2020

Physical Activity Moderates the Relationship Between APOE4 Status and Working Memory: The Health and Retirement Study

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PHYSICAL ACTIVITY MODERATES THE RELATIONSHIP BETWEEN APOE4 STATUS AND WORKING MEMORY: THE HEALTH AND RETIREMENT STUDY

by

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A thesis submitted in partial fulfillment of the requirements
for the Honors in the Major Program in Psychology
in the College of Sciences
and in the Burnett Honors College
at the University of Central Florida
Orlando, Florida

Fall 2020

ABSTRACT

The purpose of this study is to explore the relationship between physical activity and working memory decline among older adults with APOE4 status. The APOE4 allele is currently the strongest predictor of risk for Alzheimer's disease and other related dementias. The publicly available data from the Health and Retirement Study was used to complete this Retrospective Longitudinal study. Three hypotheses were explored. *H_1: It is expected that the presence of the APOE4 allele will be associated with worse overall working memory performance and a steeper rate of decline in working memory over time. H_2: Meanwhile, it is expected that participants that partake in a higher physical activity level will have better overall working memory performance and less decline in working memory than participants that only perform low or no activity. H_3: A moderation effect of physical activity on the relationship between working memory and APOE4 status is expected.* A two-way repeated measure ANOVA was performed. Results indicted main effects for physical activity and years of education on the digit span task. Additionally, it was found that vigorous activity mitigates ill-effects of APOE4 on working memory. A statistical significance was found for the interaction between APOE4 status and physical activity. Findings suggest that physical activity may be prioritized as a primary intervention method for older and middle-aged APOE4 carriers.

Keywords: APOE4 Status, Cognitive Decline, Physical Activity, Working Memory

ACKNOWLEDGEMENTS

I want to thank my thesis chair, Dr. Daniel Paulson, for helping and encouraging me throughout this process. I am grateful for the knowledge I have obtained in such a short amount of time from his mentorship that was based on guidance, instruction, and support. You have enriched my academic life in more ways than I can express, thank you.

To my committee chair member, Dr. Nichole Lighthall, thank you for your advice which enabled me to become a better researcher and presenter. I strive to be greater because of your accomplishments and professionalism.

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INTRODUCTION

A surge of research has recently focused on the Apolipoprotein E (APOE) due to its link to Alzheimer's disease (AD), related dementias, and cognitive decline in later life. There are three polymorphisms of the genome: APOE2, APOE3, APOE4. The most common allele is APOE3, and is considered to confer neutral risk for AD and cognitive decline. By contrast, APOE2 is less common and considered to cover protective effects with respect to cognitive decline whereas APOE4 confers increased risk for Alzheimer's disease and other forms of cognitive decline. These risks appear somewhat greater among women than men (Fleisher et al., 2005; Seshadri et al., 1997). The APOE gene is a lipoprotein important in lipid storage and the transportation and metabolism of cholesterol, which is located in the central nervous system (Mahley, 1988). Its purpose is to remove excess cholesterol from the blood and bring it to the liver to be processed (Shiel Jr., 2018). APOE is crucial in prevention of cardiovascular diseases as well as strokes due to its involvement with brain metabolism (Shiel Jr., 2018), thus having a significant effect on cognition. Among healthy middle-aged adults, APOE4 status is associated with working memory deficits (Parasuraman, Greenwood, & Sunderland, 2002). The rapidly growing older adult demographic (U.S. Census Bureau, 2020) and the corresponding public health care challenges highlight the importance of identifying effective prevention strategies. Physical activity has emerged as an interventional strategy with respect to cardiovascular health and overall fitness with evident downstream benefits for cognition (Northey, Cherbuin, Pumpa, Smee, & Rattray, 2018). While exercise is a common strategy for mitigating cognitive risk associated with cardiovascular decline, little is known about how physical activity and APOE4 status interact.

APOE4

The APOE4 allele is currently the strongest predictor of risk for mild cognitive decline or Alzheimer's disease (AD). While inheritance of one APOE4 allele is associated with increased risk of late-onset AD in older adults, inheritance of two APOE4 alleles increases risk even further, implicating a dosage effect (Corder et al., 1993). Although having the APOE4 allele is not sufficient to determine if one will have AD, 48% to 60% of AD patients are APOE4 carriers (Farrer et al., 1997; Ward et al., 2012). The outcome of this dangerous allele is seen as alterations in brain morphology and brain metabolism. Data collected has shown the difference between individuals with APOE4 status versus non-carriers in a multitude of cognitive areas. It was found that APOE4 carriers may have more hippocampal volume reduction (Plassman et al., 1997), the parietal metabolism is lower and hemispheric asymmetry is greater (Small et al., 1995), an increased level and volume of activation may occur as a compensatory response to perform a cognitive operation (Bookheimer et al., 2000), and memory scores are lower—including verbal memory performance and spatial working memory (Flory, Manuck, Ferrell, Ryan, & Muldoon, 2000). Further research found cognitive decline associated with APOE4 status in older adults between the ages of 65 and 69. By comparing 2 Waves of the same APOE4 carriers, 5 years apart, results showed a significant decrease in performance for speed, memory, and working memory between Wave 1 (ages 60 to 64) and Wave 2 (ages 65 to 69). The study found a marginal significant effect on general cognition, measured by the Mini Mental State Exam (MMSE), and the APOE4 allele in Wave 2 as opposed to Wave 1 (Christensen et al., 2008). In summary, APOE4 status emerges as a consistent predictor of cognitive decline among older adults.

Working Memory

Working memory is explained as a multi-component function which temporarily processes, stores, and manipulates new information to facilitate a range of cognitive activities, such as reasoning, learning and comprehension (A. Baddeley, 2003). Literature further describes working memory as having four main factors: central executive memory, verbal memory, visuospatial memory, and the episodic buffer (A. Baddeley, 2007). The central executive working memory includes attention, inhibition, task management, and set shifting functions (R. Cabeza et al., 2018). Measurement of working memory can be obtained from memory encoding tasks, selective attention tasks, and divided attention tasks (A. D. Baddeley, Eysenck, & Anderson, 2015). The digit span task, which measures verbal and central executive memory, is a frequently used neuropsychological measure of working memory. This task is described by Baddeley as one that uses recall of order, which relies on positional associations between the first and subsequent items, to measure memory span. The limits of memory span are seen when associations become progressively weaker as more items are added. "Retrieval involves competitive queueing: the strongest association is retrieved first and the associated item is emitted and then inhibited, allowing the next strongest to be retrieved and so on to the end of the list, or to the point at which the associations become too weak and the process breaks down" (A. Baddeley, 2003).

Age related declines in working memory are well established (Park, Polk, Mikels, Taylor, & Marshuetz, 2001). These differences in older adults include bilateral activation as compensatory responses to greater task demands (Roberto Cabeza et al., 1997), overactivation of neural circuits (Reuter-Lorenz & Cappell, 2008), and poorer performance on working memory

tasks such as the Sternberg task involving slower response times and lower accuracy (Schneider-Garces et al., 2010). Therefore, a decline in working memory throughout later-life is consistent with age-related cognitive change (Park et al., 2001), regardless of APOE status.

The relationship between APOE4 status and working memory specifically has been studied in dementia-free patients (Rosen, Bergeson, Putnam, Harwell, & Sunderland, 2002). Their sample of healthy older adults (M = 62 years old) completed measures of working memory performance using an operation span task, digits span task, and general memory index. Results showed no effect of APOE status on the digit span and the general memory index performances. However, it was found that APOE4 carriers had a poorer performance on the operation span task than non-APOE4 carriers (Rosen et al., 2002). The study demonstrated that the divided attention and inhibition are significantly worse among older middle-aged APOE4 carriers, and further supports a difference in working memory between APOE4 carriers and non-carriers.

Physical Activity and Cognition

Physical activity and exercise have been associated with health benefits for cognition, such as increasing the brain-derived neurotrophic factor (BDNF) associated with neuroplasticity effects (Nilsson et al., 2020). Research has studied the effect of exercise on cognitive performance in older adults as a method to off-set age-related dementias and cognitive impairments. A 6-month intervention study randomly assigned 62 healthy participants (ages 50-72) into three groups: control group (sedentary), light-intensity exercise (gymnastics), and medium-intensity exercise (nomadic walking). Groups that partook in nomadic walking or gymnastics performed these activities for 50 minutes, at least 3 times a week, over the span of 6-

months. Baseline scores for physical activity and memory performance were obtained before and after the intervention. The study found that higher exercise levels were positively associated with increased gray matter volume and changes in BDNF levels. A significant effect was found between the pooled exercise groups and episodic memory over time, measured by the German version of the Auditory Verbal Learning Test (Ruscheweyh et al., 2011). These findings demonstrating the benefits of physical activity on cognition are similarly shared in other studies (Colcombe et al., 2004; Hötting & Röder, 2013; Kramer et al., 1999; Smiley-Oyen, Lowry, Francois, Kohut, & Ekkekakis, 2008).

Prior research on the relationship between physical activity and cognition among APOE4 carriers has mostly indicated a beneficial effect. A study observing individuals that perform physical activity during mid-life found that these participants had less onset of AD & later-life dementia, while sedentary participants had higher levels of later-life dementia (Rovio et al., 2005). Another study looked at APOE4 carriers who exercised less than 1 hour per day versus carriers who exercised more than 1 hour per day. It was found that participants exercising an hour or less were at a higher risk for cognitive decline in later life (Schuit, Feskens, Launer, & Kromhout, 2001). In a longitudinal study with 6619 participants, results indicated that the presence of the APOE4 allele significantly increased and higher physical activity significantly decreased risk for dementia and AD (Luck et al., 2014).

Existing research exploring the relationship between physical activity and specifically working memory among APOE4 carriers has been conflicting. A study examined the baseline association between self-reported levels of physical activity, measured by the Nurses' Health Study Exercise Questionnaire (NHSEQ), and cognitive functioning. Every year, for 6 years, 91

healthy older participants (*M* = 64.9 years) from the Adult Children Study were assessed for working memory performance using the Animal Naming Task, Letter-Number Sequencing task and Trail Making test. Linear mixed effects modeling was used to examine the interaction between physical activity and cognitive performance overtime. It was found that physical activity and APOE4 status in combination were associated with a small but significant effect on Letter-Number Sequencing task and Trail Making test scores, while the cross-sectional analysis showed no effect on working memory (Pizzie et al., 2014). By contrast, a study examined the combined and independent effects of APOE status and physical activity among dementia-free participants between the ages of 50 and 70 years old. Although physical activity was not significantly associated with accuracy on the Sternberg working memory test (amount of words remembered correctly), it was significantly associated with response speed. Participants with APOE4 status had significantly worse reaction times in the working memory tasks, while the non-APOE4 group had no reduction. These findings suggested that, by comparison to non-carriers, APOE4 carriers benefitted more from the protective effects of physical activity (Deeny et al., 2008).

Contrasting research finds that physical activity is not a moderator of the association between APOE status and cognitive decline in older adults. The longitudinal study conducted by Najada Stringa, examined whether the gene-environment interaction between APOE genotype and physical activity was associated with cognitive decline in the general population of older adults. Dementia-free participants were assessed for their physical activity using the validated LASA Physical Activity Questionnaire and classified into categories based on exercise frequency (inactive, light physical activity, and moderate-high physical activity). Decline of

cognition was measured using the Mini-Mental State Exam. The study found that overall, there was no association between physical activity and cognitive decline in the pooled analysis of the 3 groups as well as no association between physical activity and cognitive decline when the 3 groups were meta-analyzed (Stringa et al., 2020). The discrepancies between the literature reviews may be attributed to variety in cognitive assessments or to a comparison of disparate populations that cannot be generalized to all populations. Additionally, the age population used in the different studies may suggest that physical activity has an affect earlier in life, but the benefits are not sustained into later-life. Such inconsistent findings between research with similar hypotheses calls for more studies to be done in order to gather more conclusive evidence.

Gender

With the knowledge that APOE status affects cognition, research has looked specifically at the APOE4 allele effects on gender. Not only have studies found that APOE4 affects sex disproportionately, but also in difference of severity (Fleisher et al., 2005). Female carriers are found to have increased MCI or AD risk between the ages of 55 and 70 years compared to their male counterparts (Neu et al., 2017). Above the age of 65, twice as many females have AD compared to men (Seshadri et al., 1997). This may be attributed to their longer lifespan, and it is also believed to have associations with menopause. However, it was explained that additional research yielded results showing one APOE4 allele had a substantial effect on AD risk in females relative to non-carriers, whereas their male counterparts remained at similar risk to non-carriers. This suggests that the disproportion between sexes may be partially attributable to variable APOE4-conferred dementia risk rather than well-established gender differences in

lifespan. Additionally, it is important to observe that not only is the risk greater for women with APOE4 than men, but the severity of the APOE4 effects are more significant. Female APOE4 carriers with MCI also express more prominent phenotypic features than their male counterparts, such as lower hippocampal volumes and worse memory performance (Fleisher et al., 2005). By understanding that females are more greatly impacted by the APOE4 negative effects than males, the intervention methods to prevent or slow APOE4 effects on cognition will also vary in effectiveness for each sex.

In addition to gender disparities in APOE4-related cognitive decline, similar disparities may exist for benefits associated with physical activity. Results of a meta-analysis summarizing 44 physical activity effect sizes and both male and female participants from 39 studies, it was reported that all three—aerobic training, resistance training, and mixed training—were associated with greater cognitive performance of executive functions in women than men (Barha, Davis, Falck, Nagamatsu, & Liu-Ambrose, 2017). With the accumulation of this information, it is considered that there may be a relation between greater cognitive decline and more effectiveness of physical activity. These findings suggest that, among older adults, physical activity may offer resilience to those who are disproportionately at-risk for decline by virtue of gender and APOE status. In this case, since females have more significant deterioration than men, it implies physical activity will be more beneficial to women. Thus, it may be beneficial to examine interrelationships between APOE status, activity, and cognition for men and women separately.

Education/Brain Reserve

Cognitive reserve is defined by Cabeza as a "cumulative improvement in neural resources due to genetic and/or environmental factors that mitigate the effects of neural decline caused by aging or age-related diseases" (R. Cabeza et al., 2018: p. 4). Empirical findings widely support the hypothesis that longer education engenders more effective use of cerebral networks which is a protective factor against cognitive decline (Sole-Padulles et al., 2009). The brain reserve effect may best be conceptualized as delaying the onset of clinical symptoms of a syndrome rather than completely mitigating the risks. By having a larger brain reserve, it takes longer to cross the threshold for synapse loss to become clinically apparent (Stern, 2002). Therefore, it is expected that a person with a smaller brain reserve will take less time to show clinical symptoms. The comparison of participants with dissimilar brain reserve sizes is inadequate to measure the efficacy of an intervention method. Furthermore, a recent study researching the relationship between level of education and cognitive performance found that participants with a high level of education (M = 15.3 years) had significantly better cognitive performances, including working memory, compared to those with low education attainment (M = 9.5) (Chen et al., 2019). Given the cognitive variables of interest in this study, education is thus a critical control variable.

Other Demographics

Age, socioeconomic status, race, and ethnicity are important control variables because they all relate to variability in cognitive performance. Age is a continuous variable that gradually affects performance on working memory tasks, suggested to be caused by physiological changes (Wang et al., 2012). However, this study is looking for a rapid decline associated to the effects of

APOE4 status on cognitive performance. In order to observe changes in working memory caused by APOE4, it is necessary to choose a baseline age at which cognitive decline is apparent. A study supports that APOE4 effects on cognition start to show at ages 65 to 69 (Christensen et al., 2008). By including participants ages 65 and older, cognitive decline resulting from APOE4 status would be observed.

Socioeconomic status (SES) is associated with a wide range of other demographic, healthcare, and cognitive variables including physical health (Adler & Stewart, 2010), mental health (Lorant et al., 2003), and intelligence and academic achievement (Sirin, 2005). Environmental and psychosocial factors that vary by SES affect both the brain and neurocognitive performance, including working memory (Farah, 2017). More specifically, low-education and low-occupational status were both associated with higher dementia risk (Stern et al., 1994). Thus, it is critical to control for metrics of SES, such as overall wealth and income, on cognitive performance.

Race and ethnicity will also be controlled for through statistical procedures. As people from each race/ethnicity bare a different lifestyle, along with different and unequal burdens, these factors impact health. One of the factors that is affected by difference of race and ethnicity is cognition. A study using data from the Health and Retirement Study was performed to examine the association of cognition of older adults and race/ethnicity in the USA. Cognitive functioning was assessed using a modified version of the Telephone Interview for Cognitive Status (TICSM). The results determined differences in cognitive functioning between Non-Hispanic Whites, African–Americans, and Hispanics. It was found that Hispanic older adults had lower cognitive functioning compared with Non-Hispanic Whites and African-Americans—

claimed to be largely due to differences in educational attainment since Hispanics on average have only 10 years of education while Non-Hispanic Whites have an average of 14 years and African-Americans have an average of 13 years (Diaz-Venegas, Downer, Langa, & Wong, 2016). The educational attainment gap between African-Americans and Non-Hispanic Whites is narrowing (U.S. Census Bureau, 2020), creating a more obvious deficit in the education Hispanics obtain. Supplementary research supports that stressful consequences of economic insecurity and racism, combined with risky health behaviors, may increase African-Americans' prevalence of biological risk factors for poor cognitive functioning: vascular disease, clinical depression, and physical comorbidity (Zsembik & Peek, 2001). Therefore, this study will seek to statistically control for race and ethnicity.

THE CURRENT STUDY

The primary goal of this study is to examine how working memory at baseline and over time, measured by the digit span task, will be associated with physical activity level and APOE status after controlling for age, education, socioeconomic status, race, and ethnicity. Given past findings regarding the late-60's as a common tipping point with respect to cognition among APOE4 carriers (Christensen et al., 2008), this age-range will be employed as a baseline. Hypotheses are as follow:

1. MAIN EFFECT: It is expected that the presence of the APOE4 allele will be associated with worse overall working memory performance and a steeper rate of decline in working memory over time.
2. MAIN EFFECT: Meanwhile, it is expected that participants that partake in a higher physical activity level will have better overall working memory performance and less decline in working memory than participants that only perform low or no activity.
3. MODERATION: Activity*APOE4=WM. It is hypothesized that the level of physical activity will moderate the relationship between APOE4 status and working memory performance. Specifically, it is expected that vigorous activity will mitigate ill-effects of APOE4 at baseline and will reduce the rate of decline over time for APOE4 carriers relative to non-carriers.

METHODOLOGY

Participants

This retrospective longitudinal study used secondary data from the Health and Retirement Study (HRS), a prospective cohort study on health, retirement, and aging in older adults living in the United States. The study was conducted by the University of Michigan with support from the National Institute of Aging (Juster & Suzman, 1995). The data collection process occurred in waves at 2-year intervals, starting in 1992. New cohorts were added approximately every 6 years. The method of data collection included in-person and telephone interviews, surveys, and links to personal records after obtaining consent. HRS data has been cleaned by the RAND Center for the Study of Aging and made available to the public. The Aging, Demographics, and Memory Study was done in partnership with a research team led by Brenda L. Plassman, Ph.D., director of the Epidemiology of Dementia Program at the Duke University Medical Center. The ADAMS file was used to obtain genetic information about APOE status of the participants, and their respective working memory performance measured by the digit span task. Participants performed the task in 2002, 2004, 2006, and 2008; The scores from 2002 and 2006 were used as a comparison for working memory decline. Further information on HRS survey design and data collection methods can be found in previously published reports (Fisher & Ryan, 2018). This study included 284 healthy, older adult participants (M = 77.6 years) from the HRS Wave 6 (2002) and Wave 8 (2006). The sample was almost fairly evenly distributed by gender (M = 51.8% female). The exclusion criteria consisted of participants that were under 65 years old and/or were reported to have dementia.

Measures

Demographics

The demographics that used in this study provided by the RAND HRS Longitudinal File were gender (male, female), age (birth year), years of education, race (White/Caucasian, Black/African-American, Other), ethnicity (Not Hispanic, Hispanic), and household assets. These were self-reported by respondents. Tremendous skew in household assets were accommodated by recoding the variable into quintiles.

APOE Status

Genetic information was consensually collected from participants in the HRS data set during the years of 2002-2008. This data was located in the ADAMS File under Section D. The genotyping was performed by the NIH Center for Inherited Disease Research using the Illumina HumanOmni2.5-8v1 array. Genotyping Quality Control was performed by the Genetics Coordinating Center at the University of Washington, Seattle, WA (Health and Retirement Study, 2019). Among the information collected was the presence of the APOE allele type. This information will be used to dichotomize groups in this study on the basis of APOE4 status. Therefore, the tested group consisted of solely participants with at least one APOE4 allele while to comparison group consisted of participants with either APOE3 or APOE2 alleles (non-APOE4).

Physical Activity

The level of physical activity was recorded in the RAND HRS Longitudinal File based on the response received during an interview. The respondent was asked one question: "On average over the last 12 months have you participated in vigorous physical activity or exercise three times a week or more? By vigorous physical activity, we mean things like sports, heavy housework, or a job that involves physical labor". Categorization of participants in the activity levels was assigned by the principle investigators of this study. Respondents that answered "Yes" were placed in the Vigorous Activity category, while those who responded with "No" were put in the Little/No Activity category.

Working Memory Task

Working memory was measured using the Digits Span Total task, a measure that included separate tasks of both forward and backward repetition of a series of numbers. The HRS Imputation of Cognitive Functioning Measures file explains the task involved having an examiner read a series of number sequences to the participant. For the Forward Digit Span Task, the participant had to repeat the series of numbers in the same order. During the Backward Digit Span Task, the participant repeated the series of numbers in the reverse order, as heard and remembered. The score for both tasks were then combined to create the Digit Span Total Score (a score out of 28 possible points).

Research Design

This was a retrospective quasi-experimental design. The study procedure consisted of a two-way repeated measures analysis of variance (R-ANOVA). The assumption of normality was tested visually using a histogram while homogeneity of variance was performed using Levene's test. T-tests and chi-square test of independence were used to compare baseline in demographic characteristics of active and non-active participants. Household assets were divided into quintiles. Age and years of education were included in the ANOVA as control variables. The physical activity variable was dichotomized: little/no activity and vigorous activity. The R-ANOVA included main effects for APOE status and physical activity level on working memory over two waves (2002, 2006), creating a time span of 4 years between the recorded digit span task scores. The hypothesis that physical activity level moderates the relationship between APOE4 status and working memory decline was examined using Activity*APOE4=WM. The analysis was additionally controlled for socioeconomic status, race, and ethnicity. The study was approved by the Institutional Review Board.

RESULTS

Demographic characteristics and univariate contrasts of active and inactive participants are shown in Table 1. The baseline analysis included 284 dementia-free participants (M = 77.6 years; 51.8% female). The sample was predominantly White (87.4%), with an average of 11.3 years of education. By contrast to the active group, the inactive groups was disproportionately female (X^2 = 5.3, p = .021), less wealthy (X^2 = 15.6, p = .004), have less education (t = -4.2, p = .042), less likely to be White (X^2 = 7.4, p = .025) and more likely to endorse Hispanic ethnicity (X^2 = 5.0, p = .025).

TABLE 1

Characterization of the Sample

	Mean (SD) or %	Active (n= 119)	Inactive (n=165)	Comparison t or (X2)
Age	77.6 (5.5)	76.7 (5.0)	78.2 (5.7)	2.2
Education	11.3 (4.0)	12.4 (3.5)	10.5 (4.1)	-4.2*
Total Assets				(15.6)**
0-5,000.01	11.6%	5.9%	16.4%	
5,000.01-55,590	15.1%	11.0%	18.9%	
55,590.01-144,170	20.1%	18.6%	22.0%	
144,170.01-356,120	20.4%	27%	16.4%	
356,120.01+	30.3%	37.3%	26.4%	
Digit Span Total Score A	13.9 (3.7)	14.9 (3.8)	13.2 (3.8)	-3.6
Digit Span Total Score C	12.67 (3.9)	14.7 (3.6)	12.8 (4.2)	-3.3
% Female	51.8%	43.7%	57.6%	(5.3)*
Race				(7.4)*
White	81.0%	87.4%	76.4%	
Black	16.2%	9.2%	21.2%	
Other	2.8%	3.4%	2.4%	
% Hispanic	6.3%	3.5%	9.1%	(5.0)*
% ApoE-4 Positive	25.0%	22.7%	26.7%	-0.6

*p<.05
**p<.01
***p<.001

A repeated-measures ANOVA was completed to examine primary hypotheses. The assumption of equality of variances was met ($F(9, 78272.23) = 1.31$, $p = .23$). Results from the repeated measures ANOVA, which included terms for age at baseline, physical activity level, education, APOE status, and time, indicated no within-subject's effects were found to be statistically significant. By contrast, between-subject's significant main effects on the digit span task were found for physical activity ($F(1,278) = 5.79$, $p = .02$, $\eta^2 = .02$) and years of education ($F(1,278) = 169.26$, $p < .001 = \eta^2 = .38$), but not for APOE4 status ($F(1, 278) = 1.41$, $p = .24$, $\eta^2 = .005$).

Notably, the interaction between APOE4 status and physical activity level was statistically significant ($F(1,278) = 4.07$, $p = .045$, $\eta^2 = .01$). Between-subject's effects indicated a significant main effect whereby those who participated in vigorous activity ($M = 14.9$, $SD = 3.8$) have higher digit span scores than do those who participated in little/no activity ($M = 13.2$, $SD = 3.8$) ($F(1,278) = 4.07$, $p = .045$, $\eta^2 = .01$). These statistical results can be found in Table 2 and indicate that both hypothesis 2 and 3, but not hypothesis 1, were supported.

TABLE 2

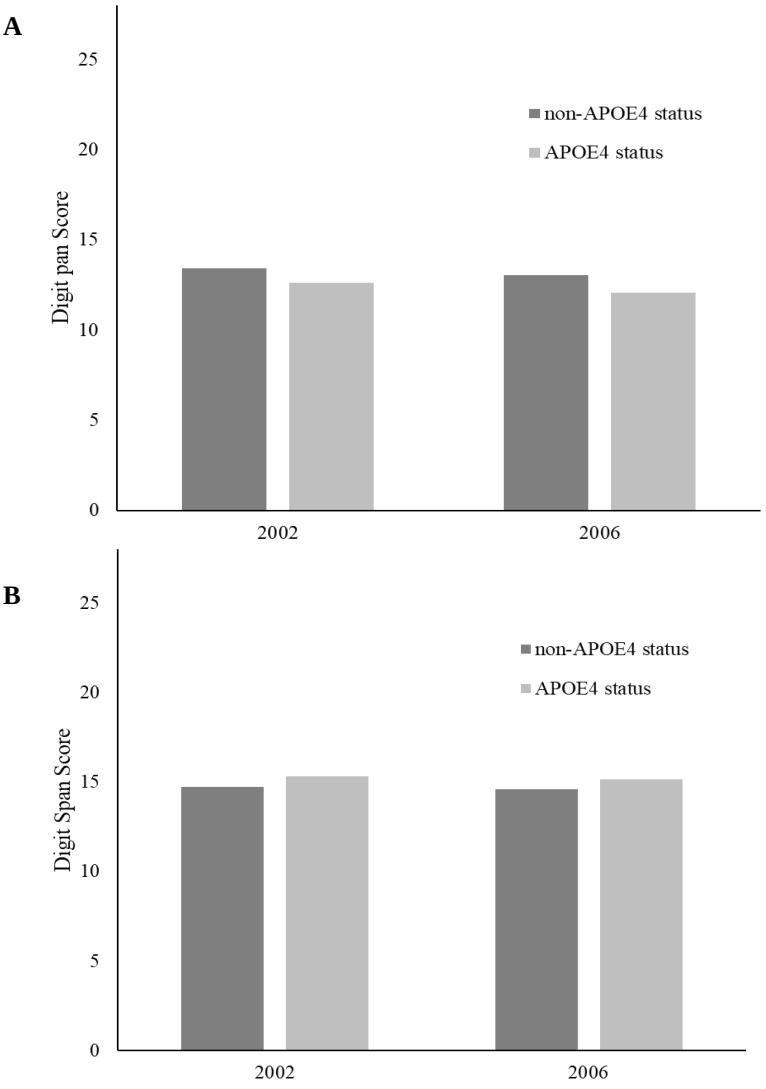
Summary of ANOVA Main Effects on Digit Span Score

Variables	*F*	*p*	η^2
Physical Activity	5.79	0.017*	0.02
APOE4	1.41	0.236	0.005
Education	169.26	< .001*	0.378
Age	3.72	0.055	0.013
Activity*APOE4	4.07	0.045*	0.014

*p<.05

FIGURE 1

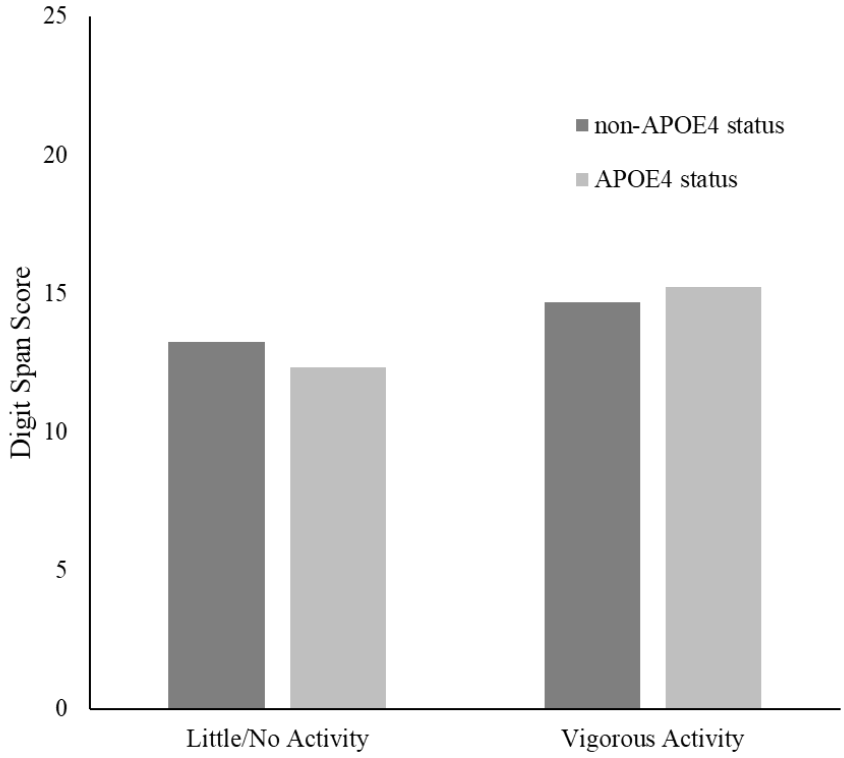
Marginalized Means of Digit Span Scores Between Activity Levels



Note. Panel A: Little/No Activity Level Effect on WM Performance Among Non-APOE4 and APOE4 carriers. Panel B: Vigorous Activity Level Effect on WM Performance Among Non-APOE4 and APOE4 carriers. These graphs demonstrate the digit span scores of participants performing little to no activity significantly decreases from 2002 to 2006 for both APOE4 carriers and non-carriers, while the scores for vigorously active participants are overall higher. The graph indicates that Vigorous Activity*APOE4 status benefit more from physical activity than non-carriers.

FIGURE 2

Moderation of Activity Level on APOE Status and WM Performance



Note. This graph demonstrates the moderation effect of physical activity on the relationship between APOE4 status and the digit span score. APOE4 carriers in the little/no activity group have the overall lowest digits span score while APOE4 carriers in the vigorous activity group have the highest digit span score, thus indicating a significant effect of APOE4 and physical activity on WM performance.

Follow-up analyses were that, among participants, activity level was significantly associated with digit span score for non-APOE4 carriers at both waves A (t = 2.44, p = .02, D = .34) and C (t = 2.92, p = .004, D =.40) and for APOE4 carriers at waves A (t = 3.09, p = .003, D = .76) and C (t = 3.10, p = .003, D = .76).

DISCUSSION

This study was an attempt to explore the hypothesis that physical activity is a moderator between APOE4 status and working memory performance. The primary findings indicate that vigorous activity significantly benefits working memory in APOE4 carriers. Specifically, APOE4 carriers who are vigorously active have a significantly higher Digit Span Score than do APOE4 carriers who perform little to no activity. Significant effects on working memory were also found for physical activity and years of education. The significant findings of vigorous activity moderating the relationship between working memory performance and APOE4 status is consistent with previous research (Deeny et al., 2008; Pizzie et al., 2014). Past literature shares our findings of a significant effect between exercise and working memory (Chang, Huang, Chen, & Hung, 2013), as for a significant effect of education on working memory performance (Chen et al., 2019). Unlike past research, a significant effect of APOE4 status on working memory was not found. It may be that this study was underpowered to identify a mean effect of APOE4 status, or a result of varying assessment strategies.

The results from this research study can be used to inform efforts on individualized health care. While it is recommended that everyone participate in routine exercise, APOE4 carriers appear to disproportionately benefit from physical activity. Therefore, exercise or physical activity could be included in an intervention plan to benefit working memory performance in APOE4 carriers. The significant findings from this study provide a more robust understanding of the interaction of physical activity on working memory in APOE4 carriers to the limited research presently available. Additionally, these findings suggest important directions for future research. In particular, future research may examine the degree to which physical activity and APOE4

status influence other cognitive subdomains, such as visuospatial memory and different functions of central executive working memory—processing speed, inhibition, and set shifting—through the inclusion of more neuropsychological measurements.

It is important to note the limitations of this study. The sample size study limited the ability to observe effects of physical activity on cognition between genders. Future research may seek to replicate these findings using more advanced longitudinal modeling techniques that preserve all baselined participants, thus enabling analysis of how gender influences these effects. Previous studies show that females with the APOE4 allele are at greater risk for cognitive decline and age-related dementias than their male counterparts (Beydoun et al., 2012; Pontifex, Vauzour, & Minihane, 2018), while other studies suggest exercise is more beneficial for women than for men (Barha et al., 2017). Based on these findings, in combination with the results of this current study, a future research project can explore the hypothesis that female APOE4 carriers who are vigorously active are expected to show significantly less cognitive decline than males APOE4 carriers who perform vigorous activity. Moreover, the sample size was relatively small in comparison to studies that found significant effects of APOE4 status on working memory. This study found a small, but non-significant effect of APOE4 status on between-subject's differences in working memory performance in APOE4 carriers. It may be that future research with a larger sample may better characterize this effect. These findings also suggest that APOE4 related differences emerge, particularly for inactive older adults, at some point possibly prior to age 65. Thus, the truncated range of ages used in this study may be a limitation. As suggested in previous studies, cognitive decline is most apparent between the ages of 65 to 75 years old and slows afterwards. Studies that explored the moderation of activity on APOE4 status and working

memory used participants that were between 50-75 years old and had a mean age that was closer to 62-65 years old (Deeny et al., 2008; Pizzie et al., 2014). The mean age of the participants in this study was 77.6 years which may have been too late to observe an effect on working memory performance. The 4-year time span used was limited in showing when the divergence between groups in digit span scores occurred. A longer epoch may be necessary to detect significant within-subjects changes related to APOE4 status. Finally, this study used the Digit Span Total task to measure working memory, which is an accumulated score of the Digit Span Forward and Digit Span Backwards tasks; however, the Digit Span Forward task does not specifically measure working memory and may have been a limitation in observing a significant effect between APOE4 status and working memory. Therefore, it may be that other measures, or additional measures, of working memory may be better suited to detection of these small effects over time.

CONCLUSION

In sum, these results suggest that vigorous activity mitigates poor working memory performance in APOE4 carriers; a risk variable conventionally regarded as non-modifiable. A higher level of physical activity as well as more years of education benefit working memory in older adults. These components can be implemented in a multi-practice plan for people at a greater risk for faster cognitive decline in later life associated with APOE4. Overall, in combination with other work, these findings may help to provide insight on the efficacy of an intervention method to aid in postponing cognitive decline in APOE4 carriers with the hope to preserve quality of life for this population at risk.

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