Incidence of Alzheimer Disease in a Biracial Urban Community

Relation to Apolipoprotein E Allele Status

Denis A. Evans, MD; David A. Bennett, MD; Robert S. Wilson, PhD; Julia L. Bienias, ScD; Martha Clare Morris, ScD; Paul A. Scherr, ScD; Liesl E. Hebert, ScD; Neelum Aggarwal, MD; Laurel A. Beckett, PhD; Rajiv Joglekar, MD; Elizabeth Berry-Kravis, PhD; Julie Schneider, MD

Context: Few studies compare Alzheimer disease (AD) incidence among black and white subjects.

Objective: To estimate incidence and the effect of the apolipoprotein E (APOE) ε4 allele in these races.


Setting: A geographically defined community of 3 adjacent neighborhoods in Chicago, Ill.

Participants: A total of 6158 persons (78.7% overall; 80.5% of the black subjects and 74.6% of the white subjects) participated; 4.1 years later, persons initially free of AD were sampled for clinical evaluation for disease incidence (overall 842 persons [74.8%] participated; 67.6% of the black subjects and 81.9% of the white subjects).

Interventions: None.

Main Outcome Measure: Incident, clinically diagnosed AD.

Results: The effect of the APOE ε4 allele on the risk of AD differed strongly for black and white subjects. Among white subjects, the presence of the APOE ε4 allele was associated with a 2.73-fold (95% confidence interval [CI], 1.40-5.32) increase in risk while among black subjects there was no increase in risk (odds ratio, 1.02; 95% confidence interval, 0.39-2.68). Black race was associated with a nonsignificantly increased risk of AD with an odds ratio of 1.84 (95% CI, 0.73-4.66) if APOE and its interaction with race are considered, and an odds ratio of 1.28 (95% CI, 0.54-2.98) if they are not. The incidence of AD was 1.45% (95% CI, 0.89%-2.01%) per year among persons 65 to 74 years old, 4.73% (95% CI, 3.83%-5.64%) among those 75 to 84 years old, and 9.11% (95% CI, 7.36%-10.9%) among those 85 years and older.

Conclusion: Apolipoprotein E ε4 led to increased risk of AD among white subjects but not black subjects.

Arch Neurol. 2003;60:185-189

Large-scale studies of Alzheimer disease (AD) and the effects of the apolipoprotein E (APOE) ε4 allele on risk are uncommon among the black population in the United States.1-4 After its initial description,5 the finding that the APOE ε4 allele is associated with increased risk of AD has been replicated in many white populations,6,7 but studies8 of populations with a large fraction of American or African black subjects have usually suggested less effect of the APOE ε4 allele on disease risk. Therefore, we studied APOE and the risk of incident AD among black and white subjects in a geographically defined population.

METHODS

THE STUDY COMMUNITY AND STUDY DESIGN

The study was conducted in a geographically defined community of 3 neighborhoods in Chicago, Ill—Morgan Park, Washington Heights, and Beverly. A census enumerated 64,911 residents; 8,509 (13.1%) were aged 65 years or older, 432 died, and 251 left the community. Of the remaining 78,26 residents, 6,158 (78.7% overall; 80.5% of the blacks, 74.6% of the whites) participated. Institutionalized persons were eligible, but of 3 nursing homes in the community 1 declined participation. Data were collected in cycles of approximately 3 years; each consisting of an in-home interview of all participants and clinical evaluation of a random, stratified sample.

The baseline cycle measured disease prevalence, provided risk factor data before incident disease onset, and identified a cohort of 3,838 persons free of AD; 729 persons were sampled for baseline clinical evaluation. Persons in the disease-free cohort had either good cognitive function at baseline, or if cognitive function was intermediate or poor, were free...
from AD at the baseline clinical evaluation. This disease-free cohort was evaluated for incident disease after an average of 4.1 years. Sampling for incident clinical evaluation was based on age, sex, race, and change in cognitive function (ie, stable or improved, small decline, or large decline). Cognitive testing was used to stratify sampling, rather than as a screening test. Persons were randomly selected for evaluation from all levels of cognitive performance (Figure), not merely from those with poor performance. Of 1249 persons sampled, 109 died and 15 moved from the study community; 842 (74.8% overall; 67.6% of the blacks, 81.9% of the whites) participated.

**CLINICAL EVALUATION**

Clinical evaluations were structured and uniform with examiners blinded to population interview cognitive testing and sampling category. Cognitive measures included the Verbal Fluency Test; Boston Naming Test; Mini-Mental State Examination; Word List Memory, Word List Recall, and Word List Recognition from the Consortium to Establish a Registry for Alzheimer's Disease battery; Logical Memory and Digit Span subtests of the Wechsler Memory Scale–Revised; East Boston Memory Test; and modified versions of the Symbol Digit Modalities Test; Judgment of Line Orientation; Complex Ideational Material; Number Comparison; Digit Ordering; Standard Progressive Matrices; and National Adult Reading Test. A neuropsychologist (R.S.W.), blinded to age, sex, race, and clinical data other than educational level, occupation, and information about sensory or motor deficits, summarized impairment in each of 5 domains (orientation, attention, memory, language, and perception). Structured neurological examination and medical history were by specially trained nurse clinicians; a board-certified neurologist (D.A.B., N.A. or J.S.) reviewed all data and reexamined each participant. Brain magnetic resonance imaging was restricted to persons with evidence of dementia and uncertainty as to whether a stroke had occurred or its relation to dementia.

Diagnosis of dementia required loss of cognitive function by the neurologist's assessment and impairment in 2 or more functions on the cognitive performance tests. This diagnosis was made using criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association for probable AD, except that persons who met these criteria and had another condition impairing cognition were retained. Vascular dementia was diagnosed by criteria of the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences International Workshop. Race was measured by years of formal schooling, Apolipoprotein E genotyping was done, blinded to all other study data, using methods adapted from Hixson and Vernier and primers described by Wenham et al. The study was approved by the Rush-Presbyterian–St Luke’s Medical Center institutional review board.

**STATISTICAL ANALYSES**

Incidence in the community population was estimated from the sample in 3 steps. First, a logistic regression model provided smoothed estimates of incidence in each stratum, taking advantage of the information in adjacent strata. Second, an empirical Bayes approach was used to combine this smoothed estimate with the observed crude incidence for that stratum, relying more heavily on the observed proportions if there was a large sample in the stratum or evidence of deviation from the model. Third, the empirical Bayes estimates from the strata were combined using the sampling weights to estimate incidence in the population. The SE estimates were obtained by bootstrap resampling. Analytic procedures were carried out using SAS software. The same procedures were used for incidence estimates of vascular dementia. The associations of age, sex, race, education, and APOE genotype to AD incidence were assessed by fitting logistic regression models adjusted for the complex sampling design. All models were validated using graphical and analytic techniques to check for violations of model assumptions and for interactions.

**RESULTS**

**INCIDENCE OF AD**

The random sample initially free of AD had 842 persons, but 7 (0.09%) supplied insufficient information for diag-
nosis. This article is based on the remaining 835 (495 women and 340 men; 373 blacks and 462 whites). The cognitive strata and number selected for clinical evaluation from each stratum are in the Figure; 139 persons had developed incident AD. In analyses weighted for sampling, the annual incidence of AD in the population aged 65 years and older was 2.72% (95% confidence interval [CI], 2.18%-3.27%). Incidence increased strongly with age; 1.45% (95% CI, 0.89%-2.01%) of persons 65 to 74 years old developed AD each year compared with 4.73% (95% CI, 3.83%-5.64%) of those 75 to 84 years old, and with 9.11% (95% CI, 7.36%-10.9%) for those 85 years and older (Table 1). The effects of age, sex, race, education, and the APOE e4 allele on disease incidence were examined (Table 2) using logistic regression models that included the interval from baseline evaluation to evaluation for incident disease for each person. The odds ratio of 1.16 (95% CI, 1.11-1.22) for age indicates that age was strongly associated with the risk of incident AD. Sex had little or no effect on risk. Education was a marker for a lower risk of developing AD. The odds ratio of 0.88 (95% CI, 0.79-0.97) indicated that each additional year of formal schooling was associated with approximately a 12% decrease in the incidence of AD. The effects of race on incidence of AD were less clear.

### Table 1. Clinically Diagnosed Incident Alzheimer Disease by Age Group and Race in a Sample of the Population Aged 65 Years and Older of a Geographically Defined Biracial Community in Chicago, Ill

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age Group, y</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>65-74</td>
<td>75-84</td>
<td>85+</td>
<td>All Ages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Black Subjects</td>
<td>White Subjects</td>
<td>Total</td>
<td>Black Subjects</td>
<td>White Subjects</td>
<td>Total</td>
<td>Black Subjects</td>
<td>White Subjects</td>
</tr>
<tr>
<td>Annual incidence of Alzheimer disease, %</td>
<td>1.79</td>
<td>0.94</td>
<td>1.45</td>
<td>6.06</td>
<td>3.75</td>
<td>4.73</td>
<td>12.72</td>
<td>8.22</td>
</tr>
<tr>
<td>95% Confidence interval, %</td>
<td>1.05-2.52</td>
<td>0.39-1.49</td>
<td>0.89-2.01</td>
<td>4.21-7.91</td>
<td>2.76-4.75</td>
<td>3.83-5.64</td>
<td>9.48-15.9</td>
<td>6.42-10.0</td>
</tr>
<tr>
<td>No. in clinical evaluation sample*</td>
<td>195</td>
<td>164</td>
<td><strong>359</strong></td>
<td>160</td>
<td>241</td>
<td><strong>401</strong></td>
<td>18</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td><strong>373</strong></td>
<td><strong>462</strong></td>
<td><strong>835</strong></td>
<td><strong>401</strong></td>
<td><strong>462</strong></td>
<td><strong>863</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Numbers are the actual numbers in the sample. All proportions are weighted to account for stratified random sampling.

### Table 2. Risk Factors for Incident Alzheimer Disease in a Random Sample of the Population Aged 65 Years and Older of a Biracial Community in Chicago, Ill*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coefficient</th>
<th>Odds Ratio*</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both Races Together</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>−2.99</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Lag, y†</td>
<td>0.108</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Age, y‡</td>
<td>0.132</td>
<td>1.16</td>
<td>1.11-1.22</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.112</td>
<td>0.89</td>
<td>0.45-1.76</td>
</tr>
<tr>
<td>Black subjects</td>
<td>0.612</td>
<td>1.84</td>
<td>0.73-4.66</td>
</tr>
<tr>
<td>Educational level, y§</td>
<td>−0.131</td>
<td>0.88</td>
<td>0.79-0.97</td>
</tr>
<tr>
<td>Any APOE e4 allele</td>
<td>1.066</td>
<td>2.90</td>
<td>1.50-5.63</td>
</tr>
<tr>
<td>Black subjects with any APOE e4 allele</td>
<td>−1.062</td>
<td>0.34</td>
<td>0.11-1.04</td>
</tr>
<tr>
<td>Black Subjects Only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>−2.44</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Lag, y†</td>
<td>0.106</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Age, y‡</td>
<td>0.167</td>
<td>1.18</td>
<td>1.11-1.26</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.048</td>
<td>1.05</td>
<td>0.40-2.79</td>
</tr>
<tr>
<td>Educational level, y§</td>
<td>−0.136</td>
<td>0.87</td>
<td>0.76-1.00</td>
</tr>
<tr>
<td>Any APOE e4 allele</td>
<td>0.024</td>
<td>1.02</td>
<td>0.39-2.68</td>
</tr>
<tr>
<td>White Subjects Only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>−2.89</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Lag, y†</td>
<td>0.112</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Age, y‡</td>
<td>0.140</td>
<td>1.15</td>
<td>1.08-1.23</td>
</tr>
<tr>
<td>Male sex</td>
<td>−0.333</td>
<td>0.72</td>
<td>0.29-1.78</td>
</tr>
<tr>
<td>Educational level, y§</td>
<td>−0.117</td>
<td>0.89</td>
<td>0.75-1.05</td>
</tr>
<tr>
<td>Any APOE e4 allele</td>
<td>1.005</td>
<td>2.73</td>
<td>1.40-5.32</td>
</tr>
</tbody>
</table>

*Odds ratios are from the logistic regression analysis weighted to account for stratified random sampling. Ellipses indicate not applicable.
†Lag is the duration of the follow-up observation.
‡Age is centered at 75 years.
§Formal education is centered at 12 years.

Abbreviation: APOE, apolipoprotein E.
In analyses including age, education, the APOE e4 allele, and the interaction between APOE and race, there was a nonsignificant increase in odds of disease for blacks, 1.84 (95% CI, 0.73-4.66). This analysis, because of the risk among blacks and whites without the whites (see below). The presence of 1 or more for blacks and for interaction between the black race and analysis for the entire population (Table 2) includes terms risk of developing AD differed markedly by race. The confidence labeled “Any e4 allele” represents the effect of this allele among whites, for whom presence of 1 or more APOE e4 alleles. Thus, the coefficient labeled “Any e4 allele” and black race is of borderline significance and approximately equal to the “Any e4 allele” term, but opposite in direction, indicating that the allele had no effect on risk among blacks. This is confirmed by separate analyses for each race (Table 2). The APOE e4 allele is associated with a 2.7-fold increase in risk in the analysis limited to whites, odds ratio 2.73 (95% CI, 1.40-5.32), and with little increase in risk in the analysis limited to blacks (odds ratio, 1.02; 95% CI, 0.39-2.68). The effect of APOE e4 status did not seem to vary with age (age x any APOE e4 interaction; odds ratio, 0.97; 95% CI, 0.90-1.06), or sex (male sex x any APOE e4 interaction; odds ratio, 1.24; 95% CI, 0.35-4.35). Repeating analyses with individual genotypes distinguished and interaction of each genotype with black race, and considering AD as an exclusive diagnosis, did not change risk factor results substantially. (Results not shown.)

**COMMENT**

These results suggest the effects of the APOE e4 allele on the risk of incident AD may differ strongly for black Americans and white Americans. The presence of an APOE e4 allele was associated with a 2.7-fold increase in risk for whites, but with no increased risk for blacks. Most studies in white populations have found that the APOE e4 allele is associated with strongly increased risk of AD. Although the relation has been less extensively examined in black populations, the results of this study are generally consistent with previous studies. Tang et al found that, compared with persons with the APOE e3/e3 genotype, having 1 or more copies of the APOE e4 allele increased the risk of AD 2.5-fold among whites but not among blacks. Sahota et al found an odds ratio of 4.83 among African Americans homozygous for the APOE e4 allele and of 1.20 among those with the APOE e3/e4 genotype.

Reasons underlying a different effect on risk by race are uncertain. One possibility is chance alone, but this seems unlikely as the result is consistent with prior studies and the sample size is large. Another is linkage disequilibrium between APOE and another locus with an allele actually responsible for the risk and uncommon in populations of African origin. Another is the diminishing effect of APOE with age, with persons in this study too old to show an effect. We found no diminution of the APOE e4 effect with age, and this diminution was also not evident in some other population studies. Another is interaction between the APOE e4 allele and some unknown environmental or genetic factor that is distributed differently across the 2 races.

The study leaves unclear whether being black, in itself, is associated with an increased risk of AD, although the nonsignificant odds ratio of 1.84 suggests it may be. Black Americans have, on average, higher levels of vascular risk factors, especially elevated blood pressure, than whites, which may increase risk of AD. Results have varied among the few previous studies of AD in biracial US populations.

Direct comparisons of population studies of AD are hazardous, as mild disease that is difficult to separate from normality is common, and even minor differences in methods can result in large differences in estimates. The East Boston Study was similar in approach to this study, and incidence estimates among whites seem comparable.

**INCIDENCE OF VASCULAR DEMENTIA**

Vascular dementia was much less common than AD. The annual incidence of probable vascular dementia was 0.28% (95% CI, 0.00%-2.72%) overall, 0.30% (95% CI, 0.00%-3.03%) among blacks and 0.26% (95% CI, 0.00%-2.39%) among whites. Other dementing conditions were uncommon; 13 persons had incident dementia due to another condition.
estimates for blacks from this study are higher than those from the Indianapolis-Ibadan study, but this likely reflects differences in study methods, not actual differences in disease incidence.

Strengths of this study include large size, incidence data to make comparison across groups with different cultural experiences, structured uniform procedures, and accepted criteria for disease. Weaknesses include indirect assessment to initially identify most of the disease-free cohort, so that a small proportion of this cohort really may have had preexisting disease. Participation in the baseline population interview was slightly higher for blacks (80.5%, compared with 74.6% for whites), but participation in the clinical evaluation sample measuring incident disease was higher for whites (81.9%, compared with 67.6% for blacks). Overall, this pattern resulted in similar participation by race.

The results of this and previous studies suggest that the effect of the APOE e4 allele may differ substantially across major ethnic lines. The implications of this finding deserve further investigation, especially examination of genetic and environmental differences between the 2 groups.29

Accepted for publication August 26, 2002.

From the Rush Institute on Healthy Aging (Drs Evans, Bienias, Morris, and Hebert), the Rush Alzheimer's Disease Center (Drs Bennett, Wilson, Aggarwal, and Schneider), the Department of Pediatrics (Dr Berry-Kravis), and the Section of Geriatric Medicine, Department of Internal Medicine (Dr Joglekar), Rush-Presbyterian–St Luke's Medical Center, Chicago, Ill; Division of Adult and Community Health, Centers for Disease Control and Prevention, Atlanta, Ga (Dr Scherr); and the Department of Epidemiology and Preventive Medicine, University of California, Davis (Dr Beckett).

Author contributions: Study concept and design (Drs Bennett, Scherr, Hebert, and Beckett); acquisition of data (Drs Evans, Bennett, Wilson, Morris, Scherr, Hebert, Aggarwal, Joglekar, Berry-Kravis, and Schneider); analysis and interpretation of data (Drs Evans, Bennett, Bienias, Beckett, and Berry-Kravis); drafting of the manuscript (Drs Evans and Bennett); critical revision of the manuscript for important intellectual content (Drs Evans, Wilson, Bienias, Morris, Scherr, Hebert, Aggarwal, Beckett, Joglekar, and Schneider); statistical expertise (Drs Bienias and Beckett); obtained funding (Dr Evans); administrative, technical, and material support (Drs Evans, Bennett, Wilson, Joglekar, Berry-Kravis, and Schneider); study supervision (Drs Evans, Bennett, Morris, Aggarwal, and Berry-Kravis).

This study was supported by grant AG11101 from the National Institutes of Health, Bethesda, Md.

We thank Ann Marie Lane for community development and oversight of project coordination; Michelle Bos, Holly Hadin, MS, Flavio LaMorticella, and Jennifer Tarpey for coordination of the study; and Linyun Zhou, MSc, Daniel Tancredi, MS, and Woojong Bang, MS, for analytic programming.

Corresponding author and reprints: Denis A. Evans, MD, Rush-Presbyterian–St Luke's Medical Center, 645 W Jackson Blvd, Suite 675, Chicago, IL 60612 (e-mail: devans2@rush.edu).

REFERENCES


