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APOLIPOPROTEIN E AND MEASURED PHYSICAL AND PULMONARY FUNCTION IN OLDER TAIWANESE ADULTS

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Abstract

The apolipoprotein E (ApoE) gene, which has three common alleles (ε2, ε3, and ε4), has been linked to a number of health outcomes and longevity. The ε2 allele has been reported to have neuroprotective effects, whereas the ε4 allele has been shown to be a risk factor for cardiovascular disease and Alzheimer's disease in various populations. The relationships between ApoE and mortality and ApoE and physical function, however, are not clearcut. We used the Social Environment and Biomarkers of Aging Study (SEBAS) to examine the relationship between ApoE polymorphisms and physical and pulmonary function in approximately 1,000 Taiwanese adults ages 53 and older in 2006. In the 2006 wave, measures of physical function included self-reported difficulties with respect to activities of daily living (ADLs) and other physical function indicators, as well as performance-based measures of grip strength (kg), 3m walking speed (m/sec), and chair stand speed (stand/sec). Peak expiratory flow (PEF; L/min) rate was also examined as an indicator of pulmonary function. We used logistic regression models to determine the association between ApoE and inability to complete each of the tests of physical and pulmonary function. This revealed no significant association between ApoE carrier status and any of the indicators of function. Among participants able to complete a given task, we next used linear regression models to examine self-reported limitations with ADLs and performance on the given test by ApoE carrier status. Similarly, there were no significant relationships between ApoE carrier status and the measures of function. Our estimates provide further confirmation that the ApoE gene may not be a risk factor for functional decline among older Taiwanese adults.

INTRODUCTION

The apolipoprotein E gene (ApoE), which has three common alleles (ε2, ε3, and ε4), has been linked to a number of health outcomes and longevity. The ε2 allele has been reported to have neuroprotective effects (Rebeck et al., 2002), whereas the ε4 allele has been shown to be a risk factor for cardiovascular disease and Alzheimer's disease in various populations (Corder et al., 1993; Eichner et al., 2002; Rosvall et al., 2009). The relationship between ApoE and mortality, however, differs among study samples. Whereas populations across Europe (e.g., Denmark, France, Finland, Italy, Sweden) have reported excess mortality risk among individuals with the ε3/ε4 genotype compared to the ε3/ε3 genotype, no significant risk has been noted in African Americans, Koreans, and Taiwanese (Ewbank, 2002, 2007).

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Findings on the association between ApoE and physical function are similarly mixed. A relationship between ApoE and self-reported physical function has been observed in a US population (Kulminksi et al., 2008), but not in a Taiwanese population of older adults (Lan et al., 2009). These results, which are consistent with the mortality findings for Taiwan (Vasunilashorn et al., 2011), suggest that the ε4 allele may not confer additional risk for mortality or functional decline in some populations. Nevertheless, it is plausible that the absence of associations in Taiwan and other populations results from methodological limitations, such as lack of statistical power or misreporting. Recently collected data from Taiwan provide an opportunity to reevaluate these results using a set of objectively measured performance assessments that have been shown to be strongly associated with survival (Guralnik et al., 1994), yield a more valid assessment of physical functioning than self-reported measures, and provide greater statistical power than studies based on mortality outcomes in high life expectancy populations. One objective of this paper was to investigate the association of ApoE with self-reported and performance-based measures of physical function in an older Taiwanese population.

Pulmonary function has been associated with mortality and physical function (Cook et al., 1991, 1995; Schunemann et al., 2000), but no one has examined the direct association between ApoE and pulmonary function. However, one study investigated whether ApoE genotype moderates the association between lung and cognitive function: among Finnish, Danish, and Italian men, midlife lung function was associated with old age cognitive function only among ApoE ε4 carriers (Giltay et al., 2009). Another objective of this paper was to test for a direct association between ApoE and pulmonary function.

METHODS

Study population

We used the second round of the Social Environment and Biomarkers of Aging Study (SEBAS) to examine approximately 1,000 Taiwanese adults ages 53 and older in 2006. SEBAS is based on a subsample of respondents from the Taiwan Longitudinal Study of Aging (TLSA), a survey that began in 1989 of older Taiwanese adults (including institutionalized individuals). SEBAS includes in-home interviews, as well as physical examinations completed in the hospital. All protocols were approved by the Institutional Review Boards at Princeton University, Georgetown University, and the Bureau of Health Promotion, Department of Health in Taiwan.

Among the participants included in SEBAS, 1497 (92% of survivors) were interviewed in 2000. A total of 1023 individuals (68% of respondents interviewed) participated in the medical exam. Although more young and old respondents (age 53–59 and 80+) refused the exam, these individuals were not significantly different from participants on socioeconomic status, sex, and self-reported health. This suggests that after controlling for age, estimates derived from the blood sample are not seriously biased (Goldman et al., 2003). Compliance with the protocol was high; ApoE genotype, for example, was determined for all but three respondents. A second round of SEBAS, collected in 2006, included interviews, medical exams, and performance tests of function for participants included in the medical portion of SEBAS 2000. About 76% of survivors in 2006 participated in this second wave. A refresher cohort that included individuals first interviewed in 2003 was also included in the second wave. The analysis in this paper is based on physical and pulmonary function measures collected in 2006. Additional information about SEBAS has been previously published (Chang et al., 2007; Glei et al., 2011).

Measures

To determine ApoE genotype, DNA was extracted from whole blood using the technique described in Gustincich et al. (1991). 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 (Goldman et al., 2003). DNA extraction was performed by Union Clinical Laboratories in Taipei, and the ApoE genotype frequencies were in Hardy-Weinberg equilibrium ($X^2 = 2.66$; df = 3; p~0.45).

Self-reported measures—Participants were asked to self-report any difficulty independently completing six activities of daily living (ADLs) and nine additional indicators of physical function. The ADLs included: bathing; dressing and undressing; eating; getting out of bed, standing up, or sitting in a chair; moving around the house; and using the toilet. The nine indicators of physical function included: standing continuously for 15 minutes; standing continuous for 2 hours; squatting; raising both hands over head; grasping or turning objects with fingers; lifting or carrying item(s) weighing 11–12 kgs; running 20–30 meters; walking 200–300 meters; and walking up two or three flights of stairs. For each of the six ADLs and nine mobility tasks, participants were asked if they had no difficulty, some difficulty, great difficulty, or were unable to do the activity. We created two dichotomous variables indicating (1) inability to perform at least one of the six ADLs and (2) inability to perform at least one of the nine mobility tasks. Among individuals able to perform all six ADLs, an ADL limitation score was created. Additionally, among participants who reported being able to perform all nine mobility tasks, a mobility limitation score was created. The ADL limitation and mobility limitation scores were calculated by summing the values (0=no difficulty, 1=some difficulty, 2=great difficulty) across the six activities for the ADL limitations score (possible range 0–12; 12 indicating the highest degree of limitations) and the nine mobility tasks for the mobility limitation score (possible range 0–18; 18 indicating the highest degree of limitations).

Performance-based measures—In the 2006 round, interviewers carried out the following tests of physical function: timed walk, timed chair stands, and grip strength. Respondents were asked to walk 3m at their usual walking speed. Due to space limitations, 10 respondents walked less than 3m. For these individuals, who walked between 2 and 2.5 m, the time was scaled up proportionally. Participants were able to use assistive devices, if required. As reported in the literature, the fastest 3m walking speed from the two trials was used (Cornman et al., 2010; Guralnik et al., 2000; Rivera et al., 2008). The Pearson correlation between the two walks was .99.

For the chair stand test, participants were asked to keep their arms folded across their chest while standing up and down from a hard seated, armless chair. The back of the chair was placed against the wall and the participants were asked to complete five chair stands as quickly as possible. Participants were timed from the starting seated position to the standing position at the end of the fifth stand. Since chair heights differed from home to home, chair stand test findings were adjusted to account for this variation in chair height (for details, see Cornman et al., 2010). Participants were classified as unable to complete the chair stand test if they could not complete the five stands, were wheelchair bound, and if the participant or the interviewer felt it was unsafe to attempt. Among those able to complete the chair stand test, chair stand speed (stand/sec) was calculated as the number of chair stands (5) divided by completion time (adjusted for chair height).

Grip strength was measured using a North Coast™ hydraulic hand dynamometer (NC70142). Measurements were taken three times for each hand while the participant was in

a seated position with the elbow flexed at 90°. Participants were encouraged to exhibit the strongest possible force, and the highest value among the six trials was used in our analysis. Participants were classified as unable to complete the handgrip strength test if they attempted but were unable to complete the task, had weakness due to stroke or frailty, if the participant or interviewer felt it was unsafe to attempt, or if the task was stopped due to participant discomfort.

Peak expiratory flow (PEF; L/min) rate, an indicator of pulmonary function, was examined using a TruZone peak flow meter. The fastest speed for PEF rate was determined from three trials. Participants were classified as unable to complete the test of pulmonary function if they were excluded based on exclusion criteria, had a stroke or illness, if the interviewer felt it was unsafe, or if they attempted but could not complete the PEF trials.

Statistical Analysis

The sample size for our analyses varies slightly across the different outcomes due to missing data (values for PEF represent the highest percent of missing information [1.4%]). Our data analysis was conducted in two stages. We first used logistic regression models to determine the association between ApoE carrier status and inability to complete any of the six ADLs, any of the nine indicators of physical function, and each of the tests of physical and pulmonary function. Among participants able to complete a given task, we next used linear regression models to examine performance on that measure or test by ApoE carrier status. To consider both the potential negative effects of ApoE ε4 and the potential positive effects of ApoE ε2, we constructed several alternative formulations of ApoE genotype: whether the participant was a carrier of the ε2 allele; whether the participant was a carrier of the ε4 allele; the number of ε4 alleles a participant had (treated as linear); and a three category parameterization. We report findings only from the three category parameterization since the classifications based on ε2 carrier status, ε4 carrier status, and ε4 allele count yielded similar results.

All statistical models were cross-sectional and included controls for age, sex, body mass index (BMI), total number of medical conditions, and urban vs. rural residence. According to other studies, the distribution of ApoE alleles varies by age (Ewbank, 2002; Ewbank et al., 2004) and to a lesser extent, by sex. Our models also adjusted for BMI and total number of medical conditions, which are likely to be associated with physical function (Coakley et al., 1998; Guccione et al., 1994). To adjust for the sampling design, we included an indicator of urban vs. rural residence.

RESULTS

The average age of the study sample was 66 years, with more males (53.9%) due to selective migration of Mainlander men – primarily Nationalist civilian and military supporters – to Taiwan around 1949 (Table 1). Participants had an average BMI of 24.8 kg/m^2 and one medical condition. The distribution of alleles in our sample of older adults was ε2 (7.8%), ε3 (84.7%), and ε4 (7.5%), with the ε3ε3 as the most common genotype (71.7%). About 2% reported being unable to complete at least one ADL, 27% reported the inability to complete at least one of the nine other measures of physical function, 2% were unable to complete the handgrip strength test, 3% were unable to complete the 3m walk, 8% could not complete the five chair stands, and 3% were unable to complete a single PEF trial.

Our results did not reveal a significant association between ApoE genotype and reported difficulty performing at least one of the six ADLs or nine physical performance measures (Table 2A). Similarly, there were no significant relationships between ApoE genotype and inability to complete any of the function measures.

Among participants able to perform the six ADLs, the nine mobility tasks, or the interviewer-assessed tasks, we next used linear regression models to examine performance by ApoE genotype (Table 2B). Similar to our logistic regression results (in Table 2A), we found no significant relationship of ApoE genotype with any of the self-reported or performance-based indicators of physical function. Similarly, there was no association between PEF rate and ApoE genotype.

DISCUSSION

This study examined the association between ApoE polymorphisms and (1) self-reported physical functioning and (2) performance-based measures of physical and pulmonary function. The proportion of participants with the potentially deleterious ε4 allele (7.5%) is similar to estimates for Chinese residing in Beijing (7.3%) (Wang et al., 1987) and Montreal, Canada (6.4%) (Wang et al., 1987), but is much lower than estimates for Americans (11.9%) (Lahoz et al., 2001). We found no significant cross-sectional associations of self-reported and performance-based physical function with ApoE genotype for several measures that have been reported previously in Western populations (Kulminski et al., 2008). The absence of an association between self-reported physical function and ApoE genotype is consistent with findings regarding the link between ApoE and self-reported risk of developing functional limitations in the same population of Taiwanese older adults (Lan et al., 2009). Our study extends this result by demonstrating lack of associations between ApoE polymorphisms and performance-based measures of both physical and pulmonary function.

To the best of our knowledge, our findings align with other studies in Taiwan that report no association between ApoE and mortality (Ewbank, 2007; Vasunilashorn et al., 2011). Another study using data from Taiwan found no relationship between ApoE ε4 carrier status and risk of having coronary heart disease (Wu et al., 2002). Hence, our results provide further confirmation that the ε4 allele may not be a risk factor for some adverse health outcomes among older Taiwanese adults. We are, however, unable to address the question as to how such differences across populations may arise. It may be that some aspects of the social or physical environment in Taiwan, such as strong social cohesion or differences in healthcare or preventive measures, may mitigate the deleterious health consequences of the ε4 allele observed in other populations.

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 self-reported functional limitations, performance-based measures of physical and pulmonary function, demographic characteristics, and genetic information. These findings contribute to the literature on ApoE and health, particularly since few studies on ApoE include Asian populations. The paucity of and biases against publications that report non-significant associations has resulted in a disproportionately high proportion of published manuscripts demonstrating statistical significance (Dickersin, Min and Meinert, 1992; Easterbrook et al., 1991). The current study seeks to counter this publication bias by reporting the non-significant associations observed across a broad range of functional measures in a Taiwan sample.

We also note some study limitations. First, the cross-sectional nature of our analysis provides a single snapshot of functional capacity based on pulmonary and physical function indicators. Changes in the level of these measures, as opposed to the absolute value at one time point, could be associated with ApoE polymorphisms. This, however, is unlikely since associations were not observed for self-reported ADLs, instrumental activities of daily living (IADLs), and mobility decline in the same population of older Taiwanese adults observed at two time points (Lan et al., 2009).

In addition, our modest sample size of about 1000 individuals may not provide enough statistical power to detect associations, if they actually exist. In terms of effect size, most of the estimated coefficients are very small. For example, in the model predicting the level of mobility limitations (Table 2B, col. 2), the coefficients imply that those with ε2ε2 or ε2ε3 genotype score 0.08 (−0.16/2.1) of a SD lower and those with ε3ε4 or ε4ε4 genotype score 0.01 (0.01/2.1) of a SD higher relative to those with ε3ε3 or ε2ε4 genotype. Effect sizes for other outcomes were similarly small. Power calculations indicate that to detect a moderate effect size (0.5 SD) for the difference in mobility between those with ε3ε4 or ε4ε4 genotype and those with ε3ε3 or ε2ε4 genotype, we would need a total sample of about 360. However, we would require a total sample of about 2,200 to detect a small effect size (0.2 SD) and nearly 9,000 to detect an effect size of 0.1 SD. Therefore, although we find no evidence of an association between APOE genotype and physical function, we acknowledge that there may be small effects that we are unable to detect.

An alternative explanation for our non-significant associations is that ApoE genotype does not, in fact, confer a risk for the examined outcomes in the older Taiwanese population. The absence of an association with ApoE genotype is consistent with findings for mortality in several studies. For instance, ApoE genotype was not associated with mortality after 8-years of follow-up in the same sample of older adults (Vasunilashorn et al., 2011). This absence of an association between ApoE and mortality has been reported in other non-Caucasian populations (e.g., Hispanics and African Americans) (Fillenbaum et al., 2002; Lee et al., 2001). Differences in these relationships across populations could be the consequence of variations in gene-environment interactions. The differences in the distribution of ApoE alleles among the Taiwanese compared to western populations and the differences in familial social support and health practices could influence the observed relationship between ApoE and our outcomes of physical and pulmonary function.

In summary, this study found no association between ApoE genotype and measures of physical and pulmonary function as well as self-reported functional limitations. This result is consistent with a previous study in Taiwan (Lan et al., 2009), but contradicts earlier studies in the U.S. (Albert et al., 1995; Blazer, Gillenbaum, Burchett, 2001; Kulminksi et al., 2008) and the Netherlands (Melzer et al., 2005). Cross-cultural variation in the observed association may stem from population differences in gene frequencies or from differences in environmental circumstances (e.g., social cohesion and lifestyle behaviors or differences in their interactions). Further investigations of these relationships in other non-western societies will contribute to our understanding of the potential effects of the ApoE gene on health across a broad range of societies.

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Table 1

Study sample characteristics

	N	Mean (SD)
Age	1031	66.3 (10.0)
Male (%)	1031	53.9
Body mass index (BMI)	1019	24.8 (3.6)
Number of medical conditions	1030	1.0 (1.1)
ApoE alleles (%)	1031	
ε2		7.8
ε3		84.7
ε4		7.5
ApoE genotype (%)	1031	
ε2ε2		0.8
ε3ε2		12.7
ε3ε3		71.7
ε4ε2		1.1
ε4ε3		13.3
ε4ε4		0.4
Unable to perform at least one ADL	1031	2.3
ADL limitation score*	1008	0.1 (0.8)
Unable to perform at least one physical function measure	1026	26.6
Physical function limitation score**	753	1.2 (2.1)
Unable to complete a grip strength test (%)	1021	2.2
Grip strength (kg)***	998	27.8 (10.6)
Unable to walk 3m (%)	1023	3.2
3m walk speed (m/sec)***	990	0.9 (0.3)
Unable to complete chair stands (%)	1022	8.1
Chair stand speed (stand/sec)***	939	0.5 (0.2)
Unable to complete a single PEF trial (%)	1017	2.6
PEF (L/min)***	991	336.1 (139.7)

ADL = activities of daily living; PEF = peak expiratory flow

Mean/SD or % values based on unweighted analysis

*Among individuals reporting the ability to perform all 6 ADLs

**Among individuals reporting the ability to perform all 9 measures of physical function

***Among individuals able to complete the test

Table 2

A. Odds ratios (ORs) from logistic regression models predicting the inability to perform an ADL or mobility task and inability to complete tests of physical and pulmonary function by ApoE genotype; B. Coefficients from linear regression models predicting the extent of difficulty with ADLs, self-reported mobility, and performance on tests of physical and pulmonary function by ApoE genotype

A.	**Self-reported limitations**		**Performance-based**			
	ADLs	**Mobility**	**Grip strength**	**3m walk**	**Chair stands**	**Peak Flow**
	N=1018	**N=1013**	**N=1009**	**N=1010**	**N=1009**	**N=1005**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
ApoE category						
ε2ε2 or ε3ε2	0.54 (0.07, 4.29)	0.84 (0.52, 1.37)	0.30 (0.04, 2.37)	1.25 (0.40, 3.88)	1.30 (0.63, 2.65)	0.32 (0.04, 2.46)
ε3ε3 or ε4ε2	Reference	Reference	Reference	Reference	Reference	Reference
ε4ε3 or ε4ε4	0.39 (0.05, 3.16)	0.96 (0.60, 1.56)	0.34 (0.04, 2.67)	0.79 (0.22, 2.80)	0.94 (0.43, 2.07)	0.79 (0.22, 2.83)

B.	**Self-reported limitations**		**Performance-based**			
	ADLs	**Mobility**	**Grip strength**	**Walking speed**	**Chair stand speed**	**Peak Flow**
	N=1004	**N=752**	**N=991**	**N=984**	**N=937**	**N=983**
	β (95% CI)	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**	**β (95% CI)**
ApoE category						
ε2ε2 or ε3ε2	0.06 (−0.07, 0.18)	−0.16 (−0.56, 0.24)	−0.38 (−1.59, 0.83)	−0.01 (−0.05, 0.04)	0.01 (−0.02, 0.05)	−2.23 (−21.38, 16.92)
ε3ε3 or ε4ε2	Reference	Reference	Reference	Reference	Reference	Reference
ε4ε3 or ε4ε4	0.03 (−0.01. 0.16)	0.01 (−0.42, 0.39)	0.41 (−0.81, 1.62)	0.01 (−0.03, 0.06)	0.01 (−0.03, 0.04)	0.59 (−18.62, 19.80)

ADLs = activities of daily living

Adjusted for age, sex, rural/urban residence, BMI, and total number of medical conditions (hypertension, renal disease, coronary heart disease, lung disease, stroke)