 | 187 (7) | 1.6 (1.2-2.0) | 1.5 (1.2-1.9) |
| Male relatives | 2846 | 109 (4) | 1.0 (Reference) | 1.0 (Reference) |
| Whites | | | | |
| Relatives of patients | 219 | 24 (11) | 1.7 (1.0-2.7) | 2.0 (1.2-3.3) |
| Relatives of controls | 1147 | 67 (6) | 1.0 (Reference) | 1.0 (Reference) |
| Female relatives | 661 | 59 (9) | 1.3 (0.9-2.1) | 1.4 (0.9-2.1) |
| Male relatives | 705 | 32 (5) | 1.0 (Reference) | 1.0 (Reference) |
| African Americans | | | | |
| Relatives of patients | 362 | 16 (4) | 1.4 (0.8-2.8) | 1.4 (0.7-2.7) |
| Relatives of controls | 687 | 22 (3) | 1.0 (Reference) | 1.0 (Reference) |
| Female relatives | 530 | 24 (4) | 1.6 (0.8-3.1) | 1.6 (0.8-3.1) |
| Male relatives | 519 | 14 (3) | 1.0 (Reference) | 1.0 (Reference) |
| Hispanics | | | | |
| Relatives of patients | 996 | 93 (7) | 1.4 (1.0-1.9) | 1.5 (1.1-2.1) |
| Relatives of controls | 2118 | 94 (4) | 1.0 (Reference) | 1.0 (Reference) |
| Female relatives | 1492 | 104 (7) | 1.6 (1.1-2.1) | 1.5 (1.1-2.1) |
| Male relatives | 1622 | 83 (4) | 1.0 (Reference) | 1.0 (Reference) |

*Cox proportional hazards analysis unadjusted and adjusted for proband's sex, education (categorical variable ≤ 8 years and > 8 years), and relative's sex. AD indicates Alzheimer disease; CI, confidence interval.

COMMENT

In this community-based study of an urban, multiethnic population, we found a 50% increased risk for AD among first-degree relatives of patients with AD compared with first-degree relatives of cognitively normal controls. This elevated RR for AD was present in all 3 ethnic groups included in the study but was not significant in African Americans due to the smaller numbers of subjects. The increased RR for AD was present primarily in siblings among whites, and in both siblings and parents of Hispanics. Among relatives of patients and controls combined, women had a 50% greater risk for AD than men.

In a previous analysis of family history data in this community,²³ investigators found that the sensitivity of reporting of a family history of AD increased from 28.6% to 71.4% and the specificity from 83.3% to 100.0% for AD probands as their educational level increased. We therefore adjusted for the proband's education as a confounder in all our analyses.

The lower RRs among African American and Hispanic siblings could be due to lower levels of education in these 2 groups, resulting in greater misclassification of family history and bias toward the null hypothesis. However, stratification on education allowed us to reject this possibility because the greater RR in white siblings was observed within families of both probands with 8 or more years of education. The difference across ethnic groups may be explained by some other, unmeasured factor associated with reporting of a family history of dementia.

Previous studies^{5,18,19} have also reported higher risk in female than male relatives, and increased risk for AD among siblings compared with parents. In 2 large popu-

lation-based studies^{18,19} of primarily white subjects, as well as a reanalysis of 7 case-control studies,⁵ risk for AD among relatives of patients was 3.6 compared with relatives of controls.

Differences in methods may partly explain our more moderately increased RRs. All our patients and controls had neuropsychological batteries rather than Mini-Mental State Examinations. The family history questionnaire was administered by a tester rather than self-administered as in one of the studies.¹⁸ We also used a stringent algorithmic approach to diagnose AD in relatives. Our population was younger and less educated than other population-based studies. If the RR of AD is manifest primarily among siblings and becomes greater with age, as we found, then one would expect a greater RR in older populations.

We chose to use stringent criteria for diagnosis of AD in a relative with our algorithm. In preliminary analyses, we evaluated the use of very liberal, liberal, and stringent criteria for a diagnosis of AD in the relative. We found that when we used liberal criteria to diagnose AD in the relative, the RR *decreased*, probably secondary to the increased misclassification of relatives. Thus, we chose to use more stringent criteria for diagnosis of AD in the relative.

We found that the cumulative incidence of AD among the relatives of patients was 2% by the age of 65 years, 6% by 75 years, and 26% by 90 years. This is comparable to a population-based study by Hirst et al³⁰ of first-degree relatives of AD patients with risks for AD of 2% by the age of 65 years, 6% by 75 years, and 23% by 88 years. At least 1 clinic-based, case-control study¹⁵ found a risk for AD in relatives of patients to be 25% by the age of 86 years, whereas other clinic-based studies—including our own—have reported higher rates of 40% to 50% by the age of 87 years.^{11-14,16,31} However, clinic-

Table 3. Unadjusted Rate Ratios for AD in Relatives of Patients and Controls*

| Relationship, Education, and Ethnicity | Proband's Status | Total No. of Relatives | No. (%) With Probable AD | Rate Ratio (95% CI) |
|--|------------------|------------------------|--------------------------|---------------------|
| All parents | Patient | 680 | 49 (7) | 1.1 (0.8-1.5) |
| | Control | 1943 | 118 (6) | 1.0 (Reference) |
| White | Patient | 96 | 6 (6) | 0.8 (0.4-1.9) |
| | Control | 635 | 52 (8) | 1.0 (Reference) |
| African American | Patient | 164 | 5 (3) | 1.0 (0.3-2.8) |
| | Control | 317 | 11 (4) | 1.0 (Reference) |
| Hispanic | Patient | 420 | 38 (9) | 1.4 (1.0-2.2) |
| | Control | 991 | 55 (6) | 1.0 (Reference) |
| All siblings | Patient | 897 | 64 (7) | 1.7 (1.2-2.4) |
| | Control | 2009 | 65 (3) | 1.0 (Reference) |
| White | Patient | 123 | 18 (15) | 3.8 (1.6-6.5) |
| | Control | 512 | 15 (3) | 1.0 (Reference) |
| African American | Patient | 198 | 11 (6) | 1.6 (0.7-3.8) |
| | Control | 370 | 11 (3) | 1.0 (Reference) |
| Hispanic | Patient | 576 | 35 (6) | 1.3 (0.8-2.1) |
| | Control | 1127 | 39 (4) | 1.0 (Reference) |
| Proband's education ≤8 years | Patient | 1092 | 75 (7) | 1.6 (1.1-2.2) |
| | Control | 1706 | 67 (4) | 1.0 (Reference) |
| Whites | Patient | 81 | 7 (9) | 2.0 (0.6-6.4) |
| | Control | 178 | 5 (3) | 1.0 (Reference) |
| African Americans | Patient | 202 | 9 (5) | 1.3 (0.5-3.4) |
| | Control | 185 | 8 (4) | 1.0 (Reference) |
| Hispanics | Patient | 809 | 59 (7) | 1.6 (1.1-2.3) |
| | Control | 1343 | 54 (4) | 1.0 (Reference) |
| Proband's education >8 years | Patient | 460 | 38 (8) | 1.5 (1.0-2.2) |
| | Control | 2234 | 116 (5) | 1.0 (Reference) |
| Whites | Patient | 135 | 17 (13) | 2.0 (1.2-3.5) |
| | Control | 968 | 62 (6) | 1.0 (Reference) |
| African Americans | Patient | 151 | 7 (5) | 1.6 (0.6-3.9) |
| | Control | 502 | 14 (3) | 1.0 (Reference) |
| Hispanics | Patient | 174 | 14 (8) | 1.4 (0.7-2.5) |
| | Control | 764 | 40 (5) | 1.0 (Reference) |

*AD indicates Alzheimer disease; CI, confidence interval. Data may not total sample size because some respondents did not answer all questions.

based samples may have an overrepresentation of patients with a positive family history.

The increase in RR for AD among parents of patients at earlier ages may be explained by recall bias. Informants may be less likely to report AD in elderly parents than in younger parents. Information regarding siblings of the same generation as the informant would be less likely to be affected by such a bias. Our results are similar to the collaborative reanalysis of familial aggregation studies by Van Duijn et al,⁵ which showed a greater increased risk in siblings than in parents of patients.

Regardless of the disease status of the proband, female relatives had higher risk for AD than male relatives. This supports the finding by Farrer et al⁴ of higher risk among female than male relatives of patients with AD. A large population-based study²¹ of women older than 75 years found that the age-adjusted odds ratio for incident AD among women compared with men was 3.1.

Overall, we found evidence for familial aggregation of AD in all 3 ethnic groups studied. Among African Americans and whites, RRs tended to be higher in siblings than in parents, which was similar to other studies,⁵ whereas among Hispanics, RR was similar for

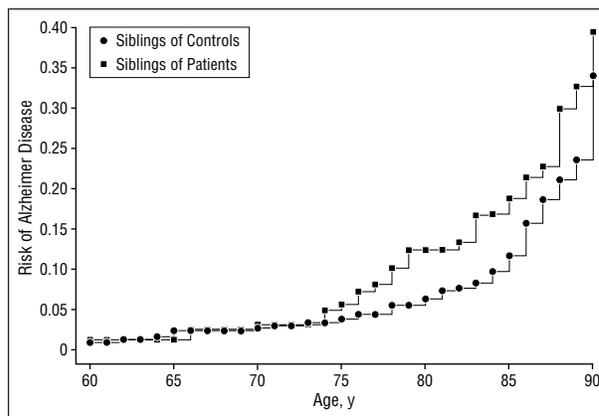


Figure 1. Lifetime risk of Alzheimer disease for siblings.

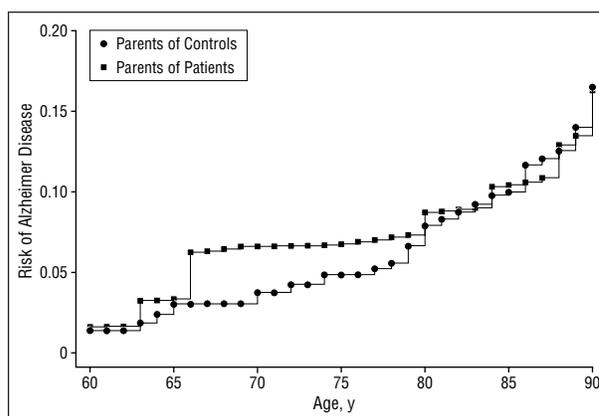


Figure 2. Lifetime risk of Alzheimer disease for parents.

parents and siblings. As in other studies,^{4,21} we found a higher risk for AD in women among all 3 ethnic groups.

Our results need to be interpreted with caution due to some limitations. Since white relatives were older, on average, than African American and Hispanic relatives, the RRs among ethnic groups may have differed slightly. Family history data were obtained from informants for patients and from direct interviews with controls, possibly leading to lower sensitivity of the data for patients than for controls. However, family information bias would possibly result in higher sensitivity of family history in patients than in controls. It is unclear what effects these 2 opposing forces may have had on our RR estimates. In a prior validation study²³ of our family history method, the investigators found that sensitivity of family history data was reasonably high (64%) among relatives of patients; however, that study did not evaluate sensitivity among relatives of controls.

We did not collect data on informants and, thus, could not control for differences in informant characteristics among ethnic groups. However, we did adjust for level of education of the proband (which correlates well with that of the informant) and found that, at higher levels of education, the sensitivity of family history among disparate informant groups was similar. Finally, we could not completely control for factors such as cultural awareness and socioeconomic status that might have influ-

enced the reporting of AD among ethnic groups. However, we attempted to adjust for these confounding factors by including education and sex of both the proband and the relative in all our analyses.

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