Original Contributions

The *APOE*-ε4 Allele and the Risk of Alzheimer Disease Among African Americans, Whites, and Hispanics

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Context.—Although the association between Alzheimer disease (AD) and the apolipoprotein E ε4 (*APOE*-ε4) allele has been confirmed worldwide, it appears to be inconsistent among African Americans, Hispanics, and Nigerians.

Objective.—To investigate the association between the *APOE*-ε4 allele and AD in elderly African Americans, Hispanics, and whites.

Design.—Prospective, population-based, longitudinal study over a 5-year period (1991-1996).

Setting.—The Washington Heights–Inwood community of New York City.

Participants.—A total of 1079 Medicare recipients without AD or a related disorder at baseline.

Main Outcome Measures.—Risk of clinically diagnosed AD in the 3 ethnic groups and among individuals with and without an *APOE*-ε4 allele.

Results.—Compared with individuals with the *APOE*-ε3/ε3 genotype, the relative risk (RR) of AD associated with 1 or more copies of the *APOE*-ε4 allele was significantly increased among whites (RR, 2.5; 95% confidence interval [CI], 1.1-6.4), but not among African Americans (RR, 1.0; 95% CI, 0.6-1.6) or Hispanics (RR, 1.1; 95% CI, 0.7-1.6). In the absence of the *APOE*-ε4 allele, the cumulative risks of AD to age 90 years, adjusted for education and sex, were 4 times higher for African Americans (RR, 4.4; 95% CI, 2.3-8.6) and 2 times higher for Hispanics (RR, 2.3; 95% CI, 1.2-4.3) than for whites. In the presence of an *APOE*-ε4 allele, the cumulative risk of AD to age 90 years was similar for individuals in all 3 ethnic groups.

Conclusion.—The presence of an *APOE*-ε4 allele is a determinant of AD risk in whites, but African Americans and Hispanics have an increased frequency of AD regardless of their *APOE* genotype. These results suggest that other genes or risk factors may contribute to the increased risk of AD in African Americans and Hispanics.

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ALTHOUGH the association between Alzheimer disease (AD) and the apolipoprotein E ε4 (*APOE*-ε4) allele has been confirmed worldwide, it has been found to be weak or nonexistent among African Americans living in New York City[1-3] and Indiana[4] and among Nigerians.[5] Hispanics of Caribbean origin also have an inconsistent association between AD and the *APOE*-ε4 allele.[2,3] While other genetic or environmental factors might account for the reduction in *APOE*-ε4–related AD risks in these ethnic groups compared with whites, none have been

identified. This prospective study was designed to compare the cumulative risk of AD by *APOE* genotypes among elderly African Americans, Hispanics, and whites residing in a New York City community. Based on our previous cross-sectional studies,[1-3] we hypothesized that the risk of AD associated with the *APOE*-ε4 allele would be lower for African Americans and Hispanics than for whites.

METHODS

Subjects and Setting

Participants were healthy Medicare recipients without dementia in 3 contiguous ZIP codes within the community of Washington Heights in northern New York City. According to the 1990 census, 9349 people older than 65 years lived in this area. The Health Care Financing Administration provided access to a random sample of approximately half of these

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recipients. In this group, 4865 individuals were then divided into 37 identical replicates, representing the demographic characteristics of the cohort, sent a letter from the Health Care Financing Administration explaining that they had been randomly selected to participate in a study of aging by investigators at Columbia University, New York, NY. Subsequently, it was determined that 470 (9.7%) had died, 896 (18.4%) no longer lived in the region, 47 (1%) were ineligible, and 1324 (37%) did not wish to participate. The frequency of participation did not differ by sex or subsample. The proportions of individuals within each ethnic group, as identified from Health Care Financing Administration records, differed only slightly between

Table 1.—*APOE* Allele Frequencies by Ethnic Group Among Individuals Who Did and Did Not Develop Alzheimer Disease*

Ethnic Group	*APOE*	Total No. of Alleles	No. (%)†	
			Healthy	Alzheimer Disease
African Americans		362	256 (70.7)	106 (29.3)
	ϵ2	38	26 (10.2)	12 (11.3)
	ϵ3	251	177 (69.1)	74 (69.8)
	ϵ4	73	53 (20.7)	20 (18.9)
Whites		474	428 (90.3)	46 (9.7)
	ϵ2	35	30 (7.0)	5 (10.9)
	ϵ3	377	344 (80.4)	33 (71.7)
	ϵ4	62	54 (12.6)	8 (17.4)
Hispanics		1322	1032 (78.1)	290 (21.9)
	ϵ2	115	91 (8.8)	24 (8.3)
	ϵ3	1019	796 (77.1)	223 (76.9)
	ϵ4	188	145 (14.1)	43 (14.8)

*The distribution of *APOE* allele frequencies differed significantly only by ethnic group (χ^2=13.5, *df*=4, *P*=.009). Within each group, there were no significant differences in allele frequencies between individuals who did or did not develop Alzheimer disease.

†For ethnic groups, the denominator for the percentages is the total number of alleles. For allele frequencies, the denominator for the percentages is the total number of alleles in the healthy or Alzheimer disease category for that ethnic group.

the total sample and those who participated (total sample: African American, 35.4%; Hispanic, 35.4%; white, 29.2%; participants: African American, 35.2%; Hispanic, 38.9%; white, 25.8%).

For the 2128 subjects who participated in the initial phase of the study, a 90-minute, in-person interview of general health and function was completed. This structured interview also included questions about years of formal education and lifetime occupation. The interview was followed by a standardized clinical assessment, including a medical history, physical and neurologic examination, and brief (approximately 1 hour) neuropsychological battery previously developed for use in this community.[6,7] These same clinical assessments were used in the annual follow-up of all participants. This study was conducted from 1991 through 1996. The interviews were conducted in either English or Spanish. The Columbia University Institutional Review Board reviewed and approved this project. All individuals provided written informed consent.

Diagnosis

The data from the initial and follow-up examinations and interviews and any existing medical records and imaging studies were used at a consensus conference of physicians and neuropsychologists to establish diagnoses. The *APOE* genotypes were never available to the clinicians during the diagnostic process. The diagnosis of dementia or the specific clinical diagnosis of AD was based on standard research criteria[8(pp205-224),9] and required evidence of cognitive deficit on the neuropsychological test battery as well as evidence of impairment in social or occupational function. Patients who met the criteria[9] for probable or possible AD with a clinical de-

mentia rating (CDR) scale (range, 0-5) score of 0.5 or higher[10] were considered to have a clinical diagnosis of AD.

Ethnic Group

Ethnic group was classified by self-report using the format of the 1990 US Census.[11] Individuals were then asked whether they were of Hispanic origin. Using this information, individuals were separated into 3 ethnic groups: African American (non-Hispanic), Hispanic, or white (non-Hispanic). Individuals were also asked to identify the country of their birth.

Family History Assessment

A structured family history interview for AD and other neurologic disorders in first-degree relatives (parents and full siblings) was conducted directly with each participant at the first interview.[12]

APOE Genotyping

Genomic DNA was amplified by polymerase chain reaction and subjected to *Cfo*I restriction analysis using APOE primers and conditions modified from those described by Hixson and Vernier.[13]

Data Analysis

Demographic characteristics were compared using χ^2 tests for categorical variables and analysis of variance for continuous variables.[14] Age, ethnic group, and education were compared among those who did and did not develop AD. *APOE* allele frequencies were determined by counting alleles and calculating sample proportions. *APOE* allele frequencies were compared among individuals who did and did not develop AD as well as between ethnic groups using χ^2 tests.

The Cox proportional hazards model[15] was used to compute the relative risks (RRs) of AD. As recommended for longi-

tudinal investigations,[16] the time-to-event variable was age at onset of AD, which required no further age adjustment. Among those who did not develop AD, we right-censored the age at death or the age at the last examination. Survival analysis was used to plot the cumulative incidence of AD at each age interval. Proportional hazards were estimated for *APOE* genotypes with and without an ϵ4 allele and adjusted by education, ethnic group, and sex. A second series of proportional hazards models was stratified by the presence or absence of an *APOE*-ϵ4 allele to estimate the relative risk by ethnic group using whites as the reference. Proportional hazards models were stratified by the median number of years of formal education. Subsequent proportional hazards models included adjustments for a family history of an AD-like dementia; a medical history of hypertension, myocardial infarction, or head injury; and a history of smoking. Martingale methods were used to check the proportional hazards assumption.[17]

RESULTS

Among the 2128 individuals interviewed at baseline, 392 (18.4%) were found to be demented, 155 (7.3%) died after the initial examination, 122 (5.7%) refused to have genotyping performed, and 237 (11.1%) refused subsequent follow-up. The proportions of individuals who were demented at baseline differed among the 3 ethnic groups (African Americans, 24%; Hispanics, 18%; whites, 11%; *P*<.001), as did the proportions of those who died after the baseline evaluation (African Americans, 12%; Hispanics, 4%; whites, 9%; *P*<.001). Compared with Hispanics, a higher proportion of African Americans and whites refused genotyping (4% vs 7% and 8%, respectively; *P*<.001) or were unavailable for follow-up (8% vs 15% and 16%, respectively; *P*<.001). We also found 25 individuals (1.2%) with Parkinson disease, 117 (5.5%) with stroke, and 1 with both Parkinson disease and stroke. Only stroke was more frequent among African Americans than either Hispanics or whites (15% vs 7.8% and 8%, respectively; *P*<.001). This left 1079 healthy elderly (731 women and 348 men) without dementia available for this follow-up investigation.

The mean age of the participants at the beginning in this investigation was 75.3 (SD, 5.8) years and the mean years of education was 8.6 (SD, 4.4). The ethnic distribution of the cohort by self-report differed from that provided by the Health Care Financing Administration. Among the 1079 healthy elderly, 16.8% described themselves as African American, 61.2% as Hispanic, and 22% as white.

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The majority (84%) of those identified as Hispanic were of Caribbean origin, while the remainder were from Mexico and Central America. The mean duration of follow-up was 2.4 (SD, 1.2) years (range, 1-5 years).

Probable or possible AD developed in 221 individuals (20.5%) over the follow-up period. Both probable and possible AD occurred significantly more frequently among African Americans and Hispanics than among whites (probable AD: 10.5%, 7.6%, and 3.4%, respectively; possible AD: 18.8%, 14.4%, and 6.3%, respectively; $\chi^2=26.4$; $P=.001$). The individuals who developed AD were older at the initial interview and had less education than those who did not develop AD (age: 78.0 [6.5] vs 75.3 [5.8] years; education: 6.2 [4.5] vs 8.6 [4.4] years; $P=.001$ for both). The proportions of men and women who developed AD were similar.

APOE allele frequencies differed significantly between ethnic groups ($P=.009$) but were not significantly different between those who developed AD and those who remained free of dementia (Table 1). However, using the *APOE*-ε3/ε3 genotype as the reference, the RR of AD to age 90 years associated with *APOE*-ε4 homozygosity was significantly increased (RR, 2.8; 95% confidence interval [CI], 1.3-6.0), while that associated with *APOE*-ε4 heterozygosity was not elevated (RR, 1.1; 95% CI, 0.8-1.6). Adjustment for ethnic group and years of education did not change the point estimates.

The distribution of *APOE* genotypes also differed significantly by ethnic group ($\chi^2= 23.5$, $df=10$, $P=.009$) (Table 2). Using the *APOE*-ε3/ε3 genotype as the reference, the RR of AD to age 90 years associated with 1 or more *APOE*-ε4 alleles was increased for whites (RR, 2.5; 95% CI, 1.1-6.4) but not for African Americans (RR, 1.0; 95% CI, 0.6-1.6) or Hispanics (RR, 1.1; 95% CI, 0.7-1.6). There were too few individuals with the *APOE*-ε4/ε4 genotype within each ethnic group to derive a meaningful independent RR estimate (Table 2).

In a second analysis we examined differences in disease risk across ethnic groups within specific *APOE* genotypes. Among individuals with 1 or more *APOE*-ε4 alleles (*APOE*-ε4/ε4, -ε4/ε-2, and -ε4/ε3), there was no significant difference in the RR of AD to age 90 years for African Americans and Hispanics compared with whites (African Americans: RR, 1.6; 95% CI, 0.7-3.8; Hispanics: RR, 0.8; 95% CI, 0.4-1.9), even after adjustment for education and sex. Thus, the cumulative risk of AD to age 90 years among individuals with an *APOE*-ε4 allele was similar for all 3 ethnic groups.

When the analysis was repeated, restricted to individuals without an

APOE-ε4 allele (*APOE*-ε3/ε3, -ε2/ε3, and -ε2/ε2), the relative risk of AD to age 90 years, adjusted for education and sex, was significantly higher for African Americans (RR, 4.4; 95% CI, 2.3-8.6) and Hispanics (RR, 2.3; 95% CI, 1.2-4.3) than for whites. Similar results were obtained when the analysis was restricted to individuals with the *APOE*-ε3/ε3 genotype (African Americans: RR, 4.3; 95% CI, 2.0-8.9; Hispanics: RR, 2.2; 95% CI, 1.2-4.3). Figure 1 illustrates that among individuals without an *APOE*-ε4 allele, the cumulative incidence of AD to age 90 years was significantly higher among African Americans and Hispanics than among whites (log-rank test, $P<.001$).

To determine if differences in education might account for the apparent increased risk of AD among African Americans and Hispanics compared with whites for individuals without an *APOE*-ε4 allele, we recalculated RRs for AD by ethnic group among individuals with the

APOE-ε3/ε3 genotype, adjusting for the number of years of education. The RRs for AD among African Americans and Hispanics were identical to the previous estimates, implying no interaction between ethnic group and education.

The frequency of a family history of dementia differed slightly but not significantly across the 3 ethnic groups (African Americans, 15%; whites, 18.7%; Hispanics, 18.3%; $\chi^2=0.6$, $P=.7$) and across *APOE* genotypes. A history of hypertension was more frequent among African Americans (63.5%) and Hispanics (61.7%) than among whites (46%) ($\chi^2=8.5$, $P=.001$), but this was not associated with the development of AD when entered as a covariate in the proportional hazards model. When family history of an AD-like illness, medical history of myocardial infarction or head injury, and history of smoking were added to the model, these likewise had no effect on the risk of development of AD.

Table 2.—Incidence of Alzheimer Disease (AD) by *APOE* Genotype and Ethnic Group*

Ethnic Groups*	*APOE* Genotype, No. (%)					
	ε3/ε3	ε2/ε3	ε2/ε2	ε4/ε2	ε3/ε4	ε4/ε4
African Americans						
Not demented	59 (46)	15 (12)	2 (2)	7 (5)	44 (34)	1 (1)
Incident AD	26 (49)	7 (13)	2 (4)	1 (2)	15 (28)	2 (4)
Whites						
Not demented	135 (63)	28 (13)	0	2 (1)	46 (21)	3 (1)
Incident AD	13 (57)	2 (9)	1 (4)	1 (4)	5 (22)	1 (4)
Hispanics						
Not demented	314 (61)	65 (13)	4 (1)	18 (3)	103 (20)	12 (2)
Incident AD	87 (60)	18 (12)	1 (1)	4 (3)	31 (21)	4 (3)

*The distribution of *APOE* genotypes differed significantly by ethnic group ($\chi^2=23.5$, $df=10$, $P=.009$).
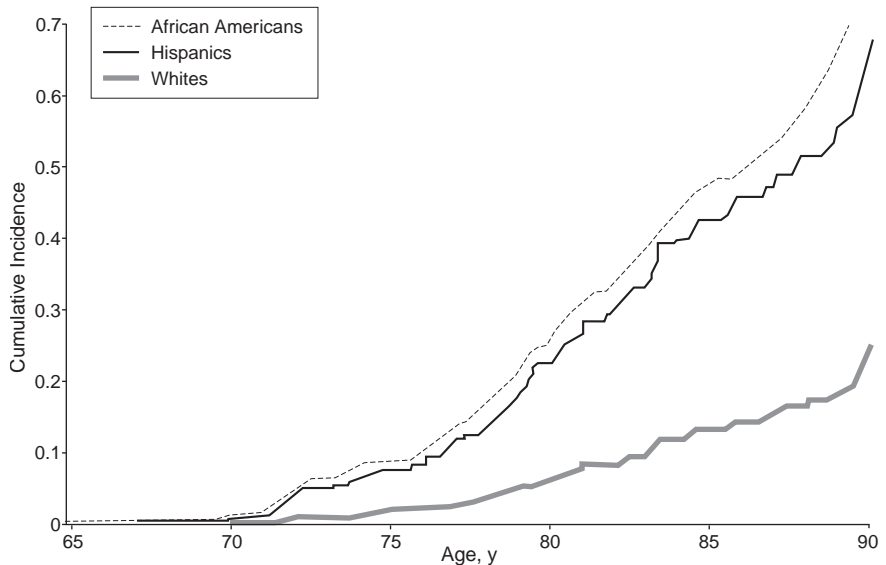

Figure 1.—Cox proportional hazards model of the cumulative incidence of Alzheimer disease to age 90 years among individuals with the apolipoprotein E (*APOE*)–ε3/ε3 genotype by ethnic group, controlled for education. In this analysis, patients with both mild and moderate disease (clinical dementia ratings of 0.5 and 1) were included as cases. The differences between African Americans and Hispanics vs whites were significant (log-rank test, $P<.001$).

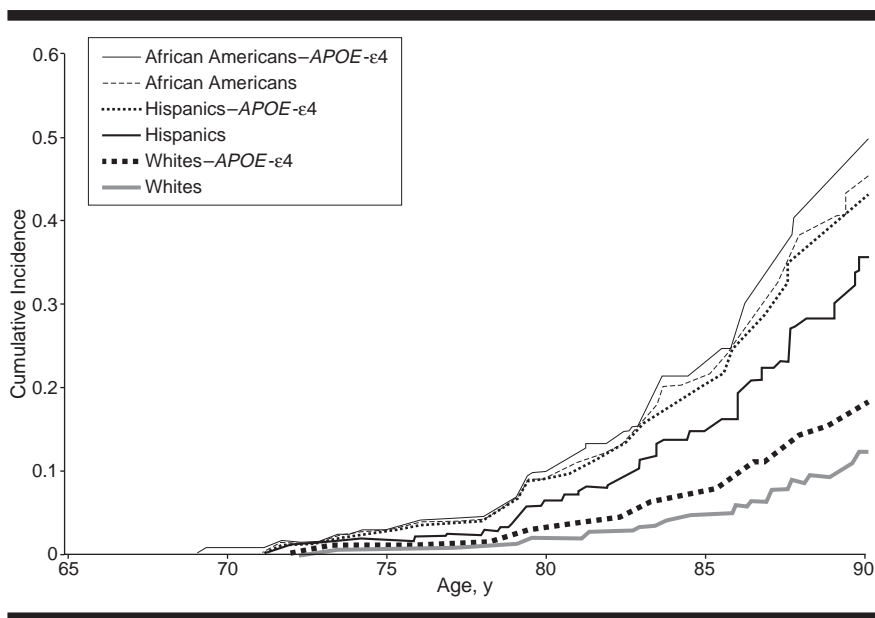The *APOE*-ε4 Allele and Risk of Alzheimer Disease—Tang et al **753**

Figure 2.—Cox proportional hazards model of the cumulative incidence of Alzheimer disease to age 90 years among individuals with and without an apolipoprotein E (APOE)–ε4 allele by ethnic group, controlled for education. Only patients with moderate disease (clinical dementia rating of 1) were classified as cases, while patients with mild disease (clinical dementia rating of 0.5) were reclassified as free of dementia. Among individuals with and without an APOE-ε4 allele, the differences between African Americans and Hispanics vs whites were significant (log-rank test, P=.001). Among individuals with an APOE-ε4 allele, African Americans and Hispanics had a slightly but not significantly higher cumulative incidence of Alzheimer disease to age 90 years vs whites (African Americans: RR, 1.9; 95% confidence interval [CI], 0.3-9.5; Hispanics: RR, 1.4; 95% CI, 0.3-6.9). Among individuals without an APOE-ε4 allele, both African Americans and Hispanics had a higher cumulative incidence of Alzheimer disease to age 90 years than whites (African Americans: RR, 4.4; 95% CI, 1.6-12.4; Hispanics: RR, 2.3; 95% CI, 1.0-6.1).

Individuals who developed AD during follow-up included patients with both mild (CDR score, 0.5) and more advanced (CDR score, 1) disease. The number of patients with mild disease (n=144) might have influenced the differences between ethnic groups, because diagnostic accuracy may be less than optimal in the initial stage of the disease. We recalculated the RRs, reclassifying patients with mild disease (CDR score, 0.5) as free of dementia. Figure 2 illustrates the difference in cumulative incidence of AD to age 90 years by ethnic group among individuals with and without an APOE-ε4 allele (log-rank test, P=.001). Among individuals with an APOE-ε4 allele, African Americans and Hispanics had a slightly but not significantly higher risk of AD to age 90 years compared with whites (African Americans: RR, 1.9; 95% CI, 0.3-9.5; Hispanics: 1.4; 95% CI, 0.3-6.9). However, among individuals without an APOE-ε4 allele, both African Americans and Hispanics had a significantly higher risk of AD to age 90 years compared with whites (African Americans: RR, 4.4; 95% CI, 1.6-12.4; Hispanics: RR, 2.3; 95% CI, 1.0-6.1).

COMMENT

African Americans and Hispanics with an APOE-ε4 allele were as likely as whites with an APOE-ε4 allele to develop AD by age 90 years in this study of elderly individuals. However, in the absence of an APOE-ε4 allele, African Americans and Hispanics were 2 to 4 times more likely than whites to develop AD by age 90 years. This increase in risk was not related to differences in education or the presence of a family history of an AD-like dementia. While hypertension was more frequent among African Americans and Hispanics than among whites, it was not related to the risk of AD. These observations provide evidence that, in addition to the APOE-ε4 allele, previously unidentified genes or other risk factors may contribute to the etiology of AD among African Americans and Hispanics.

Gurland et al[18,19] reported a relative increase in the prevalence and incidence rate of AD and other dementias among African Americans and Hispanics compared with whites in this community. Differences in the prior educational experience of individuals in these ethnic groups could have influenced psychometric testing for dementia.[20] However, Gurland et al[19] also observed a parallel decline in activities related to daily function among individuals with mild and moderate dementia compared with those who remained free of dementia. Because we used the same diagnostic assessments, it is unlikely that the

differences between ethnic groups in the frequency of AD reported here are the result of inappropriate diagnosis among African Americans and Hispanics.

Since the first report of an association between the APOE-ε4 allele and AD, the association has been confirmed by investigators throughout the world.[21-27] Indeed, APOE-ε4 has emerged as one of the most important risk factors for AD. There have been rare exceptions; we[1-3] previously reported a weaker association between AD and APOE-ε4 among African Americans and Hispanics compared with whites in this community. In contrast, Hendrie et al[25] found an increased risk of AD associated with APOE-ε4 among a small group of African Americans in Indiana, but no association between AD and APOE-ε4 was observed among Nigerians.[5] In a subsequent study[4] of African Americans in Indiana, the association between APOE-ε4 and AD was greatly reduced, similar to our earlier observations. Farrer et al[28] recently completed a worldwide meta-analysis of the relationship between APOE-ε4 and AD using numerous published and unpublished studies. They concluded that APOE-ε4 was an important determinant of AD risk for men and women after age 60 years. They also confirmed that APOE-ε4 was strongly related to AD risk among whites and Asians but that the relationship among African Americans and Hispanics remained comparatively inconsistent and weak, supporting our earlier findings.

Previous studies of AD and APOE-ε4 have computed risks using a reference genotype, such as APOE-ε3/ε3. It is possible that previous observations of an attenuated APOE-ε4 association among African Americans and Hispanics resulted from an increase in the frequency of AD among individuals with other APOE alleles.

A slight increase in AD risk associated with the APOE-ε2 allele has been observed among individuals with early-onset disease,[29] and we previously reported an association between this allele and AD among African Americans and Hispanics.[2] van Duijn et al[29] attributed the increased risk of AD among individuals with the APOE-ε2 allele to a survival effect. Scott et al[30] reported no association between AD and the APOE-ε2 allele, but they used a cross-sectional design that could not examine the effects of survival. While there is no consensus,[31] the APOE genotype may influence survival among patients with AD.[32] The prospective nature of our study lessened the possibility of a survival effect, but we draw no firm conclusions regarding the effect of the APOE-ε2 allele on AD risk

because of the low frequency of this allele in the study population.

Two studies, one autopsy-based[33] and the other clinical,[34] have previously compared the rates of AD among African Americans and whites in the United States. De la Monte et al[33] reported that AD was significantly more frequent among whites than African Americans at autopsy, but the pathologic criteria for AD and multi-infarct dementia were not described, and diagnoses were simply recorded from existing reports. In a clinical study, Bohnstedt et al[34] found the rates of AD to be comparable among African Americans and whites once differences in education were considered. We adjusted for education as a continuous variable and also stratified by the median, but the higher risk of AD in the absence of the *APOE*-ε4 allele persisted. Still, some unmeasured socioeconomic factors or cultural attributes may contribute to the higher frequency of disease observed in this study.

This study is not without limitations. One is the lack of autopsy confirmation of AD. The presence of an *APOE*-ε4 allele in whites with probable or possible AD increases the likelihood of confirmation of the diagnosis.[35] No similar data were available for African Americans or Hispanics. However, a slight decrease in the accuracy of diagnosis would not account for the 2-fold to 4-fold differences among patients without the *APOE*-ε4 allele. Because fewer Hispanics were unavailable for follow-up or refused genotyping, a larger number were included in the study, which could have contributed to the higher observed frequency of AD in this group. We do not favor this explanation for 2 reasons: (1) There were significantly more Hispanic than white patients with prevalent AD at baseline, which supports the findings in the prospective study. (2) The proportions of African Americans and whites who were unavailable for follow-up or who refused genotyping were comparable, yet the cumulative risk of AD was significantly higher among African Americans.

Our results suggest that as African Americans and Hispanics age, the frequency of AD in these populations may increase disproportionately. The elderly Hispanic population in the United States has been increasing more rapidly than that of other ethnic groups.[36] Because of the decline in function and the expense related to AD, identification of other genetic and environmental determinants of this disease among African Americans and Hispanics is an important next step.

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