Comparison of Alzheimer's disease risk factors in white and African American families

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Abstract—The associations between alcohol, smoking, and head injury and the risk of AD in 443 African American and 2,336 white participants in the MIRAGE Study were evaluated. Alcohol had a modest protective effect in whites (odds ratio [OR] = 0.82, 95% CI = 0.68 to 0.99), with a similar trend in African Americans (OR = 0.88, 95% CI = 0.54 to 1.4). Head trauma increased the risk of AD in whites (OR = 2.3, 95% CI = 1.8 to 3.0) and African Americans (OR = 2.9, 95% CI = 1.2 to 7.0). Smoking was not associated with AD risk in whites (OR = 0.88, 95% CI = 0.73 to 1.1) or African Americans (OR = 1.0, 95% CI = 0.69 to 1.5). These risks were similar across subsets stratified by the presence or absence of the APOE ϵ4 allele.

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The contributions of cultural and biological factors to the risk of AD in African Americans have been the source of recent controversy.[1] Some studies have suggested that AD is more common among African Americans than whites, whereas others have found no difference in prevalence.[2] Investigation of apolipoprotein E (*APOE*) in two community-based samples suggests some genetic differences in disease risk,[3,4] but this conclusion has recently been challenged.[5] Very little information is available that examines comparisons between whites and African Americans regarding nongenetic factors that have been associated with AD risk. In the current study, we compared the impact of alcohol, smoking, and head trauma in a large group of white and African American participants in the MIRAGE (Multi-Institutional Research in AD Genetic Epidemiology) Study.

Methods. *Subjects and data collection.* Data for 1,994 MIRAGE patients with AD meeting National Institute of Neurological and Communication Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for definite or probable AD and their 993 siblings were chosen for the analysis.[6] Subjects were 50 years or older and self-described as African American or white. After limiting the sample to those who provided information for gender, years of education, history of head trauma, and alcohol and smoking consumption, 1,868 patients (93.7%) and 911 siblings (91.7%) from 1,924 families remained. Sixty-seven (7.4%) of the siblings were also determined to have AD according to the NINCDS/ADRDA criteria, resulting in 1,935 cases and 844 nondemented sibling control subjects. The majority (99.1%) of the remaining cognitively normal siblings were administered a Telephone Interview of Cognitive Status and obtained a score of at least 27 to confirm they were not demented.

Risk factor information was collected from a primary informant for the cases. Most of the control subjects (85.0%) provided their own risk factor information. Age was treated as a continuous variable and calculated as the age at onset for AD symptoms in the cases and the age at death or time of interview in the control subjects. The number of years of education was dichotomized into a category representing those with ≥12 years of education versus those with less. Alcohol exposure was determined by first computing the number of drinks of beer, wine, or liquor per day reported for each of three age groups (16 to 39, 40 to 64, and >65 years) during the subject's lifetime. This information was then used to calculate the mean number of drinks for each subject over the course of his or her lifetime. Following US Department of Agriculture-recommended guidelines, low to no exposure was considered to be <0.25 drink/day; for moderate exposure, the number of drinks per day was defined as 0.25 to 1.0 in women and 0.25 to 2.0 in men; high exposure was considered to be >1.0 drink/day in women and >2.0 drinks/day in men. As preliminary analysis revealed that the association between AD and alcohol consumption was similar for moderate and high alcohol consumption, these two drinking categories were combined in subsequent analyses. Smokers included current and past smokers and were compared with those who never smoked. Subjects with head trauma reported experiencing a serious head injury requiring medical care and were compared with those who reported no such injury. *APOE* genotype was determined for 1,213 AD cases (63%) and 523 controls (62%) using procedures described previously.[5]

Statistical analyses. *APOE* genotype was dichotomized into those with one or two ϵ4 alleles versus those with no ϵ4 allele. Continuous variables were inspected visually for normality. To compare case and control subjects, Student's *t*-test or the Wilcoxon rank sum test was used for continuous measures and a χ^2 test for categorical measures. Odds ratios (OR) for each dichotomous variable were calculated in the total data set and separately for whites and African Americans. A Mantel–Haenszel OR was com-

*See the Appendix for a list of Group members.

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Table 1 *Subject characteristics*

Characteristics	White		African American		Total	
	Cases	Controls	Cases	Controls	Cases	Controls
Sample size	1,650	686	285	158	1,935	844
Mean (SD) age, y	70.1 (8.7)	70.5 (8.9)	71.9 (7.3)	72.9 (9.0)	70.4 (8.5)	70.9 (8.9)
Education ≥12 y, no. (%)	1,131 (68.6)	446 (65.0)	118 (41.4)	83 (52.5)	1,249 (64.6)	529 (62.7)
Males, no. (%)	675 (40.9)	287 (41.8)	69 (24.2)	53 (33.5)	744 (38.5)	340 (40.3)
Head trauma, no. (%)	370 (22.4)	78 (11.4)	27 (9.5)	6 (3.8)	397 (20.5)	84 (10.0)
Alcohol ≥0.25 drinks/d, no. (%)	702 (42.6)	327 (47.7)	57 (20.0)	35 (22.2)	759 (39.2)	362 (42.9)
Smoker ever, no. (%)	834 (50.6)	374 (54.5)	97 (34.0)	54 (34.2)	931 (48.1)	428 (50.7)

pared with the crude OR to evaluate potential confounding. The Breslow–Day test statistic was calculated to evaluate heterogeneity between racial groups.

Multivariate modeling was carried out using the generalized estimating equations specifying the logit link function for a binary response. The generalized estimating equations procedure is attractive because it can appropriately account for the correlation among subjects within families and also incorporates information from singletons. Cross-product terms were created by the multiplication of race with alcohol, smoking, or head trauma. Each cross-product term was tested in a separate model. Results are interpreted as OR. All analyses were carried out in SAS v8.2 using PROC GENMOD (SAS Institute, Cary, NC).

Results. Characteristics among case and control subjects are provided in table 1 . On average, African American subjects were older, less likely to be male, and less well educated and reported less head trauma, alcohol consumption, and smoking than white subjects (all $p < 0.0001$). Relative proportions for head trauma, alcohol consumption, and smoking between cases and controls were similar for African Americans and whites (Breslow–Day statistic $p > 0.50$ for all three risk factors). African American control subjects were more likely to be male ($p = 0.04$) and to have at least 12 years of education ($p = 0.02$) relative to cases, whereas white control and case subjects reported a similar distribution for these variables. The frequencies of the three risk factors were similar in each diagnostic and ethnic group in the subset of subjects with *APOE* genotype information compared with the total sample (data not shown).

Multivariate analysis revealed that head trauma significantly increased the odds of AD between two and three times in both whites and African Americans (table 2). Moderate to high alcohol consumption lowered the odds of AD by 18% in whites and 12% in African Americans. There was no association with past or current smoking and AD in either ethnic group. Similar results were found in the subjects with or without an *APOE* ϵ4 allele (p values for all cross-product terms representing interactions between the risk factors and ϵ4 status were >0.4).

Discussion. Results of this family-based study suggest that risk of AD among African Americans and whites is increased by head trauma, decreased by alcohol consumption, and unaffected by habitual smoking. Our findings are in agreement with results from some prospective studies but not others,[7,8] although most of these studies are small and have limited follow-up. The magnitude of the modest protective effect of alcohol was similar in both racial groups but not significant in African Americans, presumably because of a much smaller sample size. We reported previously similar patterns for these three risk factors in whites,[8,9] and in this study, we demonstrate similar associations in African American families recruited in the same way. African American subjects were included in another study of head trauma, but risk of AD was computed only for the total multiethnic sample.[7]

In a separate analysis of the MIRAGE cohort, we demonstrated that *APOE* genotype exerts a similar effect on risk of AD in African Americans and whites.[5] Recently, we reported that first-degree relatives of African Americans with AD have a higher cumulative risk of disease than those of whites with AD. This increased risk for relatives of African American probands was independent of gender or *APOE* genotype.[6] Higher risk of AD in African Americans, regardless of *APOE* genotype, has also been observed in a community study in New York City.[3]

In this study, information from cases was collected, by necessity, from knowledgeable informants, whereas control subjects, for the most part, provided their own medical history. However, we have documented excellent reliability for smoking and alcohol information but moderate reliability for head trauma information, collected by proxy within the MIRAGE Study.[10] Another limitation of the current study is the possibility that African American subjects may

Table 2 *Odds of AD for risk factors by ethnicity*

Risk factor	OR (95% CI) for whites*	OR (95% CI) for African Americans*	OR (95% CI) total†
Head trauma	2.3 (1.8, 3.0)	2.9 (1.2, 7.0)	2.4 (1.8, 3.1)
Alcohol	0.82 (0.68, 0.99)	0.88 (0.54, 1.4)	0.83 (0.69, 0.99)
Smoking	0.88 (0.73, 1.1)	1.0 (0.69, 1.5)	0.90 (0.76, 1.1)

* Models include a single interaction term for race and risk factor. Odds ratios (OR) adjusted for age, sex, education, head trauma, alcohol, and smoking.

† OR adjusted for age, sex, race, education, head trauma, alcohol, smoking, and race.

be differentially referred to clinics for evaluation. Unfortunately, there are no studies that specifically address a possible differential referral bias for African Americans. Our observation of less head trauma, alcohol consumption, and smoking in African Americans than whites suggests a possibility of underreporting of these risk factors in African Americans, but this tendency would not necessarily influence their association with AD.

Our study suggests that three well-studied environmental risk factors—smoking, alcohol consumption, and head trauma—have a similar impact on the risk of AD in African Americans and whites. Additional studies are needed to identify the genetic, medical, or lifestyle factors that explain the relatively greater risk of AD among African Americans.

Appendix

Other participating investigators from the MIRAGE (Multi-Institutional Research in AD Genetic Epidemiology) Study Group include Sanford Auerbach, MD, Department of Neurology, Boston University School of Medicine, MA; Helena Chui, MD, Rancho Los Amigos Medical Center and Department of Neurology, University of Southern California, Downey; Ranjan Duara, MD, Wein Center, Mt. Sinai Medical Center and University of Miami School of Medicine, FL; Timi Edeki, MD, PhD, Departments of Medicine and Clinical Pharmacology, Morehouse School of Medicine, Atlanta, GA; Robert P. Friedland, MD, Department of Neurology, Case Western Reserve University, Cleveland, OH; Rodney C. Go, PhD, Department of Epidemiology, University of Alabama School of Public Health, Birmingham; Patrick A. Griffith, MD, Department of Medicine, Section of Neurology, Morehouse School of Medicine, Atlanta, GA; Walter A. Kukull, PhD, Department of Epidemiology, School of Public Health, University of Washington, Seattle; Alexander Kurz, MD, Department of Psychiatry, Technische Universität München, Germany; Dessa Sadovnick, PhD, Department of Medical Genetics, Vancouver Hospital and Health Sciences Centre, Canada; and John Wells, PhD, Geriatric Research Education and Clinical Center, VA Medical Center, Bedford, MA.

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Mild cognitive impairment

Can FDG-PET predict who is to rapidly convert to Alzheimer's disease?

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Abstract—Patients with mild cognitive impairment (MCI) were assessed, and a metabolic profile associated with conversion to AD at 18-month follow-up was sought. As compared with nonconverters (n = 10), converters (n = 7) had lower fluorodeoxyglucose uptake in the right temporoparietal cortex ($p = 0.02$, corrected for cluster size), without individual overlap. Awaiting replication in an independent sample, these findings suggest that among patients with MCI, fluorodeoxyglucose PET may accurately identify rapid converters.

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Accurately predicting those subjects with mild cognitive impairment (MCI) whose disease will rapidly convert to AD would have major implications.[1] In probable AD, the earliest metabolically affected area is the posterior cingulate gyrus (PCG), followed by the temporoparietal posterior association cortex (PACx) and hippocampal region.[2,3] Most previous longitudinal studies of MCI compared converters

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