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Mortality and Apolipoprotein E in Hispanic, African-American, and Caucasian Elders

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To investigate whether mortality risk is influenced by apolipoprotein E (APOE) genotype and whether the risk differs by ethnicity, we compared the mortality risk in 2,112 individuals ≥ 65 years of age residing in northern Manhattan in New York. Mortality risks associated with the APOE genotype, adjusted for sex, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides, differed significantly by ethnic group. Among Caucasian and Hispanics, the E2/E3 genotype was associated with the lowest mortality risk in the multivariate Cox proportional hazards modeling, adjusted for lipid levels, whereas mortality risk did not differ substantially between the E4/E3 and E3/E3 genotypes. Among African-Americans, the E2/E3 genotype was not associated with the lowest mortality risk, but the E4/E3 genotype was. Adjustment for heart disease, diabetes, and stroke reduced mortality risk associated with each genotype by about 50% for all ethnic groups, but the patterns remained the same. Although we cannot rule out the possibility of a healthy survival bias, our analyses designed to examine healthy survival by comparing risk of mortality in groups who were younger or older at entry do not support this possibility. Our findings suggest that the APOE genotype is associated with mortality and that the genotypic risks differ by ethnic group. Nearly 50% of the mortality risk associated with the APOE genotype appears to act through major chronic diseases, but those diseases only partially explain the mechanism by which the genotypic risk acts. To better understand the observed ethnic differences in mortality risk by genotype, a detailed prospective study is needed to examine the relationships among APOE, other candidate genes, health conditions, and eventual death. © 2001 Wiley-Liss, Inc.

KEY WORDS: Apolipoprotein E; mortality; ethnicity

INTRODUCTION

Human longevity is the outcome of a complex interplay between genetic and environmental influences [Finch and Tanzi, 1997]. According to twin studies, the genetic contribution to longevity in humans is estimated to be between 23% and 35% [Herskind et al., 1996; Ljungquist et al., 1998]. Several studies have examined whether the apolipoprotein E (APOE) gene influences longevity, since the APOE E4 allele has been shown to increase the risk of age-related diseases, such as Alzheimers disease [Corder et al., 1993; Tang et al., 1998] and cardiovascular diseases [Davignon et al., 1988]. To date, the relationship of the APOE genotype to longevity is not well understood, especially in different ethnic groups. In a group of French centenarians,

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the APOE E2 allele frequency was elevated and the E4 allele frequency was lowered, compared with a younger comparison group, suggesting that the E2 allele enhances longevity, whereas the E4 allele leads to mortality [Schachter et al., 1994]. Similar elevated E2 allele frequencies were observed in Japanese centenarians and Finnish centenarians [Hirose et al., 1997; Louhija et al., 1994]. However, in other populations, including Canadian, British, and Italian octogenarians and a randomly chosen Han Chinese population, the frequency of the E2 allele was similar in the older and younger cohorts, and the frequency of the E4 allele was not consistently lower in the older cohort [Davignon et al., 1988; Galinsky et al., 1997; Bader et al., 1998; Jian-Gang et al., 1998]. To further elucidate the role of APOE in mortality and to examine differential effects in different ethnic groups, we studied the risk of mortality associated with the APOE genotype in Caucasians, Hispanics, and African-Americans, while controlling for risk factors that may influence an individual's survival.

MATERIALS AND METHODS

Subjects

We studied 2,112 individuals who were ≥ 65 years of age and residing in northern Manhattan in New York. A detailed description of the ascertainment and recruitment procedure is presented in an earlier paper [Tang et al., 1998]. Briefly, 5,403 individuals were randomly selected from a pool of 9,349 healthy Medicare recipients residing in northern Manhattan in New York. Of 5,403 individuals, 1,951 were ineligible because they were deceased, had moved from the designated study area, did not speak English or Spanish, or were not reachable. Two individuals appeared twice in the database under different names. Of the remaining 3,450 eligible subjects, 2,126 (62%) participated in the study. Here we included 2,112 individuals who reported their ethnicity as non-Hispanic Caucasian ($n = 447$), non-Hispanic African-American ($n = 733$), or Hispanic ($n = 932$). This classification of ethnicity conformed to the 1990 U.S. Census categories. At the time of study entry, each individual was interviewed about their general health and functional status and was given medical, physical, and neurological examinations and a battery of neuropsychological tests [Stern et al., 1992]. The same clinical assessments were administered annually from 1991-1998. The Columbia University Institutional Review Board reviewed and approved the project.

Outcomes

We obtained vital status from the follow-up interviews and from the National Death Index. Information on cause(s) of death was obtained from the relatives of the deceased and was augmented with additional information (e.g., medical records, autopsy reports, etc.) when available. Chronic health conditions were determined during the annual clinical examinations. Throughout the follow-up period, clinicians were blinded to the APOE status of the subjects.

APOE Genotyping

Genomic DNA was amplified by PCR and subjected to CfoI restriction analysis using APOE primers and conditions modified from those described by Hixson and Vernier [1990].

Statistical Methods

We used a χ^2 test to compare allele frequencies between surviving and deceased individuals [Sokal and Rohlf, 1995]. We then computed cumulative survival probability associated with APOE using the Kaplan-Meier estimator and multivariate Cox proportional hazards modeling. For the Kaplan-Meier estimator, we computed cumulative survival probability within each ethnic group. Subsequently, we computed mortality risk for nine ethnic-genotype groups using multivariate Cox proportional hazards modeling. We chose to include three genotypes (E2/E3, E3/E3, and E4/E3), because they represent 94% of the subjects, as well as a clear dose-response relationship in which each genotype reveals the additive effect of alleles 2-4, while holding constant the effect of having one E3 allele. Because APOE has been shown to modulate lipoprotein levels, we used multivariate Cox proportional hazards modeling to estimate mortality risks associated with the APOE genotype, adjusting for age, sex, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides. We then used a Cox proportional hazards model to estimate mortality risk, adjusting for chronic health conditions associated with increased mortality, namely heart disease, stroke, and diabetes. If the APOE genotype affects mortality risk first by influencing lipid levels and subsequently by influencing risks for diabetes, heart disease, and stroke, the rate ratios associated with APOE should be reduced significantly when those conditions are included in the multivariate model, since they would be mediating risk factors. In the Cox proportional hazards models, age was classified as age at death for deceased individuals and age at the time of last interview for surviving individuals. To account for a possible healthy survivor bias, we ran additional Cox proportional hazards models stratified by age at entry into the study (≤ 75 vs. > 75 years). All analyses used SPSS for Windows (version 9) [SPSS, 1998].

RESULTS

Table I shows the distribution of demographic characteristics and the APOE genotype of the study participants within each ethnic group. There were twice as many women as men participating (69.3% vs. 30.7%), and the difference in sex ratio was observed consistently across ethnic groups. The largest number of participants identified themselves as Hispanic (44.1%), followed by African-American (34.7%) and Caucasian (21.2%). A total of 456 subjects (21.6%) were reported to be deceased after they entered the study,

TABLE I. Demographic and Apolipoprotein Characteristics of the Participants by Ethnicity*

	Total		Caucasians		Hispanics		African-Americans	
Variable	N	%	N	%	N	%	N	%
Sex								
Male	648	30.7	152	34.0	285	30.6	211	28.8
Female	1,464	69.3	295	66.0	647	69.4	522	71.2
Vital status								
Deceased	456	21.6	104	23.3	173	18.6	179	24.4
Surviving	1,656	78.4	343	76.7	759	81.4	554	75.6
Education (years)								
≤ 6	787	37.3	55	12.3	572	61.4	160	21.9
7–11	655	31.0	110	24.6	252	27.1	293	40.0
≥ 12	668	31.7	282	63.1	107	11.5	279	38.1
Age at entry (years)								
≤ 75	1,046	49.5	197	44.1	494	53.0	355	48.4
> 75	1,066	50.5	250	55.9	438	47.0	378	51.6
Apolipoprotein genotype								
E4/E4	29	2.1	5	1.8	14	2.1	10	2.2
E3/E4	328	23.8	60	22.1	135	20.5	133	29.6
E3/E3	800	57.9	169	62.1	415	63.0	216	48.0
E2/E4	40	2.9	3	1.1	14	2.1	23	5.1
E2/E3	171	12.4	34	12.5	76	11.5	61	13.6
E2/E2	13	0.9	1	0.4	5	0.8	7	1.6

*Restricted to self-reported Caucasians, Hispanics, and African-Americans.

and 1,656 remained alive. Overall, the distribution of education level divided roughly by one-third among ≤ 6 years, 7-11 years, and ≥ 12 years; however, the proportion of individuals with ≤ 6 years of education was much higher in Hispanics than in other ethnic groups. The mean age at entry into the study was 75 years. This table also shows the distribution of APOE alleles; overall, the E3/E3 genotype was most common (57.9%), followed by the E4/E3 genotype (23.8%) and the E2/E3 genotype (12.4%). Further, the E3/E4 and E2/E4 genotype frequencies were somewhat higher in African-Americans than in Caucasians and Hispanics.

Table II shows that, in Caucasians, the E2 allele frequency was nearly fourfold higher in surviving individuals than in deceased individuals ($X^2 = 3.9$, $P = 0.048$; the E3 allele as the reference group), while in Hispanics, the E2 allele frequency was twofold higher ($X^2 = 4.4$, $P = 0.037$; the E3 allele as the reference group). In African-Americans, however, the E2 allele frequency was equally high in both surviving and deceased individuals (10.9% vs. 11.0%; $X^2 = 0.1$, $P = 0.739$; the E3 allele as the reference group), but the E4 allele frequency was higher in surviving individuals ($X^2 = 4.9$, $P = 0.027$; the E3 allele as the reference group). Among surviving individuals, the E4 allele

TABLE II. Allele Frequency by Vital Status Within Ethnic Group

	Allele frequency		
Allele	Total (%)	Surviving individuals (%)	Deceased individuals (%)
Caucasians	(n = 544)	(n = 456)[a]	(n = 88)
E2	7.2	8.1	2.3
E3	79.4	78.3	85.2
E4	13.4	13.6	12.5
Hispanics	(n = 1,318)	(n = 1,118)	(n = 200)
E2	7.6	8.2	4.0
E3	79.0	78.4	82.5
E4	13.4	13.4	13.5
African-Americans	(n = 900)	(n = 736)	(n = 164)
E2	10.9	10.9	11.0
E3	69.5	68.2	75.6
E4	19.6	20.9	13.4

[a]n represents the number of alleles, not individuals.

frequency was higher in African-Americans than in Caucasians or Hispanics.

Among Caucasians and Hispanics, the same pattern of cumulative survival probability was observed with increased survival for those with the E2/E3 genotype, compared with those with the E3/E3 and E4/E3 genotypes ($P = 0.0602$ for Caucasians; $P = 0.1144$ for Hispanics) (Fig. 1). Among African-Americans, the pattern differed from those in Caucasians and Hispanics in that the E4/E3 genotype was associated with the highest cumulative survival probability, while the E3/E3 genotype was associated with the lowest ($P = 0.0791$). Because mortality risk, an inverse of cumulative survival probability, was different for African-Americans than for Caucasians and Hispanics in general, we computed mortality risk by creating nine genotype and ethnicity groups using the Caucasians with the E2/E3 genotype as the comparison group. This group was chosen as the reference group because they had the lowest mortality risk.

Figure 2 shows that mortality risks associated with the APOE genotype—adjusting for sex, HDL, LDL, and triglycerides—differ by ethnic group (model 1, solid bars). Among Caucasians and Hispanics, the E2/E3 genotype was associated with the lowest mortality risk (Caucasians, RR = 1.0, reference group; Hispanics, RR = 2.1, 95% CI = 0.4-10.9), and mortality risk did not differ substantially between E3/E3 and E4/E3 genotypes (Caucasians, $RR_{E3/E3} = 5.5$, 95% CI = 1.3-23.6 and $RR_{E4/E3} = 4.7$, 95% CI = 0.9-24.14; Hispanics, $RR_{E3/E3} = 5.6$, 95% CI = 1.3-23.4 and $RR_{E4/E3} = 6.4$, 95% CI = 1.5-28.1). Compared with Caucasians with the E2/E3 genotype, African-Americans showed consistently elevated risk of mortality; however, the pattern of genotypic risk was different than among Caucasians or Hispanics. African-Americans with the E3/E3 genotype had the highest risk (RR = 9.6, 95% CI = 2.3-41.3), while the E4/E3 genotype was associated with the lowest mortality risk (RR = 4.2, 95% CI = 0.9-19.5), followed by the E2/E3 genotype (RR = 7.0, 95% CI = 1.5-32.5).

Adjustment for chronic health conditions that increase mortality (heart disease, diabetes, and stroke) reduced relative risk of mortality associated with each genotype by about 50% for all ethnic groups (model 2 in Fig. 1, hashed bars), but the patterns remained the same. That is, among Caucasians and Hispanics, the E3/E3 and E4/E3 genotypes were associated with two- to threefold increased risk (Caucasians, $RR_{E3/E3} = 3.3$, 95% CI = 0.8-14.0 and $RR_{E4/E3} = 2.2$, 95% CI = 0.5-10.7; Hispanics, $RR_{E3/E3} = 3.6$, 95% CI = 0.9-14.7 and $RR_{E4/E3} = 3.6$, 95% CI = 0.8-15.3). Among African-Americans, however, relative risk of mortality was lowest for individuals with the E4/E3 genotype (RR = 2.4, 95% CI = 0.5-10.7), followed by the E2/E3 genotype (RR = 3.7, 95% CI = 0.8-16.9) and the E3/E3 genotype (RR = 4.8, 95% CI = 1.2-20.0).

Results from our stratified analyses by age at entry to account for possible healthy survivor bias did not showed significant changes in mortality risk associated with the APOE genotype. For example, for Caucasians, the risk ratio for the E3/E3 genotype changed from 5.5

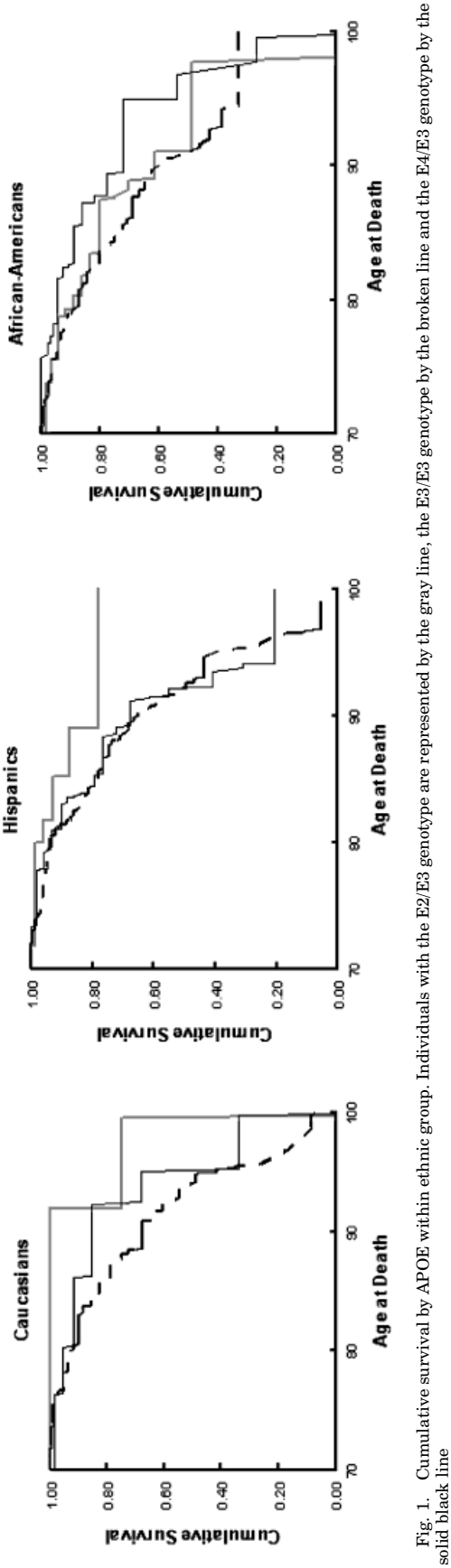

Fig. 1. Cumulative survival by APOE within ethnic group. Individuals with the E2/E3 genotype are represented by the gray line, the E3/E3 genotype by the broken line and the E4/E3 genotype by the solid black line

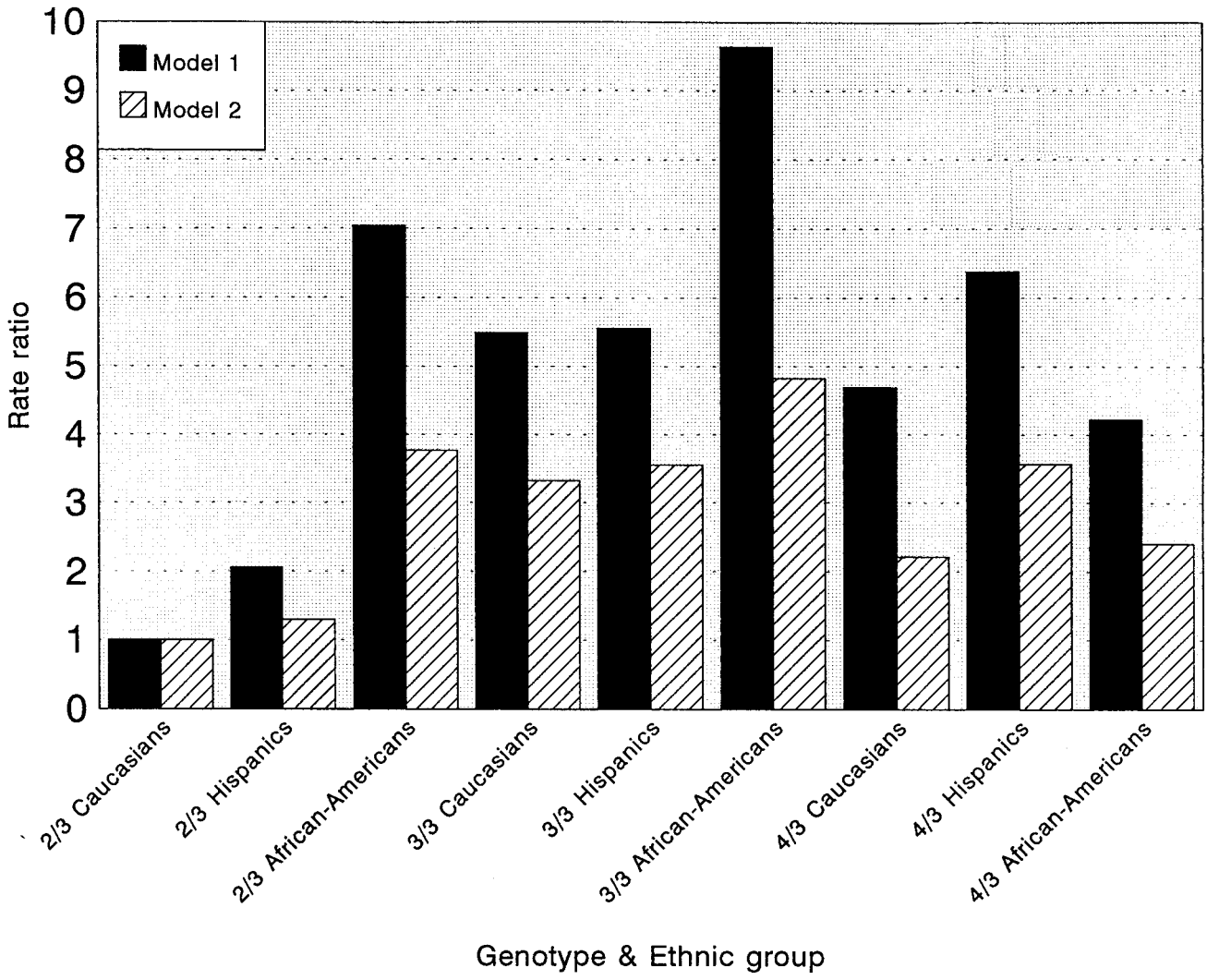

Fig. 2. Mortality risk by APOE and ethnic group. Model 1 includes APOE ethnic group, sex, HDL, LDL, and triglycerides in the Cox proportional hazards model. Model 2 includes APOE ethnic group, sex, heart disease, stroke, and diabetes.

to 5.4 after stratification; that for the E4/E3 genotype changed from 4.7 to 4.6 after stratification. For African-Americans, the risk ratio for the E2/E3 genotype changed from 7.0 to 7.4; that for the E3/E3 genotype changed from 9.6 to 7.9; that for the E4/E3 genotype changed from 4.2 to 3.7. We were unable to examine the relationship between genotype and cause of death due to a small number of cases with known causes of death.

DISCUSSION

We found that the influence of the APOE genotype on mortality varies by ethnic group. Among Caucasians and Hispanics, mortality risks associated with the E2/E3 genotype were lower than mortality risks associated with either the E4/E3 or E3/E3 genotypes. In contrast, among African-Americans, the E2/E3 genotype was not associated with low mortality risk. In the three ethnic groups, the E4/E3 genotype was not associated with increased risk of mortality; among Caucasians and Hispanics, mortality risks were comparable with those for the E4/E3 and E3/E3 genotypes, while among African-Americans, mortality risks were somewhat lower in those with the E4/E3 genotype than in those with the E3/E3 genotype.

We observed lower mortality risk associated with the E2/E3 genotype in Caucasians and Hispanics, but not in African-Americans. Previous studies show an inconsistent relationship between mortality risk and APOE. Among French centenarians, Schachter et al. [1994] found the E2 allele frequency to be higher than that in the 20-70 year old cohort (12.8% vs. 6.8%, respectively). Similarly, others observed high E2 allele frequencies in Japanese centenarians [Hirose et al., 1997], Swedish elderly (age $>$ 60 years of age) [Eggertsen et al., 1993], and the U.S. non-Black 65- to 90-year-old cohort [Cauley et al., 1993], compared with younger comparison groups. On the other hand, Bader et al. [1998] observed a lower E2 allele frequency in a health cohort

of $\geq$ 80-year-old Italians than in younger (20-70 years old) cohorts. In other populations, including Canadian and British octogenarians and a randomly chosen Han Chinese population, however, the E2 frequency did not differ significantly between the older and younger cohorts [Davignon et al., 1988; Galinsky et al., 1997; Jian-Gang et al., 1998]. The basis for these differences may be related to different ascertainment strategies and potential differences in known risk factors, such as sex, lipids, and health conditions. In our earlier report, we observed lower LDLs in individuals with E2 alleles in all three ethnic groups [Pablos-Mendez et al., 1997]. Taken together, these findings suggest that individuals with an E2 allele may have lower risk of mortality because they have lower LDL and thus lower risk of cardiovascular disease. In support of this hypothesis, we found that rate ratios for mortality were reduced by approximately 50% when chronic health conditions were included in the model, but the differences between African-Americans and Caucasians or Hispanics persisted. This suggests that the protective effect of the E2 allele is only partly explained by its relationship to disease risk.

Previous studies have reported lower E4 frequencies in older cohorts than in younger cohorts [Davignon et al., 1988; Kervinen et al., 1994; Schachter et al., 1994; van Bockxmeer, 1994], suggesting that the E4 allele increases risk for mortality. Previous investigators have suggested that the increased risk of mortality associated with the E4 allele may be mediated by increased cholesterol level and cholesterol-related disease. In our previous paper [Pablos-Mendez et al., 1997], individuals with an E4 allele had higher cholesterol levels in all three ethnic groups. In the current study, however, mortality risk associated with the E4/E3 genotype was not significantly elevated compared with the E3/E3 genotype in any ethnic group. The findings suggest that the presence of an E4/E3 genotype does not necessarily lead to early death in affected individuals, and it may lead to milder forms of these chronic diseases. Further, in a separate exploratory analysis based on a small number of cases (data not shown), the E4/E4 genotype, a known risk factor for dementia, was associated with the lowest mortality risk in Caucasians and Hispanics. The apparent lack of association between the E4/E3 genotype and mortality in our sample is in agreement with the lack of relationship between dementia and mortality in our sample (data not shown). Again, the literature on this relationship is equivocal, and a further longitudinal study is needed.

Several factors may contribute to the differences in mortality risk that we observed among ethnic groups. First, genes flanking APOE, as well as other contributing or modifying genes, may differ in the three ethnic groups and this may contribute to differential mortality risk. In 19q13.2, a cluster of APOE-CI-CI′-CII resides within a region that is approximately 25 kb long [Chartier-Harlin et al., 1994], and the LDL receptor is also linked to this region [Davignon et al., 1988]. Moreover, other genes not linked to the APOE cluster may also contribute to mortality by acting in concert to produce differential risk. Interestingly, previous studies have revealed that the E2 allele is extremely rare (0%) in Amerindians [Crawford, 1998] and very rare (2.7%-3.4%) in Africans [Weiss, 1993]. Thus, for the Hispanics in this study, who are largely from the Dominican Republic, the observed protective effect associated with an E2 allele may be due both to E2 and other genes flanking the regions derived from Spanish ancestors, since they are admixed with Amerindians, Spaniards, and Africans [Moya Pons, 1998]. Haplotype analysis in the apolipoprotein region and identification of other modifying genes will be needed to fully evaluate the variations in the genetic risks in different ethnic groups.

Second, environmental risk factors associated with increased mortality are likely to vary among ethnic groups. Differences in diet and lifestyle factors may contribute to differences in mortality risk. Thus, the variation in mortality risk associated with the E2 allele among ethnic groups may be due to interactions between gene and environment.

Third, the age requirement for participation in this study (age $\geq$ 65) may have led to a healthy survivor bias for APOE that differed among ethnic groups and might account for variation in genotypic risks. We found that mortality risk associated with the E4/E3 genotype was similar to mortality risk associated with the E3/E3 genotype in Caucasians and Hispanics, but was lower in African-Americans. If the E4 allele increases risk of cardiovascular disease in individuals with the E4/E3 genotype, leading to early death (before age 65), the observed mortality risk associated with the E4/E3 genotype would be lower than the true risk. Further, if selection bias for the E4/E3 genotype related to early cardiovascular mortality was greater in African-Americans than in Caucasians or Hispanics, the E4/E3 genotype might appear protective, when in fact it is not. To evaluate this possibility, we stratified our analyses by age at entry to the study. If the age requirement resulted in selection bias, we would expect to observe higher mortality risks associated with the E4/E3 genotype in individuals $<$ 75 years of age than in individuals who were $\geq$ 75 years of age. However, the stratified Cox proportional hazards model revealed no significant change in rate ratios. Further, for Caucasians, the E4 allele frequency in this study was comparable to that in the younger cohort (age, 45-71) from the Framingham community-based cohort study [Ordovas et al., 1987] and that in the controls from the Alzheimer's Disease Meta Analysis Consortium [Farrer et al., 1997] (13.4% vs. 13.5% vs. 13.7%, respectively), suggesting that the magnitude of selection bias with respect to APOE is unlikely to be large, at least for Caucasians in this study. Among African-Americans, on the other hand, selection bias could have occurred because individuals with more severe forms of these conditions died before reaching eligible age at entry to the study, while those with milder forms participated in this study. This possibility cannot be ruled out since the prevalence of heart disease, stroke, and diabetes was comparable in all three ethnic groups in this study, while other cohort studies have reported the prevalence

of these conditions in African-Americans to be higher than in Caucasians [Karter et al., 1998; Williams et al., 1999]. For example, prevalence of heart disease in the current study was slightly lower in African-Americans (24.6%) than in Caucasians (27.4%), and prevalence of diabetes was higher in African-Americans (16.3%) than in Caucasians (8.9%).

In sum, the E2/E3 genotype was associated with lower mortality risk in Caucasians and Hispanics, but not African-Americans, while the E4/E3 genotype was associated with lower mortality risk in African-Americans. To better understand the observed ethnic differences in mortality risk, a prospective study is needed to examine how risk for specific diseases varies with the APOE genotype in these populations, and then to examine how risk for mortality varies in affected individuals. This investigation will need to include evaluation of the effects of flanking genes in the apolipoprotein region and of other, unlinked genes that may modify APOE activity.

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REFERENCES

Bader G, Zuliani G, Kostner GM, Fellin R. 1998. Apolipoprotein E polymorphism is not associated with longevity or disability in a sample of Italian octo- and nonagenarians. Gerontology 44:293–299.

Cauley JA, Eichner JE, Kamboh MI, Ferrell RE, Kuller LH. 1993. Apo E allele frequencies in younger (age 42–50) vs older (age 65–90) women. Genet Epidemiol 10:27–34.

Chartier-Harlin MC, Parfitt M, Legrain S, Perez-Tur J, Brousseau T, Evans A, Berr C, Vidal O, Roques P, Gourlet V. 1994. Apolipoprotein E, epsilon 4 allele as a major risk factor for sporadic early and late-onset forms of Alzheimer's disease: analysis of the 19q13.2 chromosomal region. Hum Mol Genet 3:569–574.

Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261:921–923.

Crawford M. 1998. The origins of Native Americans: evidence from anthropological genetics. New York: Cambridge University Press. p 308.

Davignon J, Gregg RE, Sing CF. 1988. Apolipoprotein E polymorphism and atherosclerosis. Arteriosclerosis 8:1–21.

Eggertsen G, Tegelman R, Ericsson S, Angelin B, Berglund L. 1993. Apolipoprotein E polymorphism in a healthy Swedish population: variation of allele frequency with age and relation to serum lipid concentrations. Clin Chem 39:2125–2129.

Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. 1997. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 278:1349–1356.

Finch CE, Tanzi RE. 1997. Genetics of aging. Science 278:407–411.

Galinsky D, Tysoe C, Brayne CE, Easton DF, Huppert FA, Dening TR, Paykel ES, Rubinsztein DC. 1997. Analysis of the apo E/apo C-I, angiotensin converting enzyme and methylenetetrahydrofolate reductase genes as candidates affecting human longevity. Atherosclerosis 129:177–183.

Herskind AM, McGue M, Holm NV, Sorensen TI, Harvald B, Vaupel JW. 1996. The heritability of human longevity: a population-based study of 2872 Danish twin pairs born 1870–1900. Hum Genet 97:319–323.

Hirose N, Homma S, Arai Y, Kawamura M, Hasegawa H, Ishida H, Shimizu K, Osono Y, Homma A, Nakamura Y. 1997. Tokyo Centenarian Study. 4. Apolipoprotein E phenotype in Japanese centenarians living in the Tokyo metropolitan area. Nippon Ronen Igakkai Zasshi 34:267–272.

Hixson JE, Vernier DT. 1990. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. J Lipid Res 31:545–548.

Jian-Gang Z, Yong-Xing M, Chuan-Fu W, Pei-Fang L, Song-Bai Z, Nui-Fan G, Guo-Yin F, Lin H. 1998. Apolipoprotein E and longevity among Han Chinese population. Mech Ageing Dev 104:159–167.

Karter AJ, Gazzaniga JM, Cohen RD, Casper ML, Davis BD, Kaplan GA. 1998. Ischemic heart disease and stroke mortality in African-American, Hispanic, and non-Hispanic white men and women, 1985 to 1991. West J Med 169:139–145.

Kervinen K, Savolainen MJ, Salokannel J, Hynninen A, Heikkinen J, Ehnholm C, Koistinen MJ, Kesaniemi YA. 1994. Apolipoprotein E and B polymorphisms–longevity factors assessed in nonagenarians. Atherosclerosis 105:89–95.

Ljungquist B, Berg S, Lanke J, McClearn GE, Pedersen NL. 1998. The effect of genetic factors for longevity: a comparison of identical and fraternal twins in the Swedish Twin Registry. J Gerontol A Biol Sci Med Sci 53:M441–M446.

Louhija J, Miettinen HE, Kontula K, Tikkanen MJ, Miettinen TA, Tilvis RS. 1994. Aging and genetic variation of plasma apolipoproteins. Relative loss of the apolipoprotein E4 phenotype in centenarians. Arterioscler Thromb 14:1084–1089.

Moya Pons F. 1998. The Dominican Republic: a national history. Princeton: Markus Wiener Publishers. p 543.

Ordovas JM, Litwack-Klein L, Wilson PW, Schaefer MM, Schaefer EJ. 1987. Apolipoprotein E isoform phenotyping methodology and population frequency with identification of apoE1 and apoE5 isoforms. J Lipid Res 28:371–380.

Pablos-Mendez A, Mayeux R, Ngai C, Shea S, Berglund L. 1997. Association of apo E polymorphism with plasma lipid levels in a multiethnic elderly population. Arterioscler Thromb Vasc Biol 17: 3534–3541.

Schachter F, Faure-Delanef L, Guenot F, Rouger H, Froguel P, Lesueur-Ginot L, Cohen D. 1994. Genetic associations with human longevity at the APOE and ACE loci. Nat Genet 6:29–32.

Sokal RR, Rohlf FJ. 1995. Biometry: the principles and practice of statistics in biological research. New York: W.H. Freeman. p xix, 887.

SPSS. 1998. SPSS base 9.0 for Windows: user's guide. Chicago: SPSS, Inc.

Stern Y, Alexander GE, Prohovnik I, Mayeux R. 1992. Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. Ann Neurol 32:371–375.

Tang MX, Stern Y, Marder K, Bell K, Gurland B, Lantigua R, Andrews H, Feng L, Tycko B, Mayeux R. 1998. The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics [Comments]. JAMA 279:751–755.

van Bockxmeer FM. 1994. ApoE and ACE genes: impact on human longevity [News]. Nat Genet 6:4–5.

Weiss KM. 1993. Genetic variation and human disease: principles and evolutionary approaches Cambridge studies in biological anthropology. Cambridge; New York: Cambridge University Press. p xxiv, 354.

Williams JE, Massing M, Rosamond WD, Sorlie PD, Tyroler HA. 1999. Racial disparities in CHD mortality from 1968–1992 in the state economic areas surrounding the ARIC study communities. Atherosclerosis risk in communities. Ann Epidemiol 9:472–480.