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Apolipoprotein E, biomarkers, and mortality in Taiwanese older adults

Sarinnapha Vasunilashorn[a,*], **Dana A. Glei**[b], **Chia-Ying Lan**[c], **Ron Brookmeyer**[d], **Maxine Weinstein**[b], and **Noreen Goldman**[a]

[a]Office of Population Research, Princeton University, Princeton, NJ 08544, USA

[b]Center for Population and Health, Georgetown University, Washington, DC 20057, USA

[c]Center for Population and Health Survey Research, Department of Health, Taiwan

[d]Department of Biostatistics, University of California, Los Angeles, Los Angeles, CA 90095, USA

Abstract

Polymorphisms of the apolipoprotein E gene (ApoE) have been associated with health and longevity. Numerous studies have linked ApoE to health outcomes including cardiovascular disease and mortality, but far fewer studies have examined the relationship of ApoE to other biological markers of health. This study investigates the relationship between ApoE and mortality, as well as ApoE and a set of biomarkers related to cardiovascular and immune function, in a population-based sample of Taiwanese adults ages 54+. ApoE ε2 carriers were less likely to have at-risk levels of high-density lipoprotein (HDL-C) and total cholesterol (total-C) than non-carriers (odds ratio [OR] 0.45, 95% confidence interval [CI] 0.25-0.83 and OR 0.45, 95% CI 0.29-0.71, respectively). ApoE ε4 carriers were less likely to have elevated levels of C-reactive protein (CRP) than non-carriers (OR 0.62, 95% CI 0.39-0.96). ApoE genotype was not, however, associated with mortality after 8-years of follow-up. Our findings confirm the association between ApoE ε2 and cholesterol levels, suggesting a potential protective effect of ApoE ε2 on blood lipids. They also contribute to reports on the relationship between ApoE ε4 carrier status and lower CRP levels.

Keywords

Apolipoprotein E; Cholesterol; C-reactive protein; Mortality

INTRODUCTION

Apolipoprotein E (ApoE), a commonly investigated genetic marker that plays a central role in cholesterol and triglyceride metabolism [1], has been linked to health outcomes and longevity. The three common alleles -- ε2, ε3, and ε4 -- are associated with variation in blood lipid levels, with the order of prevalence being ε3 > ε4 > ε2 in most populations. The ε4 allele is generally shown to be a risk factor for a number of health outcomes (e.g., Alzheimer's and cardiovascular disease [2, 3], higher total cholesterol levels [4], and in

[*]Corresponding author at: Office of Population Research, Princeton University, 263 Wallace Hall, Princeton, NJ 08544, USA. Tel.: +1 609 258 6971; Fax: +1 609 258 1039. svasunil@princeton.edu (S. Vasunilashorn)..

some populations, shorter lifespans [5-7] while the ε2 allele may have protective effects (e.g., neuroprotective effects on the brain [8], lower blood lipid levels [4] and it may play a direct role as an anti-oxidant agent [9]. Other studies have suggested that the ApoE gene may be involved in immunoregulation and susceptibility to infections from bacteria, viruses, and protozoan parasites [1].

The strength of the association between the ApoE ε4 allele and survival has varied across populations [6]. A link between ApoE ε4 and higher mortality has been reported in populations of European descent, including Denmark, France, Finland, Italy, Sweden, and in the U.S. [10], with a non-significant excess mortality risk found among the Taiwanese [6]. However, excess mortality risk among ε4 carriers has not been observed among African Americans, and only a small degree of excess risk has been found among Koreans and Japanese [6]. Overall, few studies have examined this relationship in East Asian populations, despite substantial evidence that the distribution of ApoE alleles in East Asian populations differs considerably from populations in Europe and America [11]. One objective of this paper is to investigate the association between ApoE and mortality in an older Taiwanese population.

Although the ApoE gene has been associated with several biological markers related to cardiovascular disease, few studies have reported on the relationship between ApoE and other biomarkers such as obesity [12] and indicators of inflammation: C-reactive protein (CRP) [13] and interleukin-6 (IL-6) [14]. A second objective of this paper is to explore the association between ApoE and a set of biological indicators related to cardiovascular, metabolic, and immune function in a non-western sample. Similar to reports linking ApoE to mortality, most of the research related to clinical risk factors has been conducted in western populations: Europe [15] and North America [16]. One exception is a set of ApoE findings related to cholesterol and blood pressure in Asian populations (e.g., [17, 18]): ApoE ε2 carriers had lower total cholesterol (total-C) and low-density lipoprotein cholesterol (LDL-C) levels than ApoE ε3 or ε4 carriers [17, 18] and generally higher HDL-C levels than non-carriers [17, 18]. Non-significant differences in blood pressure according to ApoE carrier status were noted in a Chinese Han population [17]. In addition to examining these relationships at a single time, we assess the association of ApoE polymorphisms with changes in biomarker values over a six-year interval to ascertain whether differential alterations in physiological profiles by genotype can be detected in such a relatively short time and to assess the robustness of our cross-sectional results.

METHODS

Study Population

Our analyses are based on the Social Environment and Biomarkers of Aging Study (SEBAS). SEBAS comprises a random subsample of respondents from the Survey of Health and Living Status of the Near Elderly and Elderly in Taiwan (TLSA), a survey of older Taiwanese adults (including institutionalized individuals) that began in 1989. Respondents age 71 and older in 2000 were over sampled compared to those aged 54 to 70, as were individuals residing in urban areas. All protocols were approved by the Institutional Review Boards at Princeton University, Georgetown University, and the Bureau of Health Promotion, Department of Health, Taiwan.

Among the individuals ages 54 and older selected for SEBAS, 1497 (92% of the survivors) were interviewed in 2000. Several weeks after the interview, participants undergoing medical examinations were asked to fast overnight and report to a nearby hospital the next morning, where a physician or nurse collected blood and obtained blood pressure readings and anthropometric measurements. A total of 1023 individuals (68% of those interviewed)

participated in the medical exam. Although a disproportionate number of both the youngest (age 54-59) and the oldest respondents (age 80+) refused the exam, participants did not differ significantly from non-participants on self-reported health status, sex, and socioeconomic status. These findings suggest that after controlling for age, estimates using the biomarkers are unlikely to be seriously biased [19]. Compliance with the SEBAS protocol was very high: for example, ApoE genotypes were obtained for all but three participants.

A second round of SEBAS, fielded in 2006, comprises interviews and a medical exam for individuals who participated in the medical component of SEBAS 2000. The participation rate for this second exam, which also included a biomarker collection, was 76% among survivors. Although most of the analyses in this paper are based on data from SEBAS 2000, information from SEBAS 2006 is used to determine changes in biomarker values between the two waves.

The mortality analysis uses data on survival status and date of death that were ascertained by linking SEBAS survey records with information from the Household Registration file of the Taiwanese Ministry of Interior and the Department of Health death registration records. After excluding individuals for whom date of death was missing (n=16) from the 1020 respondents with ApoE genotype, 1004 were included in the survival analysis. Analyses of the biomarkers for 2000 are based on similar sample sizes – ranging between 1005 and 1020 because of slight variation in the number of missing values across markers. Samples for the longitudinal analysis are smaller – because of attrition between waves (mostly mortality) and non-participation in the second round – ranging between 624 and 637.

Measures

Our biomarkers include cardiovascular (blood pressure) and metabolic markers (total-C, HDL-C, triglycerides, body mass index [BMI], waist-hip ratio [WHR]), and indicators of infection and inflammation (CRP and IL-6). Cholesterol and inflammatory measures were obtained from fasting blood samples based on assays described in Glei et al. [20]; the same assay methods were used in 2000 and 2006. To determine ApoE genotype, DNA was extracted from whole blood using the technique described in Gustincich et al. [21]. The DNA was then amplified using the polymerase chain reaction amplification refractory mutation system (PCR-ARMS) and polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) analysis [22]. Biomarker assays and DNA extraction were performed by Union Clinical Laboratories in Taipei. The genotype frequencies are in Hardy-Weinberg equilibrium ($\chi^2 = 2.66$, df = 3, p~0.45).

Systolic and diastolic blood pressures (mm Hg) are measured as the average of two seated readings taken with a mercury sphygmomanometer. BMI is calculated as weight divided by height squared (kg/m^2) and WHR is based on waist circumference measured at its narrowest point and hip circumference measured at the maximal buttocks.

In cross-sectional models of the associations between ApoE genotype and biomarker levels, biomarkers are parameterized as dichotomous variables (i.e., above or below a threshold) based on the established at-risk cutpoints shown in Table 1 [23]. In models that examine the relationship between ApoE genotype and change in biomarker values, we calculate the difference between the 2006 and 2000 values, determined from continuous measures of the markers. In order to consider both the potential negative effects of ApoE4 and the potential positive effects of ApoE2, we construct several alternative formulations of ApoE genotype: whether the respondent is a carrier of the E4 allele; whether he or she is a carrier of the E2 allele; and a three category parameterization (for the survival models in Table 2).

All statistical models include control variables for age and sex. The distribution of ApoE alleles has been shown to vary by age [4, 9], and to a lesser extent, by sex. The models also include a variable for urban vs. rural residence to account for the sampling design.

Statistical analyses

We estimate a proportional hazards model to assess the association between ApoE genotype and survival, using age as the time-scale. The underlying hazard function is modeled with a Gompertz distribution, which provided a good fit to our data and is often used to describe death rates at older ages [24]. We use logistic regression models to determine the cross-sectional associations between ApoE carrier status and at-risk levels of biomarkers in 2000 and linear regression models for the longitudinal analysis of biomarkers, where we directly model the difference in value of the biomarker between the two interview dates. An alternate approach to examining change over time in the biomarkers is to model the 2006 biomarker value as the outcome while controlling for the 2000 biomarker value. The two longitudinal models yield similar estimates; we report the results from models of the change in biomarker values. Since the longitudinal analysis is based on continuous values of the biomarkers, we considered the sensitivity of findings to extreme values of the markers. Because very high IL-6 values (>120 pg/ml) for two participants (one person with a value measured in 2000 and one in 2006) substantially influenced the relationship between change in IL-6 and ApoE, we report results that exclude these two outliers. Finally, we explored the effect on our findings of excluding persons with the E4E2 genotype, who may experience both positive and negative effects on survival and biomarkers (1.5% of the sample) and found little change; we have retained E4E2 individuals in the analytic sample.

Descriptive statistics for the variables included in our analysis are weighted to account for oversampling by age and urban residence. For regression models, we use unweighted data, but control for age and urban residence to adjust for the sampling design. Because of the multistage sampling design, we use a robust estimator of variance and adjust for clustering by primary sampling units to produce corrected standard errors. All analyses were carried out with STATA version 11.

RESULTS

The average age of the study sample is 67 years, with an excess of males (57%) owing to selective migration of Mainlander men – primarily Nationalist civilian and military supporters – to Taiwan around 1949 (Table 1). As expected, E3 is the most prevalent ApoE allele (85%), with a near equal representation of the E2 and E4 alleles (8% and 7%, respectively). The proportion of individuals with the potentially deleterious E4 allele (7.3%) is similar to estimates for Chinese residing in Beijing (7.3%; [25]) and Montreal, Canada (6.4%, [25]), but is considerably lower than estimates for Americans (11.9% [26]). By the end of 2008, 21% of the 2000 SEBAS sample had died.

We did not find an association of ApoE with death after 8-years of follow-up (Table 2). This conclusion is robust to alternative classifications of ApoE genotype.

The estimated odds ratios shown in Table 3 reveal that at-risk levels of blood lipids and inflammatory markers are significantly associated with ApoE carrier status. Compared with ApoE2 non-carriers, E2 carriers are less likely to have at-risk levels of total-C (odds ratio [OR]: 0.45, 95% CI 0.25-0.83) and HDL-C (OR: 0.45, 95% CI 0.29-0.71). In contrast, ApoE4 carriers are significantly less likely to have elevated CRP levels than E4 non-carriers (OR: 0.62, 95% CI 0.39-0.96) and are marginally significantly less likely ($p<.10$) to have at-risk levels of IL-6 (OR: 0.62, 95% CI 0.37-1.04).

The association between ApoE and change in biomarker values over a six-year period is shown in Table 4. None of the changes are significantly associated with ApoE carrier status.

DISCUSSION

This study examines the association between ApoE and (1) mortality and (2) a broad range of biomarkers related to chronic disease in a population of older Taiwanese adults. Significant cross-sectional associations of biomarkers with ApoE are found for several measures that have been reported previously in Western populations. Our finding of an association between the ApoE2 allele and lower levels of total-C and HDL-C measured at a single time has been reported in France, Finland, the U.S., Japan, and Singapore [6, 18, 26], but we do not find an association of ApoE and blood lipids (as reported in other populations). The noted association of ApoE and cholesterol is consistent with our knowledge that ApoE is a cholesterol transport protein that binds to the low-density lipoprotein receptor and is central to blood lipid metabolism. Studies report that coding changes that affect cholesterol binding of the three ApoE isoforms (i.e., proteins that are encoded by the three distinct alleles) may explain about 10% of the variance in total-C levels [27].

As illustrated in our cross-sectional findings, ApoE4 carriers have significantly lower CRP levels and marginally significantly lower IL-6 levels. Our finding of lower inflammation in ApoE4 carriers is consistent with the literature on lower CRP among individuals with the E4 allele. While not reported in other studies, our observed lower levels of IL-6 among ApoE4 carriers seems plausible given that both CRP and IL-6 are systemic markers of inflammation and that the major stimulus for CRP production is IL-6, which is released from activated cells at the site of inflammation. The association between having an ApoE4 allele and lower CRP levels has been found in several populations, including Finnish nonagenarians [28], Germans [29], and Icelanders [13]. There are no definitive explanations for this relationship but various mechanisms have been hypothesized, including a “non-inflammatory” and a “true inflammatory hypothesis” [29].

According to the non-inflammatory hypothesis, lower CRP levels among ApoE4 carriers are not causally linked with inflammation, but are attributable to hepatic clearance of CRP with involvement of the mevalonate pathway [28], an important cellular metabolic pathway responsible for a range of functions including the production of cholesterol and growth control. This supposition is supported by studies of statin use, which inhibits a major rate limiting step of the mevalonate pathway that converts hydroxymethyl glutaryl coenzyme A (HMG-CoA) into mevalonate. This step in turn seems to yield lower CRP levels [30]. While some researchers use these studies to suggest direct anti-inflammatory effects of statins, it is difficult to understand how these lipid lowering medications directly alter inflammatory levels at locations outside the liver given that the majority of oral statin doses are transported to the liver [29]. Although this argument attempts to explain the relationship between ApoE4 and CRP levels, it fails to indicate how the ApoE alleles are involved in the mevalonate pathway. It is unlikely that the lower levels of CRP among ApoE4 carriers are due to the differential use of lipid lowering medications compared with non-E4 carriers, since the observation of lower CRP levels among ApoE4 carriers was reported among both statin users and non-users [13].

The true inflammatory hypothesis is related to structural and functional differences in the allele isoforms that ultimately lead to differential binding of ApoE4 to very low-density lipoprotein cholesterol (VLDL-C) (Austin et al., 2004). The ApoE isoforms differ in amino acid residues at positions 112 and 158 [31], which results in differences in structure and function. The varying formations among the major ApoE alleles are thought to elicit a

preferential binding of ApoE4 to larger lipoproteins (e.g., VLDL-C and LDL-C) and preferential binding of ApoE2 and ApoE3 to smaller lipoproteins (e.g., HDL-C) [32]. The higher circulating levels of larger lipoproteins among ApoE2 carriers act as a proinflammatory agent on the vessel wall and contribute to the maintenance of a low-grade systemic inflammation. This is in contrast to the quick removal of these larger lipoproteins by ApoE4 carriers, causing an anti-inflammatory effect that may explain the observed lower levels of circulating CRP.

These hypotheses suggest that CRP and cholesterol levels should exhibit similar relationships to ApoE4, but this speculation is not supported by our results: ApoE4 carrier status is associated with lower CRP levels but not (significantly) higher total-C levels. While these hypotheses may partly explain the observed relationship between ApoE and CRP levels, each hypothesis reflects one among many potential pathways that can influence CRP and cholesterol levels. Moreover, it is likely that influences independent of the different binding affinities for the ApoE isoforms and biosynthesis of cholesterol through the mevalonate pathway explain at least part of the relationship between ApoE and cholesterol levels. Future research on experimental models is needed to directly test the validity of these hypotheses.

We also noted a marginally significant association of ApoE4 carrier status with lower IL-6 levels. To our knowledge, very few studies have investigated the relationship between ApoE genotype and circulating IL-6 levels in community-dwelling populations. A study of Alzheimer's Disease in Greek patients reports a non-significant difference in IL-6 levels by ApoE4 carrier status [14]. A larger body of research on IL-6 and ApoE has investigated polymorphisms of the IL-6 gene and ApoE [33, 34]. Wang and Jia [34] find differences in allele and genotype distributions of the IL-6 gene −572 (rs1800796) C/G promoter polymorphism only among ApoE4 carriers. In a population of German older adults, Baune et al. [35] link IL-6 levels to IL-6 gene polymorphisms (at rs1800796) and find a higher, though non-significant, IL-6 level among C allele carriers compared to non-carriers for the IL-6 gene polymorphism. These studies suggest a potential relationship between ApoE carrier status and IL-6 levels, although this must be further investigated as IL-6 gene polymorphisms do not necessarily translate into differences in circulating IL-6 levels [33].

Despite several significant cross-sectional associations, none of the associations is significant in the longitudinal models. This may be partly a result of lower statistical power (i.e., the longitudinal sample is roughly 60 percent as large as the cross-sectional one). The longitudinal analysis provides a more stringent test of association given that it requires a change in biomarker level to be apparent within a relatively short time. This is also true for our survival measure given the modest length of the follow-up period (eight years). Moreover, the cross-sectional and longitudinal analyses measure different aspects of the relationship between ApoE and biomarkers: the level of the marker compared to rate of change. For instance, it may be that ApoE influences the level of blood lipids that persists throughout adulthood, but not the rate of change, at least at older ages.

Behavioral factors and measurement issues may also lead to apparent differences between the cross-sectional and longitudinal results. Blood levels of biomarkers are likely influenced by multiple genetic variants. In examining a single genetic marker (ApoE), we are limiting our ability to determine how genetic influences are related to indicators of health and age-associated outcomes such as mortality. It is also probable that interactions between ApoE and environmental factors or other genetic variants affect survival, potentially leading to a different relationship between ApoE and mortality in our Taiwan sample from those identified in western samples. Differences in the time of day when blood samples are drawn may also influence the cross-sectional and/or follow-up values measured in our sample. For

instance, IL-6 levels generally peak in the morning and decrease in the afternoon and evening [36]. Although morning blood samples for both 2000 and 2006 measures were collected in SEBAS, even random differences in the timing of the blood draw could introduce "noise" which would attenuate the effect of ApoE on IL-6 levels in the longitudinal analysis.

We do not find an association between ApoE genotype and mortality after 8-years of follow-up. In several European and American populations, the ApoE4 allele has been associated with shorter life expectancy [4, 5, 9] (Ewbank, 2002, 2004, 2007) and was found to be near absent among centenarians [37] (Schachter et al., 1994). The absence of an association between ApoE and mortality in our study has been reported among other non-Caucasian populations (e.g., Hispanics and African Americans) [38, 39]. However, our result is inconsistent with that for Taiwan reported by Ewbank [5], who estimates a relative risk of death of 1.3 associated with the E3E4 genotype based on the genotype distribution by age in SEBAS 2000 (although his estimate is significant only when the Taiwan data are combined with data from China). An alternate explanation for the lack of an association between ApoE and mortality is that ApoE4 carrier status does not, in fact, confer a mortality risk in our population. This could be due to antagonistic pleiotropy such that the seemingly deleterious effects of the E4 allele on higher levels of cholesterol (which has been reported in prior studies) may be countered by the beneficial influences of ApoE4 on lower inflammation levels. More generally, such variation across populations could be the consequence of the types of gene-environment interactions discussed above.

Our current study has a number of strengths. This unique dataset of a population-based sample of older Taiwanese adults includes a broad range of biomarkers, demographic characteristics, and genetic information. These findings are an important contribution to the literature on ApoE and health, as a limited number of studies on ApoE include Asian populations.

In summary, this study finds an association between ApoE2 and E4 carrier status with at-risk levels of blood lipids in a population-based older adult sample. These results support previous findings, mostly in western populations, of a protective effect of ApoE2 on blood lipids. Our findings highlight a less frequently noted relationship between ApoE4 and lower CRP levels and suggest a potential relationship between ApoE and IL-6. Further investigations regarding the mechanisms underlying the relationship between ApoE and inflammatory markers will contribute to our understanding of the effects of ApoE genotype on health and survival.

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Table 1

Sample characteristics of Taiwanese older adults at baseline (2000)

			Mean ± SD or %*	
	At-risk cutoff	**N**	**2000**	**2006**
Age		1023	66.5 ± 8.1	
Men (%)		1023	56.6	
APOE alleles (%)‡		1020		
E2			8.0	
E3			84.7	
E4			7.3	
ApoE genotype (%)		1020		
E2E2			0.4	
E3E2			13.6	
E3E3			71.0	
E4E2			1.5	
E4E3			13.2	
E4E4			0.3	
Biomarkers				
Body mass index (kg/m^2)	>30	1022	24.5 ± 3.6	24.8 ± 3.7
Waist-hip ratio	males ≥0.95 females ≥0.80	1020	0.9 ± 0.1	0.9 ± 0.1
Systolic blood pressure (mm Hg)	≥140	1023	137.5 ± 20.8	134.7 ± 20.6
Diastolic blood pressure (mm Hg)	≥90	1023	82.6 ±11.2	72.7 ± 10.6
Total cholesterol (mg/dl)	≥240	1022	200.8 ± 39.2	197.6 ± 37.8
High-density lipoprotein cholesterol (mg/dl)	<40	1022	49.0 ± 13.7	47.9 ± 13.8
Triglycerides (mg/dl)	≥200	1022	123.5 ± 92.5	110.9 ± 64.4
C-reactive protein (mg/l)	≥3	1000	3.0 ± 6.7	3.1 ± 7.9
Interleukin-6 (pg/ml)	≥4.64	1006	3.5 ± 5.4	4.5 ± 9.8
Died by end of 2008		1004	21.3	

ApoE=apolipoprotein E

‡Frequency based on unweighted analysis

*Mean/SD or % values based on weighted analyses

Table 2

Mortality risk (between 2000 and the end of 2008) by ApoE status

	Model I HR (95% CI)	Model II HR (95% CI)	Model III HR (95% CI)
Females (vs. males)	0.70 (0.53-0.91)†	0.70 (0.54-0.91)†	0.70 (0.53-0.91)†
ApoE2 carrier (vs. non-carrier)	1.02 (0.72-1.45)		
ApoE4 carrier (vs. non-carrier)		0.93 (0.64-1.36)	
ApoE category			
E2E2 or E3E2			1.00 (0.69-1.45)
E3E3 or E4E2			Reference
E4E3 or E4E4			0.91 (0.65-1.07)
Number of respondents	1004	1004	1004

Adjusts for rural/urban residence

† p<.05

Table 3

Odds ratios from logistic regression models predicting at-risk levels of biomarkers (in 2000) by ApoE2 and ApoE4 carrier status

		ApoE2 carrier [§]	ApoE4 carrier [§]
	N	OR (95% CI)	OR (95% CI)
Biomarker outcome			
Body mass index (>30 kg/m^2)	1019	1.43 (0.77-2.66)	0.96 (0.48-1.93)
Waist-hip ratio (males: ≥0.95; females: ≥0.80)	1017	0.94 (0.61-1.45)	1.02 (0.66-1.59)
Systolic blood pressure (≥140 mm Hg)	1020	1.03 (0.73-1.46)	1.03 (0.72-1.47)
Diastolic blood pressure (≥90 mm Hg)	1020	1.14 (0.78-1.67)	1.09 (0.74-1.62)
Total cholesterol (≥240 mg/dl)	1020	0.45 (0.25-0.83)[†]	1.14 (0.71-1.84)
High-density lipoprotein cholesterol (<40 mg/dl)	1020	0.45 (0.29-0.71)[†]	1.26 (0.86-1.56)
Triglycerides (≥200 mg/dl)	1020	1.29 (0.77-2.17)	1.03 (0.58-1.81)
C-reactive protein (≥3 mg/l)	1000	1.08 (0.73-1.58)	0.62 (0.39-0.96)[†]
Interleukin-6 (≥4.64 pg/ml)	1004	1.05 (0.68-1.64)	0.62 (0.37-1.04)[‡]

OR=odds ratio; CI=confidence interval

Adjusts for age, sex, and rural/urban residence

[§] vs. non-carrier (ref group)

[†] p<.05

[‡] p<.10

Table 4

Coefficients from linear regression models predicting change in biomarkers (2006-2000) by ApoE2 and ApoE4 carrier status

		ApoE2 carrier §		ApoE4 carrier §	
	N	B	p-value	B	p-value
Change in biomarkers					
Body mass index (kg/m2)	627	0.23	0.24	−0.17	0.41
Waist-hip ratio	626	0.01	0.23	0.00	0.56
Systolic blood pressure (mm Hg)	637	−0.06	0.98	0.41	0.86
Diastolic blood pressure (mm Hg)	637	1.23	0.32	−1.20	0.35
Total cholesterol (mg/dl)	635	3.79	0.29	−5.24	0.15
High-density lipoprotein cholesterol (mg/dl)	635	0.69	0.57	1.07	0.38
Triglycerides (mg/dl)	635	−8.74	0.28	7.90	0.33
C-reactive protein (mg/l)	624	0.14	0.17	0.00	0.97
Interleukin-6 (pg/ml)	625	−0.01	0.99	1.10	0.17

Adjusts for age, sex, and rural/urban residence

§ vs. non-carrier (ref group)