Risk of Dementia Among White and African American Relatives of Patients With Alzheimer Disease

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Context Evidence exists that the incidence of Alzheimer disease (AD), as well as risk attributable to specific genetic factors such as apolipoprotein E (*APOE*) genotype, may vary considerably among ethnic groups. Family studies of probands with AD offer an opportunity to evaluate lifetime risk of dementia among relatives of these probands.

Objective To compare lifetime dementia risk estimates among relatives of white and African American probands with probable or definite AD.

Design and Setting Risk analysis using data collected by questionnaire and supplemental records between May 1991 and March 2001 at 17 medical centers contributing to the Multi-Institutional Research in Alzheimer's Genetic Epidemiology Study.

Participants A total of 17639 first-degree biological relatives and 2474 spouses of 2339 white AD probands, and 2281 first-degree biological relatives and 257 spouses of 255 African American AD probands.

Main Outcome Measures Cumulative risk of dementia by age 85 years, stratified by ethnicity and sex of relatives and by *APOE* genotype of probands.

Results Cumulative risk of dementia in first-degree biological relatives of African American AD probands by age 85 years was 43.7% (SE, 3.1%), and the corresponding risk in first-degree biological relatives of white AD probands was 26.9% (SE, 0.8%), yielding a relative risk (RR) of 1.6 (95% confidence interval [CI], 1.4-1.9; $P<.001$). The risk in spouses of African American AD probands of 18.5% (SE, 8.4%) was also higher than the risk in white spouses of 10.4% (SE, 1.7%) but did not reach statistical significance (RR, 1.8; 95% CI, 0.5-6.0; $P=.34$), likely due to the smaller sample size of African Americans. The proportional increase in risk of dementia among white first-degree biological relatives compared with white spouses of 2.6 (95% CI, 2.1-3.2) was similar to that of 2.4 (95% CI, 1.3-4.4) in African American first-degree biological relatives compared with African American spouses. Female first-degree biological relatives of probands had a higher risk of developing dementia than did their male counterparts, among whites (31.2% vs 20.4%; RR, 1.5; 95% CI, 1.3-1.7; $P<.001$) as well as among African Americans, although this was not significant among African Americans (46.7% vs 40.1%; RR, 1.2; 95% CI, 0.9-1.7, $P=.30$). The patterns of risk among first-degree biological relatives stratified by *APOE* genotype of the probands were similar in white families and African American families.

Conclusion First-degree relatives of African Americans with AD have a higher cumulative risk of dementia than do those of whites with AD. However, in this study, the additional risk of dementia conferred by being a first-degree relative, by being female, or by the probability of having an *APOE* ϵ4 allele appeared similar in African American and white families. These data provide estimates of dementia risk that can be used to offer counseling to family members of patients with AD.

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Well-established risk factors for the development of Alzheimer disease (AD) in white populations include age, family history, female sex, and the presence of 1 or 2 copies of the apolipoprotein E (*APOE*) ϵ4 allele.[1,2] Family studies have shown that relatives of white AD patients are at greater risk than nonrelatives for the development of dementia, and that these risks are higher with increasing age, female sex, and the likelihood of carrying 1 or 2 copies of the *APOE* ϵ4 allele.[3-6] The risks associated with AD in other US ethnicities and among populations in other countries have been less thoroughly studied, but there is evidence that the incidence of disease, as well as the risk attributable to specific genetic factors such as *APOE* genotype, may vary considerably among ethnic groups.[2,7-10]

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Family studies of probands with AD who have been identified by uniform criteria offer an opportunity to evaluate the lifetime risk of dementia among relatives of these probands. Comparisons of risk in biological relatives and nonbiological relatives (such as spouses) can help distinguish genetic from nongenetic factors within families. The impact of *APOE* genotype on the risk of dementia among relatives can be assessed indirectly by stratifying the lifetime risk estimates among biological relatives according to the *APOE* genotype of the proband. We have collected these types of data for 10 years within the Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study, and the lifetime risk estimates obtained in white populations have already provided clinically applicable estimates of risk among first-degree relatives in families of white patients with AD.[1,5,6] We have now collected family history data on the largest number of African American families ever studied for AD, to our knowledge. In this study, we report the lifetime risk estimates of dementia for the first-degree biological relatives of probands with AD by ethnicity, and examine the additional risk of dementia conferred on relatives by being female and by the probability of having an *APOE* ϵ4 allele. Risk estimates generated by this analysis also provide empirical data to which clinicians can refer when counseling the relatives of their patients with AD who are concerned about their own risk of developing AD.

METHODS

Participants and Data Collection

The details of MIRAGE Study data collection procedures, protocols for obtaining family histories, and reports demonstrating the validity of proxy reporting in participating families have been published elsewhere.[6,11,12] In brief, probands or individuals with probable or definite AD by research criteria[13] were identified at specialty clinics for dementia by experienced clinician-researchers at 17 centers between May 1991 and March 2001. The structured and validated MIRAGE questionnaires were distributed to family members to elicit health information and dementia status on the entire family. Information on both patients and family members was supplemented by multiple informants, medical records including autopsy reports, death certificates, and nursing home records. Informed consent was obtained from family members who did not have dementia, and a combination of consent or assent, along with informed consent by proxy, was obtained from participants with dementia.

Family history information was available for 2594 probands meeting criteria for definite or probable AD. Age, sex, and dementia status information was incorporated from 19920 first-degree biological relatives of these probands, as well as from 2731 of the probands' spouses. Data on other risk factors for AD were elicited as described elsewhere.[6,11,14] In a subset of 1331 family members 50 years or older who were reported by family informants not to have dementia, cognitive status was confirmed to be normal in 1298 (97.5%) by the modified Telephone Interview of Cognitive Status (mTICS).[15,16]

Of the first-degree biological relatives, 4681 were parents of the proband (817 affected), 8474 were siblings (715 affected), and 6765 were children (11 affected). There were 1093 families with at least 1 affected first-degree biological relative, indicating that about 42% of the probands had a family history of AD. Of these 1093 families, 784 (71.7%) had 1 affected first-degree biological relative, 216 (19.8%) had 2 affected first-degree biological relatives, and 93 (8.5%) had more than 2 affected first-degree biological relatives.

Ethnicity of participating families was classified by self-report, then reclassified prior to the analysis following the format of the 1990 US Census.[17] This analysis was restricted to families in which the proband met criteria for African American or white ethnicity. Age represented the age at which dementia symptoms began in relatives with dementia, or the age at which information was obtained on relatives who did not have dementia. Blood for *APOE* genotyping was collected on a subset of 1191 (45.9%) of the probands. A standard polymerase chain reaction procedure[18] was used for *APOE* genotyping. Of these samples, 458 (38.5%) were genotyped as *APOE* ϵ2/ϵ2, ϵ2/ϵ3, or ϵ3/ϵ3; 561 (47.1%), *APOE* ϵ2/ϵ4 or ϵ3/ϵ4; and 172 (14.4%), *APOE* ϵ4/ϵ4. The *APOE* genotype of the proband was grouped into the following 3 categories: ϵ2/ϵ2, ϵ2/ϵ3, or ϵ3/ϵ3; ϵ2/ϵ4 or ϵ3/ϵ4; and ϵ4/ϵ4 genotypes.

Statistical Analysis

A maximum likelihood procedure similar to a Kaplan-Meier survival analysis was used to estimate the lifetime risks and age at onset distribution for first-degree biological relatives and spouses of the AD probands.[5,19] The Kaplan-Meier method takes into account the possibility that those censored at the time of the study may be susceptible and acquire AD after the study end point and that those who died of a competing risk might have acquired AD if they had survived. Our method incorporates these elements into the analysis, but we additionally incorporate affected individuals with unknown ages of onset and nonaffected individuals with unknown censoring ages, thereby avoiding a downward bias in the estimation of mean onset age that would otherwise occur.[19] We used maximum likelihood estimation for 5 groups of individuals: (1) affected individuals with known age of onset, (2) unaffected individuals with known censoring age, (3) affected individuals with unknown onset age but with known censoring age, eg, death, (4) affected individuals without known onset age or censoring age, and (5) unaffected individuals without any censoring information. The expectation-maximization algorithm was applied to take into account censored information. In our analysis, 1459 of the 19920 first-degree biological relatives of probands were included in the analysis that would not have been included in the traditional Kaplan-Meier method.

Asymptotically normal distributions of maximum likelihood statistics were used to compute *Z* tests by using parameter estimates for risk and their SEs at the maximum common age of 95 years for each ethnic group, and for comparison across groups using risk by age 85 years.

Risk estimates were calculated with stratification by sex, ethnicity, and both sex and ethnicity of the relatives and spouses. Risk estimates among first-degree biological relatives were also stratified according to *APOE* genotype category of the proband.

All analyses were performed using SAS software version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

Cumulative risk was estimated based on information gathered from the families of 2339 white and 255 African American probands. The characteristics of the probands, first-degree biological relatives, and spouses are reported in TABLE 1. Cumulative risk estimates for first-degree biological relatives, stratified by ethnicity, sex, and by the *APOE* genotype of the proband, and cumulative risk estimates for spouses stratified by ethnicity are shown in TABLE 2. Curves illustrating the cumulative risks at different ages are shown in FIGURE 1, FIGURE 2, and FIGURE 3. As shown in Figure 1, the cumulative risk (SE) of dementia to age 95 years among first-degree biological relatives of white probands was 43.7% (1.9%) while the risk of dementia to age 95 years among first-degree biological relatives of African American probands was 57.1% (5.6%) (relative risk [RR], 1.3; 95% confidence interval [CI], 1.03-1.6; $P=.02$).

The results that follow refer to cumulative risks of dementia by age 85 years. The cumulative risk (SE) of dementia among first-degree biological relatives of white probands was 26.9% (0.8%) while the risk of dementia among first-degree biological relatives of African American probands was 43.7% (3.1%) (RR, 1.6; 95% CI, 1.4-1.9; $P<.001$). Data from spouses provided cumulative risk estimates of dementia in a population that shared environmental, but not genetic, background with the proband. The cumulative risk of dementia among spouses of white probands was 10.4% (1.7%) while for spouses of African American probands it was 18.5% (8.4%) (RR, 1.8; 95% CI, 0.5-6.0; $P=.34$). The proportional increase of 2.4 (95% CI, 2.1-3.2) in risk between spouses and first-degree biological relatives of African American probands was very similar to the proportional increase of 2.6 (95% CI, 1.3-4.4) in risk between spouses and first-degree biological relatives of white probands. Within ethnic groups, each of these comparisons was significant ($P<.005$ for both).

As shown in Table 2 and Figure 2, among the first-degree biological relatives of probands, women had a greater risk of dementia than men, within each ethnic group. African American women had a 1.2-fold higher risk than African American men (RR, 1.2; 95% CI, 0.9-1.7; $P=.30$) while white women had a 1.5-fold higher risk than white men (RR, 1.5; 95% CI, 1.3-1.7; $P<.001$). The absolute increase in risk among women compared with men was of similar magnitude within each ethnic group as illustrated in FIGURE 4, although it did not reach significance among African Americans.

Among the 980 white probands with *APOE* genotyping, 466 (47.6%) had 1 ϵ4 allele and 124 (12.7%) had the ϵ4/ϵ4 allele. Among the 211 African American probands with *APOE* genotyping, 95 (45.0%) had 1 ϵ4 allele and 48 (22.7%) had the ϵ4/ϵ4 genotype (Table 1). The risk of AD among white and African American probands and its modification with the ϵ4 allele is described in a separate report.[10] As shown in Table 2 and Figure 3, the ϵ4 status of the pro-

Table 1. Characteristics of Probands, First-Degree Biological Relatives, and Spouses

Characteristics	All	White	African American
Probands			
No.	2594	2339	255
Age at onset, mean (SD), y	70.0 (9.0)	69.9 (9.1)	71.3 (7.6)
Education, mean (SD), y	12.1 (3.5)	12.3 (3.3)	10.0 (4.2)
Women, No. (%)	1601 (61.7)	1416 (60.5)	185 (72.6)
Blood samples, No. (%)	1191 (45.9)	980 (41.9)	211 (82.7)
ϵ2/ϵ2 or ϵ2/ϵ3 or ϵ3/ϵ3*	458 (38.5)	390 (39.8)	68 (32.2)
ϵ2/ϵ4 or ϵ3/ϵ4*	561 (47.1)	466 (47.6)	95 (45.0)
ϵ4/ϵ4*	172 (14.4)	124 (12.7)	48 (22.7)
First-Degree Biological Relatives			
Affected			
No.	1543	1323	220
Age at onset, mean (SD), y	74.4 (9.1)	74.5 (9.2)	74.0 (8.3)
Women, No. (%)	1023 (66.3)	883 (66.7)	140 (63.6)
Unaffected			
No.	18 377	16 316	2061
Age, mean (SD)†	58.7 (18.9)	58.9 (19.1)	57.3 (17.8)
Women, No. (%)	9058 (49.3)	8009 (49.1)	1049 (50.9)
Spouses			
Affected			
No.	76	68	8
Age at onset, mean (SD), y	75.8 (7.9)	75.2 (7.9)	82.0 (4.5)
Women, No. (%)	18 (23.7)	15 (22.1)	3 (37.5)
Unaffected			
No.	2655	2406	249
Age, mean (SD)†	73.4 (11.9)	72.5 (12.2)	78.6 (9.8)
Women, No. (%)	1057 (39.8)	983 (40.9)	74 (29.7)

*Percentages expressed as percentage of the group with a blood sample.
†Age at data collection or death.

band altered the cumulative risk estimates of the relatives. For example, the presence of a single ϵ4 allele in the proband increased the risk in African American relatives by 1.3 (95% CI, 0.9-2.5; $P=.13$) and in white relatives by 1.5 (95% CI, 1.3-1.8; $P<.001$). The presence of 2 ϵ4 alleles in the proband increased the risk in African American relatives by 1.8 (95% CI, 1.1-2.8; $P=.01$) and in white relatives by 1.5 (95% CI, 1.1-2.0; $P=.008$). As shown in Figure 3 and FIGURE 5, the pattern of increased risk in relatives conferred by the presence of 1 or 2 ϵ4 alleles in the proband is similar between African American and white families even though with the smaller sample size among the African Americans, the 95% CIs for 1 ϵ4 allele include 1.

Because the educational level of the proband could be a considered a proxy for the educational level of the relatives, the risk estimates in relatives were stratified by educational level among both whites and African Americans (data not shown). The risk estimates for relatives of African American probands were higher within each strata of proband education than the same estimates in whites. Therefore, educational levels of the probands do not confound the risk differences observed between ethnicities.

COMMENT

In the clinical setting, family members of patients with AD realize that AD has a heritable component, and they often ask the clinician for some measure of their own risk. This report provides clinically relevant estimates of dementia risk in a large clinic-based population of white and African American families. These data confirm and enhance the precision of the cumulative risk curves that we have already published for white families.[5,6] Our large sample of African American families allows us to present, for the first time, precise age-specific risks of dementia among first-degree biological relatives of African American patients with AD. By examining the risk curves for relatives in Figure 1, clinicians can now ascertain empirical estimates of risk that may be useful for counseling white and African American family members of AD patients.

Our data indicate that relatives of African American patients are 1.6 times more likely than relatives of white patients to become demented by age 85 years. This finding could potentially reflect a higher degree of familial aggregation in African American families, a

Table 2. Estimated Cumulative Risk of Dementia Among First-Degree Biological Relatives and Spouses of Alzheimer Disease Probands*

Comparison Groups	No. of Probands	No. of Relatives: Affected	No. of Relatives: Unaffected	Age at Onset, Mean (SE), y	Oldest Onset Age Among Affected Biological Relatives, y	Comparison Risk at 85 Years (SE)	Comparison RR (95% CI)
First-degree blood relatives							
African Americans	255	220	2061	79.9 (1.2)	95	43.7 (3.1)	1.6 (1.4-1.9)
Whites	2339	1323	16 316	82.3 (0.6)	96	26.9 (0.8)	1.0
Spouses							
African Americans	247	8	249	85.6 (1.6)	89	18.5 (8.4)	1.8 (0.5-6.0)
Whites	2221	68	2406	82.0 (1.3)	90	10.4 (1.7)	1.0
Whites							
First-degree blood relatives	2339	1323	16 316	82.3 (0.6)	96	26.9 (0.8)	2.6 (2.1-3.2)
Spouses	2221	68	2406	82.0 (1.3)	90	10.4 (1.7)	1.0
African Americans							
First-degree blood relatives	255	220	2061	79.9 (1.2)	95	43.7 (3.1)	2.4 (1.3-4.4)
Spouses	247	8	249	85.6 (1.6)	89	18.5 (8.4)	1.0
First-degree blood relatives							
Whites							
Women	2312	883	8009	82.2 (0.6)	96	31.2 (1.1)	1.5 (1.3-1.7)
Men	2308	440	8307	81.9 (1.3)	96	20.4 (1.1)	1.0
African Americans							
Women	252	140	1049	79.7 (1.2)	95	46.7 (3.8)	1.2 (0.9-1.7)
Men	248	80	1012	78.5 (1.3)	89	40.1 (5.1)	1.0
Comparison Among White First-Degree Blood Relatives							
APOE genotype of the proband							
ϵ2/ϵ4 or ϵ3/ϵ4	466	322	3020	79.9 (1.0)	95	33.6 (1.9)	1.5 (1.3-1.8)
ϵ4/ϵ4	124	90	851	78.6 (1.2)	90	32.2 (3.4)	1.5 (1.1-2.0)
ϵ2/ϵ2 or ϵ2/ϵ3 or ϵ3/ϵ3	390	190	2691	84.2 (1.3)	96	22.0 (1.8)	1.0
Comparison Among African American First-Degree Blood Relatives							
APOE genotype of the proband							
ϵ2/ϵ4 or ϵ3/ϵ4	95	101	762	81.0 (1.9)	95	47.7 (4.7)	1.3 (0.9-2.5)
ϵ4/ϵ4	48	42	362	77.1 (1.1)	85	64.6 (9.4)	1.8 (1.1-2.8)
ϵ2/ϵ2 or ϵ2/ϵ3 or ϵ3/ϵ3	68	57	616	78.9 (1.8)	90	36.6 (5.5)	1.0

*RR indicates relative risk; CI confidence interval; and *APOE*, apolipoprotein E.

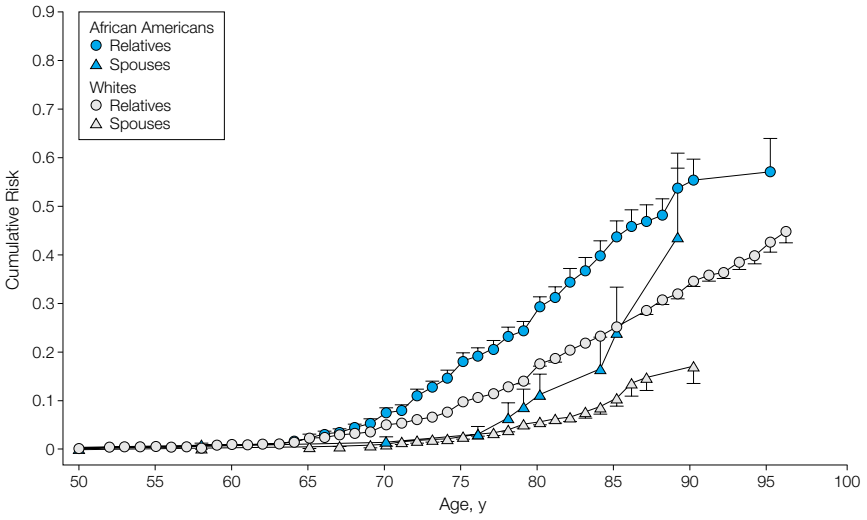
higher baseline risk of dementia, or both. These possibilities can be distinguished by examining the risk of dementia among spouses of our AD patients who are matched by age and share many environmental determinants. We find that spouses of African American patients with AD are 1.8 times more likely to develop dementia than spouses of white patients, and that the proportionate *additional* risk conferred by being a first-degree relative is quite similar in each ethnic group (2.6 in whites vs 2.4 in African Americans). Thus we conclude that risk attributable to familial aggregation is very similar in African American families and white families.

As shown in Table 2 and Figure 2, female relatives are at higher risk than male relatives. Figure 4 suggests that while the risk associated with African American ethnicity is much larger than that associated with sex of the relative, the degree to which sex influences risk within each ethnic group is similar.

In the subset of AD patients for whom we assessed *APOE* genotype, we were also able to calculate risks in relatives stratified by the genotype of the patient. Although the genotypes of the relatives themselves were not available, this stratification serves as an estimate of the probability of finding an ϵ4 allele in the relatives of each strata.[5] Figure 3 and Figure 5 once again suggest that ethnicity is a more powerful risk factor for dementia in relatives than the presence of an ϵ4 allele in the proband. And, although the curves implied in Figure 5 are not completely parallel, with relatively wide SEs around the point estimates in the African American relatives, they too suggest that the increase among relatives that can be attributed to the probability of having an ϵ4 allele is quite similar in both ethnic groups.

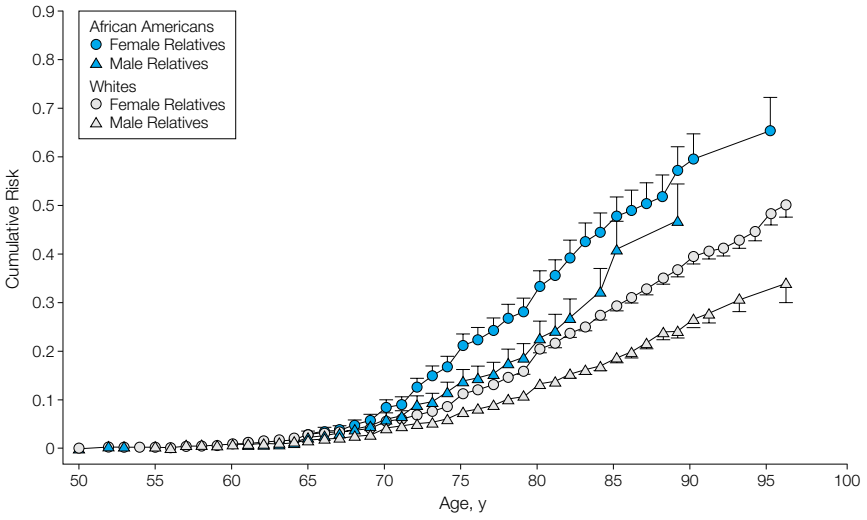
The only other study to estimate familial risk in African American families solicited family history information from incident cases of AD and controls in a community-based study of white, African American, and Caribbean Hispanics in northern Manhattan.[20,21] Devi et al[21] studied 57 white patients with AD with 219 relatives and 112 African American patients with AD with 362 relatives but did not report cumulative risk estimates by ethnicity. They used Cox proportional hazard analysis to adjust for proband's sex, educational level, and the sex of the relatives, to calculate adjusted rate ratios. They found relatives of white patients to have a rate ratio of 2.0 (95% CI, 1.2-3.3) compared with the relatives of controls, and the relatives of African American patients to have a rate ratio of 1.4 (95% CI, 0.7-2.7) compared with the relatives of controls. No comparisons were drawn between the risks to African American relatives and the risks to white relatives of AD patients. The magnitude of the increase in risk between

Figure 1. Cumulative Risk of Dementia in First-Degree Biological Relatives and in Spouses of Probands, Stratified by Ethnicity of Probands



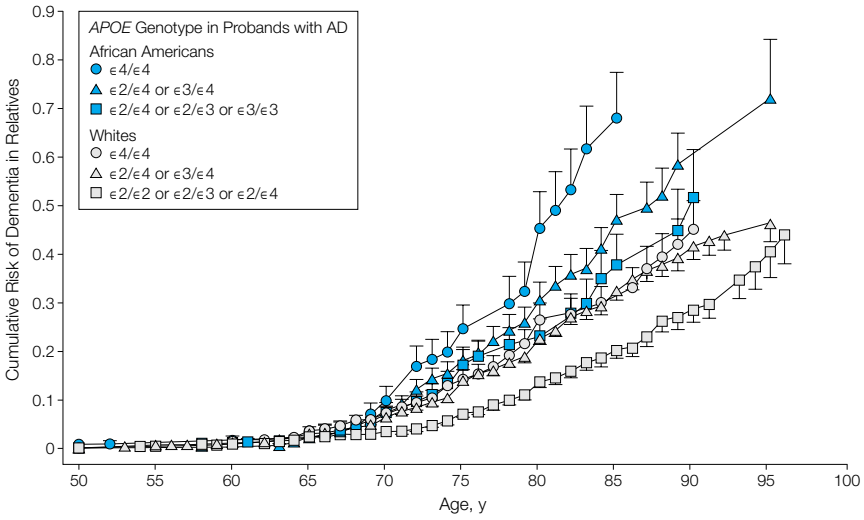
Error bars indicate SE.

Figure 2. Cumulative Risk of Dementia in First-Degree Biological Relatives of Alzheimer Disease Probands, Stratified by Relatives' Sex and Ethnicity



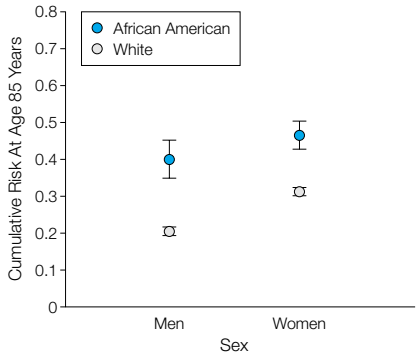
Error bars indicate SE.

Figure 3. Cumulative Risk of Dementia in First-Degree Biological Relatives of Alzheimer Disease (AD) Probands, Stratified by Probands' Apolipoprotein E (*APOE*) Genotype and Ethnicity



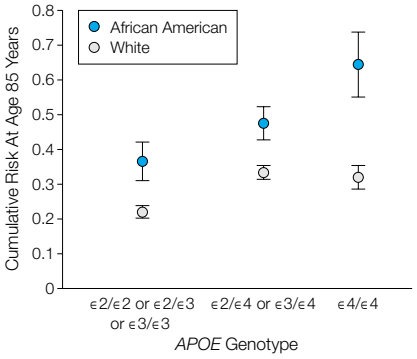
Error bars indicate SE.

Figure 4. Risk of Dementia at Age 85 Years in Male and Female First-Degree Biological Relatives of Alzheimer Disease Probands, Stratified by Sex and Ethnicity



Error bars indicate SE.

Figure 5. Risk of Dementia at Age 85 Years in First-Degree Biological Relatives of Alzheimer Disease Probands, Stratified by Probands' Apolipoprotein E (*APOE*) Genotype and Ethnicity



Error bars indicate SE.

the relatives of their patients compared with the relatives of their controls is similar to the magnitude of increased risk among both white and African American relatives in our study in comparison to spouses.

In a population of 101 white patients and 195 African American patients, Devi et al[20] also examined the additional risk conferred by the presence of an ε4 allele in the proband. Direct comparisons with our results are not straightforward because they did not compare risk across ethnic groups, and their data were stratified by the presence of at least 1 ε4 allele while ours were stratified into 3 groups (no, 1, or 2 ε4 alleles). Among relatives of patients with AD, Devi et al found that the presence of at least 1 ε4 allele doubled the adjusted risk among whites and tripled the adjusted risk among African Americans, which appears consistent with our findings.

Our findings are based on cross-sectional data from clinic-based recruitment at 17 major medical centers, within both large and small cities. Our findings in African Americans are based on families recruited primarily in Atlanta, Ga; Birmingham, Ala; Boston, Mass; and Charleston, SC. Although this sampling scheme does not represent the population at large, it is an appropriate population from which to derive risk estimates for family members of clinic-based AD patients who are seeking risk information. African American probands and their families were recruited in exactly the same way as white probands and their families.

Limitations

Our study has several limitations. It is possible that white and African American informants might be differentially referred or self-referred to clinics, or might differentially report dementia among family members. A selection or reporting bias of this nature could explain some of the risk differences that we found. There are few data on the differences in referral patterns of African American and white families with affected members. However, there are data to suggest that there is relative underreporting of cases among African American families.[22-24] If true, a bias of this nature would reduce the estimated risk of dementia among African American relatives and bias the relative risks between white and African Americans toward the null.

Data on educational level were not available for the relatives of probands, and therefore the risk estimates presented herein could not be adjusted for education. Educational level was available for the probands, and on average the white probands in the study were more highly educated than the African American probands. However, stratification by educational level of the proband did not change the overall results.

Despite the large number of families overall, there are considerably fewer African American probands and relatives, which, when stratified, result in wide CIs. Also, the results of this study are most relevant to clinic-based populations, particularly those at referral cen-

ters, and may be less representative of families who are not evaluated by clinicians or who are evaluated in primary care settings or in community practices.

The relatives of the affected probands in this study were often deceased or unavailable so that the categorization of affected relatives was made on the basis of historical information. Since most affected relatives lacked a definitive diagnosis, we have described the familial risk of dementia rather than ascribing a particular diagnosis such as AD to the relatives. Since cerebrovascular risk factors such as hypertension and diabetes are more common among African Americans, it is possible that differential rates of cerebrovascular disease among African American relatives could explain some of the differences described herein. Furthermore, we did not have measures of comorbid illness of the probands. However, validation studies in other populations have produced evidence that the family history method is valid and that cognitively impaired relatives of AD patients overwhelmingly have AD.[25,26]

Implications

A number of epidemiological studies have examined the risk of dementia or of AD in white and African American people, and recent studies have consistently supported a higher age-specific prevalence of dementia,[27] cumulative risk of AD,[28] and incidence rates of AD[29] among African Americans compared with non-Hispanic whites. Most relevant to our findings, Tang et al[31] reported that the cumulative risk of AD among African Americans by age 90 years is 4 times that of whites.

The association between *APOE* genotype and risk of AD is well established in white populations,[2] and the association in African Americans is of great interest. A number of studies have suggested a weaker association between ϵ4 and AD in African Americans than in whites[30-32] as well as a weaker association among elderly Nigerians[33] and Kenyans.[34] The data on risk in family members presented in this article do not address this question, but our analysis of *APOE* information from a large group of MIRAGE probands, siblings, and unrelated controls indicates that ϵ4 is an important risk factor for AD in African Americans, particularly among those younger than 70 years.[10] Taken together, our data suggest that genetic factors other than *APOE* play an important role in the heritable component of AD in both white and African American families.

Figures 1 and 2 provide clinicians with information that can be used to advise family members of patients with AD who ask about their own average risk of developing dementia. Figure 1 provides a contrast between the average risk of a first-degree biological relative and that of the general population, as estimated through the spouses of probands, although this should be interpreted with caution because spouses are not truly representative of the population at large and because the number of affected African American spouses is so low. Figure 2 provides the most refined category of risk estimate, stratified by ethnicity and sex. Because *APOE* genotyping is not currently advocated to help estimate risk,[35-40] Figure 3 is of scientific interest but should not be used for clinical counseling.

In conclusion, our findings in this report support the growing body of data that risk of dementia and AD is higher in African Americans than in whites.[27,29] However, within each ethnic group, the additional risk conferred by being a first-degree biological relative, by being female, or by the probability of having an ϵ4 allele is of very similar magnitude. Our data provide estimates of dementia risk that can be used to provide counseling to family members of patients with AD.

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Flowers changed the face of the planet. Without them, the world we know—even man himself—would never have existed. Francis Thompson, the English poet, once wrote that one could not pluck a flower without troubling a star. Intuitively he had sensed like a naturalist the enormous interlinked complexity of life. Today we know that the appearance of the flowers contained also the equally mystifying emergence of man.
—Loren Eiseley (1907-1977)