Apolipoprotein E, health, and mortality in Taiwanese older adults

Sarinnapha Vasunilashorn[1], Dana A. Glei[2], Chia-Ying Lan[3], Ron Brookmeyer[4]
Maxine Weinstein[2], Noreen Goldman[1]
[1]Office of Population Research, Princeton University
[2]Center for Population and Health, Georgetown University
[3]Center for Population and Health Survey Research, Department of Health, Taiwan
[4]Department of Biostatistics, University of California, Los Angeles

Introduction

Apolipoprotein E (ApoE), a commonly investigated genetic marker, has been linked to health outcomes and longevity. ApoE has three common alleles: E2, E3, and E4, with E3 being the most prevalent allele in most populations. The E4 allele is a common genetic risk factor for Alzheimer's and cardiovascular disease (Corder et al., 1996; Eichner et al., 2002; Lahoz et al., 2001; Rosvall et al., 2009), and in some populations, shorter lifespans (Ewbank, 2004, 2007; Schachter et al., 1994; Smith, 2002). The presence of one or two E4 alleles has been [documented as] associated with higher total cholesterol levels among both individuals undergoing and those not undergoing lipid-lowering treatment (Dufouil et al., 2005). The E2 allele may also have neuroprotective effects on the brain (Higgins et al., 1997; Rebeck, Kindy, LaDu, 2002), as it may play a direct role as an anti-oxidant agent (Miyata & Smith, 1996). While several studies have examined the relationship between ApoE and cardiovascular risk factors, few studies have examined the relationship of ApoE to a variety of other biological indicators of health or to indicators of performance-based measures of physical and cognitive function or depressive symptoms. The purpose of this study is to investigate these relationships between ApoE and biomarkers of health, depressive symptoms, and indicators of physical and cognitive function.

Methods

We use the Social Environment and Biomarkers of Aging Study (SEBAS) in Taiwan to examine how ApoE relates to outcomes that have been previously reported in the literature. SEBAS is based on a subsample of respondents from the Survey of Health and Living Status of the Near Elderly and Elderly in Taiwan (TLSA), a nationally representative survey of Taiwanese adults (including institutionalized individuals) that began in 1989. Two rounds of SEBAS data collection include in-home interviews and the collection of biomarkers from medical exams in hospitals. The first round, conducted in 2000, is based on 1023 randomly selected individuals aged 54 and older; the second round, fielded in 2006, follows individuals from SEBAS 2000 and includes a younger refresher cohort. Survival status and date of death were ascertained by linkage of survey records with death certificate information.

This study investigates the relationship between ApoE and mortality, cardiovascular (blood pressure) and metabolic markers (total cholesterol [total-C], high-density lipoprotein cholesterol [HDL-C], triglycerides, body mass index [BMI], and

waist-hip ratio [WHR]); and indicators of infection and inflammation (C-reactive protein [CRP], interleukin-6 [IL-6]).

For markers with an established at-risk cutpoint, we compare the proportion of ApoE4 carriers and non-carriers (as well as ApoE2 carriers and non-carriers) above (and below) the established threshold (measured in 2000). In models linking ApoE genotype to survival, participants with blood samples taken for genotyping in 2000 are followed until 2008.

We also examine interviewer-assessed performance-based measures of physical function (measured in 2006, including grip strength, chair stands, and 3m walking speed), depressive symptoms (measured in 2000 based on a short form of the Center for Epidemiologic Studies Depression Scale [CES-D]), and cognitive function (measured in 2000, based on a number of memory and cognitive tasks) in relation to the presence of an ApoE2 and ApoE4 allele.

Statistical analyses

We use a proportional hazards model with a Gompertz distribution to assess the association between ApoE genotype and survival, using age as the time-scale. In these survival analyses, three models that incorporate different categorizations of ApoE status adjust for age and sex; a fourth model further adjusts for marital status and education. These covariates are included in our analyses as they have been previously associated with mortality (Barford et al., 2006; Johnson et al., 2000; Lleras-Muney, 2005). Logistic and ordinary least squares regression models are used to determine the associations between ApoE carrier status and the extent of at-risk levels of biomarkers, depressive symptoms, and measures of physical and cognitive function. All analyses are carried out with STATA version 11 (StataCorp, College Station, TX).

Preliminary Results

The average age of the study sample is 67 years old, with slightly more men than women (57%) (Table 1). The majority of respondents are currently married (75%); 24% have more than six years of education. For ApoE, the E3 allele is the most prevalent (85%), with a near equal representation of the E2 and E4 alleles (8% and 7%, respectively). By the end of 2008, 21% of the sample had died.

Our preliminary findings suggest that ApoE (presence or absence of E2 or E4) is not associated with death after 8-years of follow-up (Table 2). This conclusion is robust to alternative classifications of ApoE genotype. At-risk levels of blood lipids are associated with the ApoE2 allele (Table 3). A smaller proportion of E2 carriers have at-risk levels of HDL-C than among non-E2 carriers (OR: 0.44; 95% CI 0.31-0.62). ApoE4 carriers are less likely to have elevated CRP levels compared to E4 non-carriers (OR: 0.69 95% CI: 0.45-1.01) With respect to physical function, ApoE2 and E4 carrier status are not associated with the ability to complete chairs stands (Table 3), grip strength or 3m walk speed (Table 4). ApoE2 and E4 carrier status are also not associated with depressive symptoms or tests of cognitive function (Table 4). Future analyses will examine the relationship between ApoE and declines in cognition function and changes in depressive symptoms.

Conclusions

Our preliminary findings suggest that ApoE is associated with blood lipid levels. This relationship of ApoE to cholesterol levels has been similarly reported in other populations in France, Finland, and the U.S. (Dufouil et al., 2005; Kivipelto et al., 2002; Lahoz et al., 2001). We do not, however, find relationships between ApoE genotype and mortality, depressive symptoms, and physical and cognitive functioning. The absence of an association between ApoE and mortality, which has been reported in other studies (Ewbank, 2002, 2004, 2007; Little et al., 2009), may be due to our relatively small sample size.

An interesting finding is the lower levels of CRP among ApoE4 carriers. Similar associations with ApoE4 have been reported in Finnish nonagenerians (Rontu et al., 2006), Latinos, Japanese Americans (Aiello et al, 2008; Austin et al., 2004), and the Tsimane of Bolivia (Vasunilashorn et al., forthcoming). These associations could arise from various mechanisms, including differential binding of apoE4 to very low density lipoprotein cholesterol (Austin et al., 2004) and hepatic clearance of CRP with involvement of the mevalonate pathway (Rontu et al., 2006).

Additional analyses that more thoroughly examine these relationships in comparison with other findings in the literature will better contribute to our understanding of the influence of genetics on health and age-associated outcomes in Taiwan and other populations.

References

Aiello AE, Nguyen H-O, Haan MN. 2008. C-reactive protein mediates the effect of apolipoprotein E on cytomegalorvirus infection. J Infect Dis 197:34-41.

Barford A, Dorling D, Davey Smith G, Shaw M. 2006. Life expectancy: Women now on top everywhere. Br Med J 332:808.

Austin MA, Zhang C, Humphries SE, Chadler WL, Talmud PJ, Edwards KL, Leonetti DL, McNeely MJ, Fujimoto WY. 2004. Heritability of C-reactive protein and association with apolipoprotein E genotypes in Japanese Americans. Ann Human Genet 68:179-188.

Corder EH, Lannfelt L, Viitanen M, Corder LS, Manton KG, Winblad B, Basun H. 1996. Apolipoprotein E genotype determines survival in the oldest old (85 years or older) who have good cognition. Arch Neurol 53:418-422.

Dufouil C, Richard F, Fiévet N, Dartigues JF, Ritchie K, Tzourio C, Amouyel P, Alpérovitch A. 2005. APOE genotype, cholesterol level, lipid-lowering treatment and dementia: The Three-City Study. Neruol 64:1531-1538.

Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE, Stroehla BC. 2002. Apolipoprotein E polymorphism and cardiovascular disease: A HuGE Review. Am J Epidemiol 155:487-495.

Ewbank DC. 2002. Mortality differences by APOE genotype estimated from demographic synthesis. Genet Epidemiol 22:146-155.

Ewbank DC. 2004. The APOE gene and differences in life expectancy in Europe. J Gerontol A Biol Sci Med Sci 59:16-20.

Ewbank DC. 2007. Differences in the association between apolipoprotein E genotype and mortality across populations. J Gerontol Biol Sc Med Sci 62:899-907.

Heijmans BT, PE Slagboom, J Gussekloo, Droog S, Lagaay AM, Kluft C, Knook DL, Westendorp RGJ. 2002. Association of APOE ε2/ ε3/ε4 and promoter gene variants with dementia but not cardiovascular mortality in old age. Am J Med Genet 107:201-208.

Higgins GA, Large CH, Rupniak HT, Barnes JC. 1997. Apolipoprotein E and Alzheimer's Disease: A review of recent studies. Pharmacol Biochem Behav 56:675-685.

Johnson NJ, Backlund E, Sorlie PD, Loveless CA. 2000. Marital status and mortality: the national longitudinal mortality study. Ann Epidemiol 10:224-238.

Kivipelto M, Helkala E-L, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, Iivonen S, Mannermaa A, Tuomilheto J, Nissinen A, Soininen H. 2002. Apolipoprotein E ε4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer Disease. Ann Int Med 137:14-155.

Lahoz C, Schaefer EJ, Cupples LA, Wilson PWF, Levy D, Osgood D, Parpos S, Pedro-Botet J, Daly JA, Ordovas JM. 2001. Apolipoprotein E genotype and cardiovascular disease in the Framingham Heart Study. Atherosclerosis 154:529-537.

Little DM, Crooks VC, Petitti DB, Chiu V, Schellenberg GD, Slezak JM, Jacobsen SJ. 2009. Mortality, dementia, and apolipoprotein E genotype in elderly white women in the United States. JAGS 57: 231-236.

Lleras-Muney A. 2005. The relationship between education and adult mortality in the United States. Rev Econ Studies 72:189-221.
Miyata M, Smith JD. 1996. Apolipoprotein E allele-specific antioxidant activity and effects on cytoxicity by oxidative insults and beta-amyloid peptides. Nature Genet 14:55-61.
Rebeck GW, Kindy M, LaDu MJ. 2002. Apolipoprotein E and Alzheimer's disease: The protective effects of ApoE2 and ApoE3. J Alzheimers Dis 4:145-154.
Rontu R, Ojala P, Hervonen A, Goebeler S, Karhunen PJ, Nikkilèa M, Kunnas T, Jylhä M, Eklund C, Hurme M, Lehtimèaki T. 2006. Apoplipoprotein E genotype is related to plasma levels of C-reactive protein and lipids and to longevity in nonagenarians. Clin Endocrinol 64:265-270.
Rosvall L, Rizzuto D, Wang H-X, Winblad B, Graff C, Fratiglioni L.2009. APOE-related mortality: Effect of dementia, cardiovascular disease and gender. Neurobiol Aging 20:1545-1551.
Schachter F, Faure-DiDelanef 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.
Smith JD. 2002. Apolipoproteins and aging: Emerging mechanisms. Ageing Res 1:345-365.
Vasunilashorn S, Finch CE, Crimmins EM, Vikman SA, Stieglitz J, Gurven M, Kaplan H, Allayee H. Forthcoming. Inflammatory gene variants in the Tsimane, an indigenous Bolivian population with a high infectious load. Biodemography and Social Biology.

Table 1. Sample characteristics of Taiwanese older adults at baseline (2000)

	N	Mean ± SD or %*
Age	1023	66.5 ± 8.1
Men (%)	1023	56.6
Marital status (%)	1023	
Never married		2.9
Married		74.5
Separated, divorced, or widowed		22.6
Education (%)	1023	
No formal education		33.2
1-6 years		43.1
7+ years		23.7
Number of medical conditions†	1023	0.8 ± 0.9
APOE alleles (%)‡	1020	
E2		8.0
E3		84.7
E4		7.3
APOE genotype (%)	1020	
E2E2		0.4
E3E2		13.6
E3E3		71
E4E2		1.5
E4E3		13.2
E4E4		0.3
Biomarkers		
Body mass index (kg/m^2)	1022	24.5 ± 3.6
Waist-hip ratio	1020	0.9 ± 0.1
Systolic blood pressure (mm Hg)	1023	137.5 ± 20.8
Diastolic blood pressure (mm Hg)	1023	82.6 ±11.2
Total cholesterol (mg/dl)	1022	200.8 ± 39.2
High-density lipoprotein cholesterol (mg/dl)	1022	49.0 ± 13.7
Triglycerides (mg/dl)	1022	123.5 ± 92.5
C-reactive protein (mg/L)	1000	3.0 ± 6.7
Interleukin-6 (pg/ml)	1006	3.5 ± 5.4
Total number of ADL limitations	1023	0.1 ± 0.6
Total number of IADL limitations	1023	0.1 ± 1.3
*Physical function***		
Grip strength (kg)	706	26.1 ± 10.2
% Unable to complete chair stands	634	0.8
3m walking speed (m/sec)	698	0.8 ± 0.3
Depressive symptoms		
CESD	989	5.5 ± 5.4
Cognitive function		
24-item test	1002	16.6 ± 3.6
14-item test	1002	7.3 ± 2.6
Died by end of 2008	1020	21.3

ApoE=apolipoprotein E; ADLs=activities of daily living; IADLs=instrumental activities of daily living
†Includes self-reported history of: high blood pressure, kidney disease, high cholesterol, heart disease, diabetes mellitus, lung disease, stroke
‡ Frequency based on unweighted analysis
*Mean or % values based on weighted analyses
**Measured only in 2006

Table 2. Mortality risk (at end of 2008) by ApoE2 and E4 carriers status*

	Model I		Model II		Model III		Model IV	
	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)	HR	(95% CI)
Males (vs. females)	**0.70**	**(0.52-0.94)**	**0.70**	**(0.51-0.95)**	**0.69**	**(0.51-0.94)**	**0.67**	**(0.46-0.96)**
Married							1.07	(0.80-1.43)
Education								
No formal education							**1.46**	**(1.09-1.96)**
Any primary education							**1.55**	**(1.12-2.13)**
Secondary education or higher							Reference	
ApoE2 carrier*	0.98	(0.70-1.38)						
ApoE4 carrier*			0.90	(0.61-1.32)				
ApoE category								
E2E2 or E3E2					0.92	(0.65-1.31)	0.91	(0.63-1.32)
E3E3 or E4E2					Reference		Reference	
E4E3 or E4E4					0.84	(0.57-1.25)	0.88	(0.59-1.29)

Models I through III adjust for sex

Model IV adjusts for sex, marital status, and education

*Sample based on the cohort of respondents age 54+ who were examined 2000 (N=961)

**vs non-carrier; based on weighted analysis

Table 3. Logistic regression models predicting at-risk levels of biomarkers (in 2000) according to the presence or absence of ApoE2 and ApoE4*

		ApoE2 carrier §		ApoE4 carriver §	
	N	OR	(95% CI)	OR	(95% CI)
Biomarkers					
Body mass index (>30 kg/m^2)	1019	1.32	(0.69-2.55)	0.90	(0.41-1.96)
Waist-hip ratio (males: ≥0.95; females: ≥0.80)	1017	1.02	(0.69-1.50)	1.12	(0.75-1.67)
Systolic blood pressure (≥140 mm Hg)	1020	1.00	(0.66-1.50)	1.08	(0.76-1.53)
Diastolic blood pressure (≥90 mm Hg)	1020	1.07	(0.67-1.69)	1.21	(0.80-1.81)
Total cholesterol (≥240 mg/dl)	1020	0.51	(0.24-1.05)‡	1.10	(0.57-2.12)
High-density lipoprotein cholesterol (<40 mg/dl)	1020	**0.44**	**(0.31-0.62)**†	1.39	(0.93-2.08)‡
Triglycerides (≥200 mg/dl)	1020	1.44	(0.81-2.57)	1.02	(0.55-1.90)
C-reactive protein (≥3 mg/L)	1000	1.04	(0.68-1.59)	0.69	(0.46-1.01)‡
Interleukin-6 (≥4.64 pg/ml)	1005	1.12	(0.71-1.76)	0.71	(0.40-1.28)
Indicator of function					
Unable to complete chair stands	633	1.22	(0.11-13.79)	0.37	(0.06-2.38)

OR=odds ratio; CI=confidence interval

Adjusted for age, sex, marital status, and education (ORs changed little if only age and sex adjusted)

§ vs. non-carrier (ref group)

† Bold indicates significant at the p<.05 level

‡ Significant at the p<.10 level

*Sample is based on the cohort of respondents who were examined in 2000; based on weighted analyses

**Measured only in 2006

Table 4. Linear regression models predicting performance-based measures and depressive symptoms

		ApoE2 carrier §		ApoE4 carrier §	
	N	B	p-value	B	p-value
Indicators of function					
Grip strength (kg)*	704	0.44	0.45	-0.12	0.88
3m walking speed (m/sec)**	696	0.01	0.64	0	0.92
Depressive symptoms					
CESD***	992	-0.49	0.30	-0.06	0.89
Cognitive function					
Full Cognitive test score (range: 0-24)	999	-0.09	0.77	0.32	0.27
Shorter Cognitive test socre (range: 0-14)	999	-0.06	0.77	0.18	0.44

Adjusted for age, sex, marital status, and education (ORs changed little if only age and sex adjusted)
Indicators of function measured only in 2006
§ vs. non-carrier (ref group)
*max of 3 trials on both hands
**faster of 2 trials
***summary measure of depressive symptoms created from 10 items (range: 0-30)