

# Association of leisure-time physical activity with cognition by apolipoprotein-E genotype in persons aged 60 years and over: the National Health and Nutrition Examination Survey (NHANES-III)

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**Objective:** To test the hypothesis that aerobic-related leisure-time physical activity (PA) is associated with better cognitive function and that the effect varies among apolipoprotein E (APOE) genotype groups.

**Design:** Cross-sectional study of persons examined in the Third National Health and Nutrition Examination Survey (NHANES-III; 1988–1994).

**Setting:** US noninstitutionalized population.

**Participants and methods:** From a sample of 7159, aged  $\geq 60$  years, we analyzed data for 1799 older American men and women who had information on PA, a short mental status examination (SMSE), and were genotyped at the apolipoprotein E gene locus.

**Results:** In the initial bivariate analysis, non- $\epsilon 4$  carriers and  $\epsilon 4$ -heterozygotes performed better than  $\epsilon 4$ -homozygotes in the 60–69 age group. After controlling for multiple confounders including mobility limitation, PA correlated with a higher SMSE score in non- $\epsilon 4$  carriers ( $P = 0.014$ ), but not in  $\epsilon 4$  carriers ( $P = 0.887$ ). At  $\geq 70$  years, PA also correlated with higher adjusted SMSE scores in non- $\epsilon 4$  carriers ( $P = 0.02$ ); but this association became nonsignificant after controlling for mobility limitation ( $P = 0.12$ ).

**Conclusion:** In a nationally representative sample, PA was associated with enhanced cognition, an effect that was differentially influenced by apolipoprotein E genotype. Experimental studies are needed to determine whether or not PA can attenuate cognitive decline.

**Keywords:** cognition, physical activity, apolipoprotein E gene, aging

## Introduction

Alzheimer's disease (AD) is the most common type of dementia, constituting two-thirds of all late-life dementias.<sup>1,2</sup> Its prevalence increases about 15-fold from 3% among individuals aged 65–74 years to 47% among persons aged  $\geq 85$  years.<sup>3–6</sup> In 2010, the annual US health care cost for AD reached about US\$144 billion.<sup>7</sup> Similarly, total 2010 health care, including long-term care payments for AD and other dementia care, was expected to reach US\$172 billion.<sup>7</sup> Given this cost and the projected increase in elderly population by the year 2050, identifying effective mechanisms to prevent AD is an important public health goal.

Until recently, the influence of lifestyle adaptation on AD risk had received very little attention in the scientific literature. Emerging evidence now indicates that PA can enhance cognitive processes.<sup>8–18</sup> Whereas many of such studies examined the type of physical activities performed, others focused on the relationship of the number,<sup>19</sup>

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frequency,<sup>20</sup> or intensity<sup>21</sup> of such activities with cognitive processes. A summary of published literature by Colcombe and Kramer, using a meta-analysis of 18 studies, concluded that fitness training benefitted an array of neurocognitive process in nondemented older adults.<sup>22</sup> Conclusions from these studies mostly suggest significant association of low and high levels of physical activity (PA) with reduced and enhanced cognitive processes, respectively; however, the sample sizes were often small, nonrepresentative, and lacked uniformity in their definition of PA and the characterization of the cognitive phenotype.

Despite the evidence showing that high levels of PA are mostly beneficial, significant interindividual variations of these benefits remain. This may suggest effect modification at the genetic level. Variation at the apolipoprotein E (APOE) gene locus is the most consistent nondeterministic genetic risk factor for late-onset Alzheimer's dementia.<sup>23–26</sup> Its contribution to AD risk is graded across its three known common isoforms (E2, E3, and E4) in humans encoded by  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$  alleles. Whereas,  $\epsilon 2$  allele is associated with lower risk,  $\epsilon 4$  associates with increased AD risk, an effect that is differentially influenced by age.<sup>27–29</sup> Interindividual variation in the  $\epsilon 4$  allele-associated risk may also indicate additional effect modification at the environment level such as imposed by lifestyle. A prior longitudinal study examined the potential benefits of interactions between APOE and PA, with varying results.<sup>19</sup> Whether the APOE gene modifies the effects of PA on cognition in a nationally representative sample such as the Third National Health and Nutrition Examination Survey (NHANES-III) study is yet to be determined. We hypothesized that PA will associate with enhanced cognition and that this effect will differ with age and APOE genotype in a nationally representative sample of older Americans.

## Methods

### Study subjects

The NHANES-III was a cross-sectional, stratified, multistage probability sample of 33,994 civilian, noninstitutionalized Americans in the 50 states and the District of Columbia aged from 2 months to 99 years old, making it the first NHANES to include persons aged  $\geq 75$  years. The study, conducted by the Center for Disease Control's National Center for Health Statistics between 1988 and 1994, oversampled Mexican Americans, African Americans, and those  $> 60$  years.<sup>30,31</sup> Of persons aged  $\geq 60$  years, 5724 (86%) had an assessment of cognitive function. A subset of this sample (1799) included in this analysis were genotyped at the APOE locus.

## General assessments

Overall, the questionnaires were designed for administration in a bilingual (English/Spanish) format so that respondents could be interviewed in their preferred language. During a home interview, an interviewer collected the demographic variables such as age, gender, and level of education to be used in this analysis.

### PA

Participants were asked, "In the past month, did you engage in any leisure-time physical activity?" If their answer was "yes," they were asked, "In the past month, how often did you ...?" (specify number of times) for the following: jogging or running, riding a bicycle or exercise bicycle, swimming, aerobic dancing, other dancing, calisthenics or floor exercises, gardening or yard work, and weight lifting.<sup>32,33</sup> Open-ended questions assessed up to four other activities. Participants were also asked about how often they walked  $\geq 1$  mile. Persons responding "no times" to all of the activities above were classified "no PA." Mobility limitation was also categorized on the basis of participants' responses to two questions asking about difficulty experienced walking two or three blocks and walking up to ten steps without resting. Persons reporting no difficulty were considered to not have limited mobility. These two questions have been used by other investigators to assess mobility limitation.<sup>34,35</sup> Serious chronic illnesses included a self-reported history of chronic obstructive pulmonary disease, congestive heart failure, myocardial infarction, cancer, diabetes, and stroke.

### Assessment of cognitive function

Questions assessing mental cognition were asked only of respondents aged  $\geq 60$  years. The neuropsychological measures used in the NHANES-III study were selected to assess cognitive functions typically affected in dementia.<sup>36</sup> The evaluations, including measures of learning and memory, were obtained during home interviews and at the mobile examination center. These questions, along with recall questions and "serial 3 subtraction" found on the adult questionnaire, constituted a short mental state examination (SMSE).<sup>36,37</sup> Details of the content and administration of the SMSE used during the NHANES-III have been previously published.<sup>38</sup> Overall scores on the SMSE calculated from the sum of orientation, recall, and attention ranged from 0 to 17. The SMSE was carried out during a home examination in 8.6% of the sample for participants who were unable or unwilling to come to a mobile examination center for a complete examination.

## Genetic data

Blood lymphocytes were collected from participants aged  $\geq 12$  years and stored in liquid nitrogen as cell cultures immortalized with Epstein–Barr virus. DNA in the form of crude cell lysates was made available for approved research projects for 7159 persons examined between 1991 and 1994. Genetic data generated from those projects from 1999 to 2006 were submitted to the National Center for Health Statistics and stored upon successful completion of a three-part quality-control analysis. We used data for participants genotyped at the APOE locus (dbSNP ID: rs7412 and rs429358). To maintain confidentiality of individual-level data, analysis occurred at the National Center for Health Statistics Research Data Center in Hyattsville, MD. Approval of the Howard University Institutional Review Board was obtained prior to the analysis.

## Statistical analysis

Initial analyses using SAS 9.2 (SAS Institute, Cary, NC) included *t*-test and chi-square test and examined for group differences in age, gender, ethnicity, educational attainment, and body mass by level of self-reported history of PA, as well as the effects of PA on cognition within age strata. Using multiple regression analysis, we then examined the relationship of PA to cognition, while adjusting for a priori defined confounders. Given the declining levels of PA with age and lower levels of PA in Blacks than in Whites, model 1 included adjustment for age and ethnicity effects on cognition and physical function, whereas model 2 discounted the effects of chronic medical illnesses on cognitive processes and on PA levels. To discount the contribution of education on differences in performance on cognitive tasks<sup>39</sup> and the association of body mass index (BMI) with cognition across populations,<sup>40,41</sup> model 3 additionally adjusted for education and BMI. Given that persons with mobility limitation are less likely to exercise, this variable was included in model 4. Because of evidence indicating that the effect of APOE on cognition is probably influenced by age,<sup>27–29</sup> and to further discern the effect of age from other predictors of cognitive outcome and important confounders, we constructed separate models for the age groups 60–69 and  $\geq 70$ . Least square means adjusted for age, gender, ethnicity, and education were derived using analysis of variance (general linear model). Similar, but separate, models were constructed for APOE genotype groups. To mitigate sample-size limitation, we dichotomized the sample as non- $\epsilon 4$  carriers ( $\epsilon 4$  allele absent), and  $\epsilon 4$  carriers (at least one copy of  $\epsilon 4$ ).

To address the peculiarity of the multistage complex survey design of NHANES-III, final analyses were performed

using SUDAAN (RTI International, Research Triangle Park, NC), software that accounts for the multistage sampling of NHANES-III in computing variance estimates.<sup>42</sup> Appropriate sampling weights were used to account for oversampling and nonresponse. SUDAAN Proc Crosstab and Descript were used to estimate percentages and means, respectively, across groups. Proc Reg was used for linear regression.

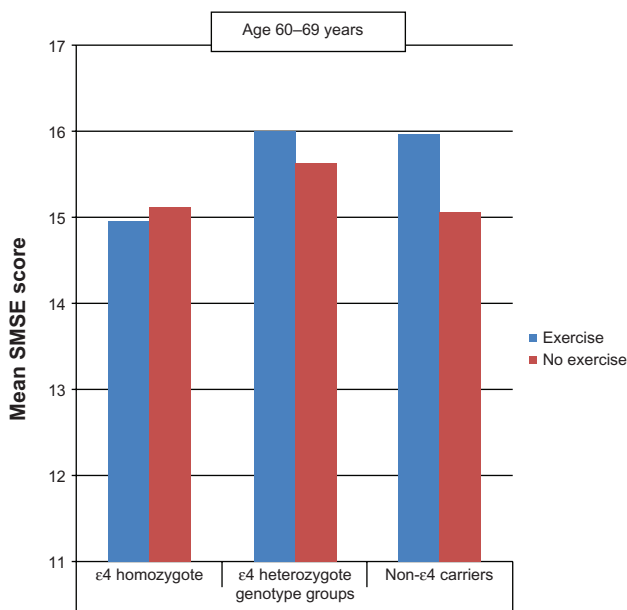
## Results

Overall, 56.9% had any PA, while 43.1% did not. Those who engaged in any PA were relatively younger, more likely to be men, and had more formal education (Table 1). Compared with other ethnic groups, Whites in the sample were about twice as likely to engage in PA as Blacks and Mexican Americans (61.6%, 32.8%, and 38.9%, respectively). However, both groups had comparable BMI. APOE genotype was in Hardy–Weinberg equilibrium ( $P < 0.05$ ). The respective frequencies of allele combinations paralleled those reported in the literature. In the entire sample, Blacks were more likely to be carriers and homozygotes for the risk allele ( $\epsilon 4$ ) (39.19 and 4.89, respectively), compared with Whites (28.02 and 2.19, respectively), and Mexican Americans (19.34 and 1.61), respectively.

Between the ages of 60 and 69 years (Figures 1 and 2), persons who performed PA tended to score higher on the SMSE among heterozygotes and noncarriers but not among

**Table 1** Characteristics of the sample (percent by leisure-time physical activity)

Leisure-time physical activity	Yes	No	P value
Age (years)			
60–69	60.22	39.78	0.0134
$\geq 70$	53.66	46.34	
Gender			
Men	56.89	43.11	<0.0001
Women	49.67	50.33	
Ethnicity			
White	61.55	38.35	<0.0001
Black	32.81	67.19	
Mexican	38.94	61.06	
Other	32.22	67.78	
Education (years)			
<12	47.00	53.00	0.0002
12	59.05	40.95	
>12	66.67	33.33	
Body mass index			
<25	56.87	43.13	0.9651
25–29	57.40	42.60	
$\geq 30$	56.13	43.87	

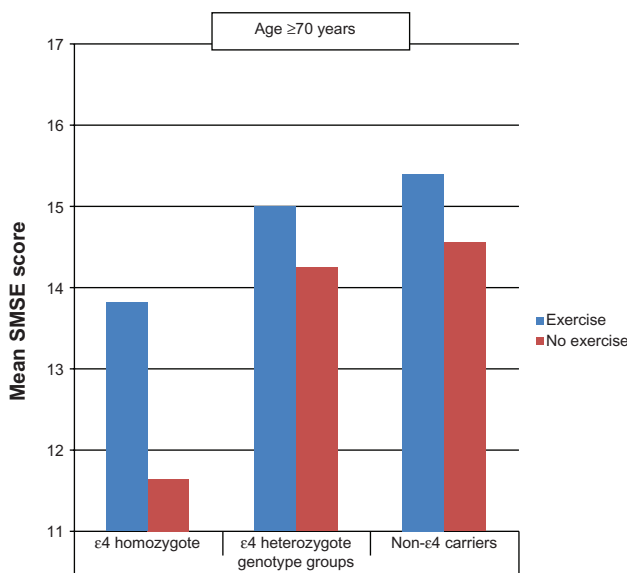


**Figure 1** Mean short mental state examination (SMSE) score by physical activity and apolipoprotein E genotype (age 60 to 69 years).

homozygotes. At age  $\geq 70$  years, similar associations were observed not only in heterozygotes and noncarriers but also in homozygotes.

## Multiple regression analysis

In the initial analysis restricted to the non- $\epsilon 4$  carrier genotype group aged 60–69 years and adjusted for age and ethnicity (model 1), PA was significantly associated with cognitive performance ( $\beta = 0.68 \pm 0.2$ ;  $P = 0.006$ ) (Table 2). This model accounted for 9.8% of the observed variance. With additional



**Figure 2** Mean short mental state examination (SMSE) score by leisure-time physical activity and apolipoprotein E genotype (age  $\geq 70$  years).

adjustment for serious chronic medical illnesses (congestive heart failure, chronic obstructive pulmonary disease, cancer, diabetes, myocardial infarction, and stroke) (model 2), this statistically significant association remained unchanged ( $\beta = 0.68 \pm 0.2$ ;  $P = 0.007$ ). However, after accounting for differences in BMI and education (model 3), PA maintained a statistically significant but reduced association with cognitive function ( $\beta = 0.52 \pm 0.2$ ;  $P = 0.007$ ). In the last model, controlled for mobility limitation in non- $\epsilon 4$  carriers (model 4), the significant association of PA ( $\beta$  coefficient  $0.43 \pm 0.2$ ,  $P = 0.014$ ) with SMSE score persisted though slightly attenuated. However, among the  $\epsilon 4$  carriers of this age group, PA did not significantly associate with cognitive performance.

We also examined the relationship of PA to SMSE in the  $>70$  year old age group (Table 3). In noncarriers, PA associated with performance on the cognitive test in models 1, 2, and 3. With the introduction of mobility limitation ( $\beta = -0.78 \pm 0.2$ ,  $P < 0.001$ ) in model 4, the association of PA to cognitive performance became attenuated and nonsignificant ( $\beta = 0.37 \pm 0.2$ ,  $P = 0.117$ ). Among  $\epsilon 4$  carriers, similar associations with cognitive performance were observed in models 1–4, but did not attain statistical significance. This could be due to the smaller sample size.

## Discussion

PA was associated with better performance on cognitive tasks in a sample of age  $\geq 60$  non- $\epsilon 4$  carriers but not in carriers. These findings were independent of linear age, gender, ethnicity, education, income, and history of serious chronic illness. This adds to growing evidence that increased levels of PA may offer an important primary intervention strategy to attenuate neurocognitive loss, especially in non- $\epsilon 4$  carriers. Delay in significant cognitive loss and considerable public health impact are likely to be realized if these findings are confirmed in experimental studies.

Evidence showing that PA can enhance cognition includes cross-sectional, prospective studies and a limited number of controlled trials.<sup>8–11,17–20,22</sup> Many studies examined the effects of aerobic fitness on cognition in nondemented older adults, while others determined whether or not lifestyle factors can reduce or delay late-onset Alzheimer's dementia. In concordance with our observations from this study, a beneficial effect of PA was often reported.<sup>19–21,43</sup> Whereas Albert and colleagues reported that strenuous but not moderate intensity daily PA enhanced cognition,<sup>44</sup> Yaffe et al showed that moderate daily PA can also improve cognitive processes.<sup>45</sup> Together, these reports are consistent with our hypothesis and results from this study that PA is beneficial to cognitive health.

**Table 2** Regression analysis dependent variable: short mental state examination (age 60–69 years)

Variables	Age and ethnicity adjusted		Model 1 plus chronic disease (model 2)		Model 2 plus education and BMI (model 3)		Model 3 plus mobility limitation (model 4)	
	$\beta$	95% CI	$\beta$	95% CI	$\beta$	95% CI	$\beta$	95% CI
<b>Non-<math>\epsilon 4</math> carriers (n = 585)</b>								
R-squared (%)	(9.8)		(9.6)		(16.1)		(17.5)	
Aerobic activity	0.68 ± 0.23	0.21 ± 1.15	0.68 ± 0.23	0.21 ± 1.15	0.52 ± 0.18	0.16 ± 0.89	0.43 ± 0.16	0.10 ± 0.76
Age	-0.04 ± 0.03	0.03 ± -0.09	-0.04 ± 0.02	-0.09 ± 0.01	-0.03 ± 0.02	-0.08 ± 0.02	-0.03 ± 0.02	-0.08 ± 0.02
Ethnicity								
Whites	0.24 ± 0.40	0.40 ± -0.58	0.23 ± 0.41	-0.61 ± 1.07	0.27 ± 0.37	-0.49 ± 1.03	0.28 ± 0.38	-0.50 ± 1.05
Black	-0.94 ± 0.53	0.53 ± -2.03	-0.94 ± 0.54	-2.06 ± 0.18	-0.68 ± 0.52	-1.76 ± 0.40	-0.61 ± 0.52	-1.69 ± 0.47
Hispanic	-1.13 ± 0.49	0.49 ± -2.14	-1.13 ± 0.49	-2.14 ± 0.12	-0.70 ± 0.49	-1.70 ± 0.31	-0.70 ± 0.51	-1.75 ± 0.36
Chronic disease			-0.08 ± 0.38	-0.86 ± 0.70	0.07 ± 0.41	-0.77 ± 0.92	0.10 ± 0.40	-0.73 ± 0.93
LogBMI					0.37 ± 0.69	-1.05 ± 1.80	0.50 ± 0.69	-0.93 ± 1.94
Education					0.60 ± 0.12	0.36 ± 0.84	0.56 ± 0.11	0.34 ± 0.78
Mobility limitation							-0.51 ± 0.30	-1.13 ± 0.1
<b><math>\epsilon 4</math> carriers (n = 210)</b>								
R-squared (%)	(5.7)		(7.8)		(18.2)		(18.5)	
Aerobic activity	0.15 ± 0.24	-0.35 ± 0.64	0.18 ± 0.24	-0.32 ± 0.68	0.01 ± 0.23	-0.47 ± 0.50	0.04 ± 0.26	-0.57 ± 0.49
Age	-0.04 ± 0.04	-0.12 ± 0.05	-0.04 ± 0.04	-0.13 ± 0.05	-0.05 ± 0.04	-0.13 ± 0.03	-0.05 ± 0.04	-0.13 ± 0.04
Ethnicity								
White	0.05 ± 0.52	-1.03 ± 1.13	0.03 ± 0.49	-0.97 ± 1.04	-0.28 ± 0.45	-1.22 ± 0.66	-0.27 ± 0.45	-1.20 ± 0.66
Black	-0.56 ± 0.56	-1.71 ± 0.59	-0.54 ± 0.50	-1.58 ± 0.51	-0.77 ± 0.43	-1.67 ± 0.12	-0.77 ± 0.42	-1.64 ± 0.11
Hispanic	-1.86 ± 0.81	-3.54 ± -0.18	-1.76 ± 0.78	-3.38 ± -0.14	-1.66 ± 0.64	-2.99 ± -0.33	-1.57 ± 0.64	-2.89 ± -0.24
Chronic disease			-0.72 ± 0.32	-1.39 ± -0.05	-0.73 ± 0.23	-1.21 ± -0.26	-0.71 ± 0.23	-1.18 ± -0.23
LogBMI					0.34 ± 0.77	-1.26 ± 1.94	0.41 ± 0.72	-1.08 ± 1.91
Education					0.73 ± 0.31	0.09 ± 1.36	0.72 ± 0.31	0.07 ± 1.36
Mobility limitation							-0.24 ± 0.38	-1.03 ± 0.56

**Notes:** Significant level for alpha was set at <0.05; model P values are all <0.0001; serious chronic illnesses included history of chronic obstructive pulmonary disease, congestive heart failure, myocardial infarction, cancer, diabetes, and stroke.  
**Abbreviations:** BMI, body mass index; CI, confidence interval.

**Table 3** Regression analysis dependent variable: short mental state examination (age ≥ 70 years)

Variables	Age and ethnicity adjusted (model 1)			Model 1 plus chronic disease (model 2)			Model 2 plus education and BMI (model 3)			Model 3 plus mobility limitation (model 4)		
	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value	β	95% CI	P value
<b>Non-ε4 carriers (n = 700)</b>												
R-squared (%)	(12.7)			(13.3)			(18.9)			(21.1)		
Aerobic activity	0.67 ± 0.23	0.20, 1.15	0.007	0.63 ± 0.25	0.12, 1.15	0.018	0.56 ± 0.23	0.09, 1.03	0.022	0.37 ± 0.23	-0.10, 0.85	0.117
Age	-0.08 ± 0.01	-0.11, -0.05	<0.001	-0.07 ± 0.01	-0.10, -0.04	<0.001	-0.06 ± 0.02	-0.09, -0.02	0.002	-0.04 ± 0.02	-0.08, -0.01	0.024
Ethnicity												
White	0.73 ± 0.95	-1.23, 2.69	0.446	0.77 ± 0.94	-1.18, 2.72	0.420	0.30 ± 0.79	-1.34, 1.93	0.711	0.34 ± 0.69	-1.10, 1.78	0.629
Black	-1.40 ± 0.97	-3.41, 0.61	0.163	-1.32 ± 0.96	-3.30, 0.66	0.180	-1.24 ± 0.79	-2.88, 0.41	0.133	-1.20 ± 0.69	-2.63, 0.22	0.094
Hispanic	-1.25 ± 1.03	-3.39, 0.89	0.238	-1.11 ± 1.04	-3.27, 1.05	0.297	-1.07 ± 0.89	-2.91, 0.77	0.241	-1.01 ± 0.79	-2.65, 0.62	0.212
Chronic disease												
LogBMI				-0.61 ± 0.39	-1.41, 0.19	0.130	-0.61 ± 0.41	-1.46, 0.25	0.158	-0.52 ± 0.39	-1.32, 0.28	0.189
Education							0.75 ± 0.74	-0.79, 2.28	0.324	0.96 ± 0.77	-0.64, 2.55	0.227
Mobility limitation							-0.61 ± 0.41	-1.46, 0.25	0.158	0.69 ± 0.11	0.46, 0.91	<0.001
										0.37 ± 0.2	-1.11, -0.46	0.117
<b>ε4 Carriers (n = 214)</b>												
R-squared (%)	(16.9)			(17.6)			(21.2)			(22.6)		
Aerobic activity	0.52 ± 0.33	-0.17, 1.21	0.136	0.69 ± 0.36	-0.06, 1.43	0.067	0.58 ± 0.35	-0.14, 1.30	0.109	0.31 ± 0.42	-0.56, 1.17	0.470
Age	-0.18 ± 0.05	-0.28, -0.08	0.001	-0.17 ± 0.05	-0.27, -0.08	0.001	-0.16 ± 0.04	-0.24, -0.07	0.001	-0.14 ± 0.04	-0.23, -0.05	0.003
Ethnicity												
Whites	1.29 ± 1.37	-1.55, 4.13	0.358	1.48 ± 1.40	-1.42, 4.38	0.302	1.22 ± 1.59	-2.07, 4.51	0.452	1.29 ± 1.61	-2.04, 4.63	0.431
Blacks	0.07 ± 1.42	-2.87, 3.0	0.963	0.22 ± 1.43	-2.75, 3.18	0.882	0.12 ± 1.50	-2.99, 3.22	0.938	0.28 ± 1.53	-2.90, 3.45	0.858
Hispanic	0.73 ± 1.32	-1.99, 3.46	0.582	0.83 ± 1.34	-1.95, 3.60	0.543	0.82 ± 1.34	-1.96, 3.59	0.549	0.81 ± 1.34	-1.96, 3.58	0.550
Chronic disease												
LogBMI				0.70 ± 0.50	-0.33, 1.72	0.174	0.53 ± 0.48	-0.46, 1.52	0.280	0.54 ± 0.50	-0.49, 1.57	0.289
Education							2.18 ± 0.93	0.25, 4.11	0.029	2.46 ± 0.98	0.43, 4.50	0.020
Mobility limitation							2.18 ± 0.93	0.25, 4.11	0.029	0.41 ± 0.30	-0.21, 1.02	0.183
										-0.77 ± 0.49	-1.80, 0.25	0.133

**Notes:** Significant level for alpha was set at <0.05; model P values are all <0.0001; serious chronic illnesses included history of chronic obstructive pulmonary disease, congestive heart failure, myocardial infarction, cancer, diabetes, and stroke.

**Abbreviations:** BMI, body mass index; CI, confidence interval.

However, unlike previous cross-sectional studies, the use of a representative sample of US noninstitutionalized population enhanced the generalizability of our findings beyond that previously reported in cross-sectional studies.

Consistent with our second hypothesis, the relationship of PA to performance on the SMSE test varied with APOE genotype and age group. In the adjusted model, the apparent relationship between APOE and PA observed in the unadjusted model became attenuated in those aged >70 years. This may suggest that the APOE effect becomes attenuated with age, allowing other determinants of cognitive function such as PA to become more apparent. Similar to the cognitively beneficial effects of PA observed in non- $\epsilon 4$  carriers in our study, Podewils et al demonstrated that performance of  $\geq 4$  types of activity lowered dementia risk at age  $\geq 65$  years in the Cardiovascular Health Cognition Study, an effect that was marked in non- $\epsilon 4$  carriers but absent in  $\epsilon 4$  carriers.<sup>19</sup> Conversely, we confirmed a lack of association of PA with cognitive performance in  $\epsilon 4$  carriers in the 60–69 age group. Persons suffering from serious medical illnesses may perform at lower levels of PA and have lower cognition. However, the statistically significant association of PA with enhanced cognition at age 60–69 years in our final model suggests that the association of PA with enhanced cognition in the younger non- $\epsilon 4$  carriers is likely independent of mobility limitation and chronic medical illnesses.

An additional important finding from this study is the improved performance in the >70 age group exercisers compared with nonexercisers in all genotype groups, suggesting that the favorable effects of PA in this group may not be significantly influenced by the  $\epsilon 4$  allele of the APOE gene (Figure 2). The favorable effects of PA on memory in non- $\epsilon 4$  carriers remained unaltered, notwithstanding adjustment for serious chronic medical illness, but not after accounting for the effect of mobility limitation. However, a three-group ( $\epsilon 4$ -homozygote,  $\epsilon 4$ -heterozygote, and noncarriers) analysis to confirm that PA can enhance cognition at age  $\geq 70$  years regardless of genotype group was constrained by sample size.

Because mobility limitation is a surrogate marker for PA, its significant association with poorer performance on cognitive tests after discounting the effects of serious chronic medical illness supports its role as an indicator of sedentary lifestyle. Previously, it was suggested that pathologies underlining frailty may partially explain the association of low levels of PA with poor cognitive performance.<sup>46</sup> The coexistence of frailty with serious chronic medical condition and low BMI prompted us to examine their contributions to

cognitive outcome in our sample. However, the significant effect of PA after adjustments for serious chronic medical conditions and BMI, makes frailty a less tenable explanation for our findings in older adults but supports mobility limitation as a surrogate marker for low levels of PA. Given the nonspecific pattern of association of APOE genotype groups with limitation in physical function, this relationship probably does not explain our findings either.

Contrary to studies reporting a beneficial effect of PA and/or aerobic fitness on neurocognitive processes, few have reported negative results.<sup>47,48</sup> Verghese et al reported that a one-point increment in the PA score did not significantly improve performance on cognitive tasks,<sup>47</sup> and that levels of PA did not associate with incident amnesic mild cognitive impairment.<sup>48</sup> However, the authors failed to account for a few important components of PA such as walking, gardening/yard work, and house chores. Interestingly, our observation of no association in the 60–69 age group  $\epsilon 4$ -carriers is also analogous to the overall conclusions of Verghese et al, except that such subgroup analyses were not considered by the authors. Such methodological differences in the assessments of cognition and PA may contribute to inconsistencies in the literature. In comparison with previous cross-sectional studies, this study has the advantage of adjustment for serious chronic illnesses and mobility limitation, is age-specific, and involves APOE genotype-stratified analysis in addition to a representative sample. Though the mechanisms by which APOE mediates differential PA-induced changes in cognition may involve its role in lipid metabolism, further clarification of this process is needed.

## Advantages and limitations

NHANES-III is the largest study to provide population-based data on the association of cognitive function and PA in a nationwide representative sample of older Americans. Because age is one of the most important risk factors for dementia, the relatively large sample size of the NHANES-III permits age-stratified analysis, adjustment for multiple confounders, and, therefore, more detailed assessment of the relationship of PA with cognitive outcome. Limitations of this study include possible bias from survey nonresponse and from missing values for some variables and the large number without APOE data.

Due to its cross-sectional nature, the study does not provide information on the temporal sequence of PA with SMSE score. For questionnaires administered in the Hispanic language, translational bias cannot be excluded in spite of rigorous staff training and standardizations. Randomized controlled trials

using a more rigorous standardized aerobic exercise-training protocol together with detailed neuropsychological measures are needed to determine the duration, intensity, frequency, and ultimately the volume of exercise that are beneficial.

## Conclusion

In a large national sample of noninstitutionalized Americans aged  $\geq 60$  years, PA associated with better cognitive outcomes. Between the ages of 60 and 69 years, this effect varied by APOE gene group, the effects being observed only in non- $\epsilon 4$  carriers. Randomized controlled trials are needed to establish causality. Also, the APOE genotype or its genotype must be taken into account while designing such studies. These may lay the groundwork for the prescription of aerobic training as an intervention to attenuate AD risk in those at risk.

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## Disclosure

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