The Physical Activity and Alzheimer's disease (PAAD) study: Cognitive outcomes

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Abstract:

Background: Alzheimer's disease is a progressive disease that degrades cognitive functioning and ultimately results in death. Currently, there is no cure for Alzheimer's disease and, hence, the identification of preventative strategies is important. Physical activity (PA) is a behavioral intervention that holds promise with respect to delaying the onset of Alzheimer's disease. **Purpose:** The purpose of this study was to explore the differential cognitive benefits achieved in response to PA as a function of a person's genetic risk for AD. **Methods:** Older cognitively normal adults (50–65 years) with a family history of AD (FHxAD) participated in an 8-month PA program. Cognitive performance was measured at baseline, pretest, midtest, and posttest and changes over time were assessed as a function of apolipoprotein E (*APOE*) status (carriers: 1–2 copies of the ε4 allele; noncarriers: 0 copies of the ε4 allele). **Results:** Improvements in memory were associated with PA participation irrespective of *APOE* ε4 carrier status. **Conclusions:** Future experimental studies are needed to confirm that PA causes improvements to cognitive performance in older cognitively normal adults with a FHxAD and that these improvements are equivalent for cognitively normal *APOE* ε4 carriers and noncarriers.

Keywords: Exercise | *APOE* | Genetic risk | Executive function | Memory | Information processing

Article:

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that afflicts approximately 5.4 million Americans [1] with expectations that its prevalence will triple from 2010 to 2050. Currently, there is no cure for AD, thus researchers are exploring preventive strategies that could

delay its onset [2]. One preventive strategy that is receiving attention is physical activity (PA). The cognitive reserve hypothesis provides a rationale for why PA might positively influence cognition, slow age-related cognitive decline, and delay the onset of AD [3]. This hypothesis suggests that cognitive reserves may be passive (related to brain structure) or active (related to brain function) and that reserves are decreased with advancing age or brain pathology. However, the hypothesis also postulates that cognitive reserves can be increased through lifestyle behaviors including formal education, mental stimulation through one's occupation, and PA [4]. Considered together, these two propositions suggest that persons who have increased their cognitive reserves will have a lesser risk of dementia [4–6]. In support of the cognitive reserve hypothesis, there is evidence that PA benefits cognitive performance and reduces the risk of AD and dementia.

When reviewed meta-analytically, prospective evidence shows that PA is predictive of less cognitive decline [7] and a reduced risk of AD and dementia [8, 9] with advancing age. There is also experimental evidence showing that PA results in improvements in cognitive performance by older cognitively normal adults [10]. One important question to consider, however, is the extent to which PA can be protective for individuals who have an increased risk for AD. Individuals who have a family history of AD (FHxAD) are at increased risk of cognitive decline and AD [11–13]. In addition, apolipoprotein E (*APOE*) is a susceptibility gene for AD [14–19]. There is a dose-response relationship between the *APOE* epsilon 4 (ε4) allele and the risk of AD, with one copy of the ε4 allele resulting in 3–4 times [20, 21] and 2 copies of the ε4 allele resulting in 5–18 times [22] greater risk as compared to persons without the ε4 allele (noncarriers). Hence, it is important to understand the extent to which PA is protective against AD in persons with a FHxAD and as a function of *APOE* genotype.

Evidence from cross-sectional [23, 24] and prospective studies [25–32] shows that the relationship between PA or aerobic fitness and cognitive performance is moderated by *APOE* genotype. In particular, results from cross-sectional studies and from six of the eight prospective studies [25, 27–29, 31, 32] indicate that the benefits of PA for cognitive performance are largest for those at greatest genetic risk for AD. However, to our knowledge, there are no human studies that have experimentally tested *APOE* genotype as a moderator of the effect of PA on cognitive performance. Hence, the goal of this study was to conduct a PA intervention with older adults with a FHxAD to assess the extent to which these individuals could benefit from PA and to compare the cognitive benefits observed as a function of *APOE* ε4 carrier status.

Methods

Detailed methods and a consort flow diagram for the Physical Activity and Alzheimer's Disease (PAAD) study have been previously published [33]. Hence, the study methods are briefly described herein.

Participants

Older (50–65 years) cognitively normal adults with a FHxAD were recruited in three cohorts to participate in an 8-month PA program. Recruitment took place via newsletters, radio advertisements, presentations, news columns, and flyer distribution targeted toward older adults.

Recruitment efforts resulted in 136 individuals completing a telephone interview to initially determine eligibility relative to inclusion criteria and exclusion criteria. To be included in the study, participants had to be between 50 and 65 years of age, speak English, and fail to meet PA recommendations (i.e., perform fewer than 150 min of moderate intensity PA per week over the previous 3 months) based upon the Guidelines of the American College of Sports Medicine [34]. During this interview, eligibility was also determined relative to exclusion criteria for cognitive performance (see Cognitive Tests) and major contraindications to exercise. Of the 136 individuals who completed the telephone interview, 20 decided not to participate after learning more about the required commitment and 50 were determined to be ineligible. Thus, 66 participants completed baseline testing. Additional exclusion criteria were assessed at baseline testing as follows: participants were excluded from the study if they had any additional contraindications to PA based upon ACSM guidelines and risk categorizations (high risk were excluded, moderate risk were included with signed permission from their physician), had any chronic illness (e.g., mild-cognitive impairment, depression) or medication use (e.g., medication for memory problems) that would be expected to influence cognitive performance, or had uncorrected vision or hearing that would preclude participation in cognitive testing. After baseline testing, nine individuals decided they did not want to participate and three were excluded for health reasons. Thus, 54 participants were ultimately enrolled in the PA program.

Cognitive Tests

The modified Telephone Interview for Cognitive Status (TICS-m) [35] and the Folstein Mini-Mental Status Exam (MMSE) [36] were used to screen out participants with cognitive impairment (mild-cognitive impairment, AD, or other forms of dementia). Participants were included in the study if TICS-m scores were ≥36 [35] and MMSE scores were ≥27 (including a score between one and three on the recall subtest) [36].

Cognitive performance relative to the PA intervention was assessed across cognitive domains including attention (Paced Auditory Serial Addition Test [PASAT]), memory (Rey Auditory Verbal Learning Test [AVLT], Rey-Osterrieth Complex Figure Test [CFT], Digit Span), information processing (Wechsler Adult Intelligence Scale III Digit Symbol Substitution Task [WAIS-DS], Trail-Making Test A [TMT A], Stroop Color Test, Stroop Word Test), and executive function (EF; Trail-Making Test B [TMT B], Stroop Color-Word Test, set-switching [TMT B – TMT A], interference [Color-Word – average of Color and Word], Tower of London [TOL]). These measures have well established psychometrics, were selected because they have been used to assess cognitive performance in cognitively normal older adults in studies focused on AD [37, 38], and are expected to be sensitive to the early stages of dementia [39] and/or the effects of PA [10]. Specific measures for each test included in the statistical analyses are shown in Fig. 1.

PA Intervention

Participants were asked to come to the University campus to participate in the PA program at least 3 days per week for 8 months. All exercise sessions were led by an American College of Sports Medicine certified exercise physiologist who was assisted by graduate students in Kinesiology. Each session consisted of aerobic exercise (walking around the perimeter of the

gymnasium for 15–20 min) and strength training for 30–40 min (time increased over the course of the 8 months). Participants were encouraged to walk at a speed that kept their heart rate at 60% of estimated maximal heart rate reserve (recalculated at 8-week intervals) and heart rate was recorded after 10 min of walking at every session. The strength training portion consisted of exercises completed with TheraBand resistance bands. The resistance level of the band, the number of exercises, the number of repetitions, and the number of sets gradually and individually increased over the 8-month period in response to strength gains. Exercise sessions were offered on 3 days of the week at three different times of day and the number of participants who were present at a given session ranged from 1 to 22 with six being the most common number of participants present at a session. Relative to prescribed sessions, the average attendance rate for participants who completed all of the cognitive testing sessions was 76% (see [40] for additional details regarding adherence). There were not significant differences in adherence as a function of *APOE* carrier status, $p > .05$.

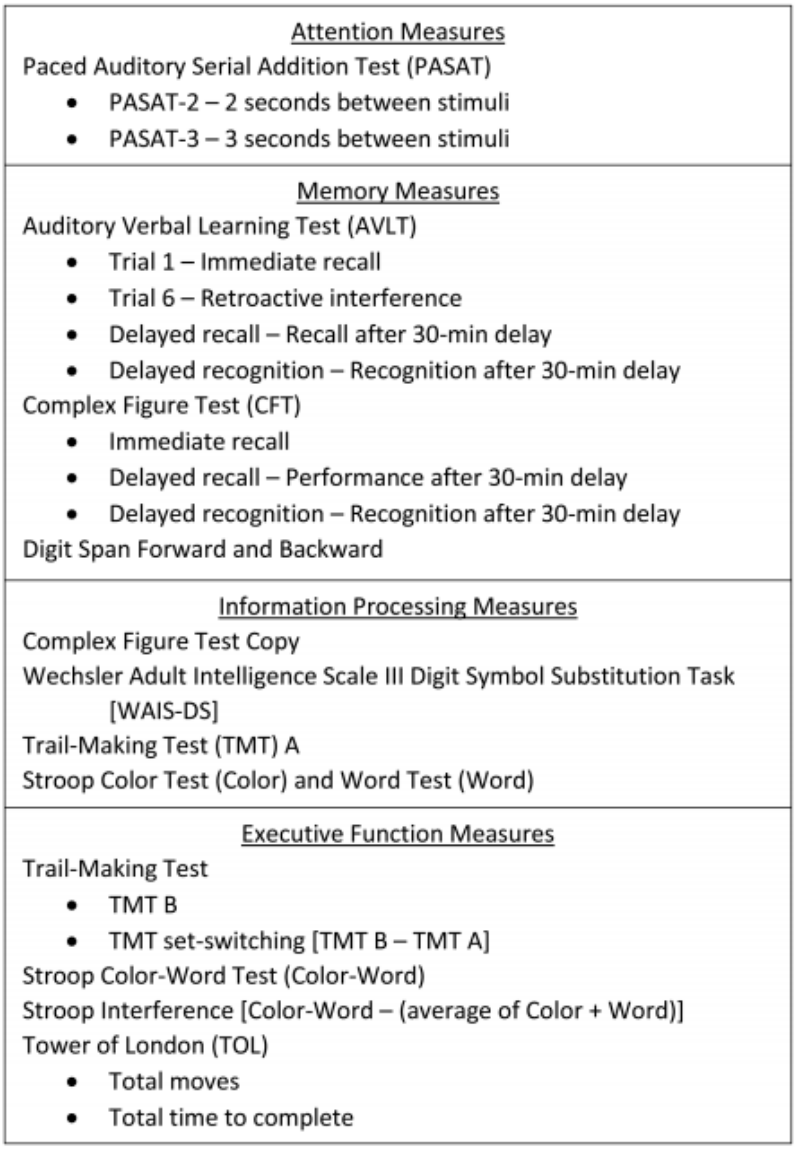

Fig. 1. Cognitive domains assessed in the study and the specific cognitive tests that were used.

Genotyping

Genomic DNA was extracted from buccal cell preparations at the University of North Carolina at Greensboro Molecular Core Laboratory for single nucleotide polymorphism (SNP) testing. The SNPs associated with the two amino acid residues (codons 112 and 158) were used to identify participants as *APOE* ε4 carriers (one or two copies of ε4) or *APOE* ε4 noncarriers (0 copies of ε4). Experimenters were blinded to the participants' genotype for all exercise and testing sessions.

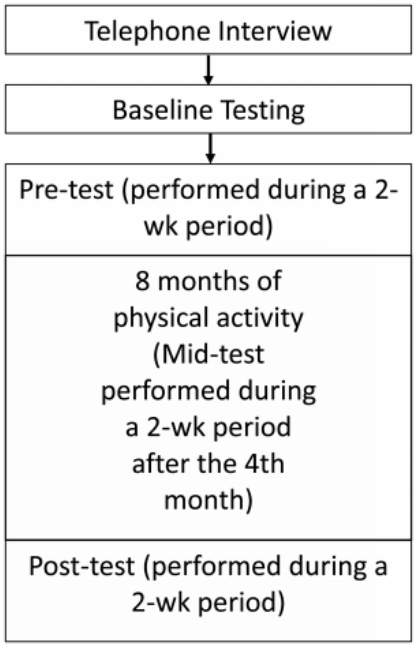

Fig. 2. Depiction of the study procedures.

Procedure

See Fig. 2 for an overview of the procedures. Screening for eligibility for the study took place in two parts. First, interested participants were interviewed over the telephone. This interview was used to more fully describe the study and to assess initial inclusion (50–65 years of age, FHxAD, not regularly physically active) and exclusion (contraindications to exercise, TICS-m score) criteria. Eligible participants were invited to baseline testing during which they were asked to sign a consent form approved by the University's Institutional Review Board. At this time, depression (using the Geriatric Depression Scale), a medical health history, the American Heart Association/ACSM Health/Fitness Facility Preparticipation Screening Questionnaire, and the MMSE were completed to further assess eligibility, and baseline cognitive measures were taken. Cognitive measures were obtained at baseline to allow for a dual-baseline method whereby the most pronounced practice effects were expected to occur between baseline and pretest allowing for less substantial practice effects from pretest to midtest to posttest. Those participants who remained eligible and interested in participating after baseline screening were then assigned in three cohorts to begin the 8-month PA intervention. Because participants began the PA intervention in cohorts, variable amounts of time passed between baseline testing and the pretest,

but for each cohort, each test (pre-, mid-, and post-) was performed within a 2-week period. Cognitive testing took place in a quiet laboratory space on the University campus and was conducted at the pretest (prior to beginning the intervention), midtest (following the 4th month of the intervention), and posttest (following the 8-month intervention). In addition, at pretest, midtest, and posttest, distance covered during a 6-min walk was assessed to provide an estimate of aerobic fitness [41].

Statistical Analysis

Descriptive information for the sample is presented in Table 1, and descriptive data for performance on the cognitive outcomes at each time point is presented in Table 2. Change in fitness across time was assessed using a repeated measures analysis of variance (ANOVA) with a Huynh-Feldt adjustment made in the case of violation of the sphericity assumption. Linear trajectories of change in cognitive performance across time were estimated using latent growth curve modeling (LGCM) [42]. Given the exploratory nature of this study, separate models were estimated for each cognitive outcome. This resulted in a total of 22 estimated models, grouped into four cognitive domains: Attention, Memory, Information Processing, and Executive Function. Time metrics were set at 0, 4, and 8 to model measures taken at pretest, midtest (4 months), and posttest (8 months) relative to the PA intervention. Cognitive performance at baseline and *APOE* ε4 carrier status (0 = noncarrier, 1 = carrier) were entered into the models as predictors of intercept and slope, respectively (see Fig. 3). Baseline cognitive performance was included as a predictor rather than as the first outcome time point to guard against the inflation of the slope coefficient due to practice or maturation effects [43], and because participants did not take part in the intervention during the time between baseline and pretest measures. Basic demographic variables (i.e., age, sex, and BMI) were also included as predictors of intercept and slope factors in initial models. However, they were only very sparsely associated with either growth factor, did not substantively alter associations between baseline performance and intercepts or between carrier status and slopes, and their inclusion did not improve model fit. Therefore, these covariates were excluded from the final models. Race and education variables were also excluded due to homogeneity of the sample (87% White, 88.9% higher education). Decisions involving inclusion or exclusion of covariates were held constant across all cognitive outcomes (n = 22) in order to facilitate interpretation of results. Had any of the basic demographics been associated with either of the latent growth factors for even a moderate portion of outcomes, they would have been retained in all models. The only decisions that were made on a model-by-model basis involved instances in which it had to be determined whether particular model parameters should be fixed or remain freely estimated. The most common example was a model that yielded a small, negative, nonsignificant residual variance estimate for the slope factor (i.e., nonpositive definite latent variable covariance matrix). In this case, the residual variance for slope was fixed to zero and the model re-estimated. These restrictions were only imposed when doing so substantively improved reliability of the parameter estimates and model fit.

Table 1. Descriptive data for study participants (n = 54)

	M	***SD***	**Range**
Age (years)	56.98	4.61	50–65
BMI	28.13	4.12	20.3–35.6
MMSE	29.00	3.97	27–30

	M	*SD*	Range
	n	%	
Gender			
Female	43	79.6	
Male	11	20.4	
Race			
White	47	87.0	
Black	6	11.1	
Hispanic	0	0.0	
Native American	0	0.0	
Asian	0	0.0	
Other/unknown	1	1.9	
Education			
Up to high school	6	11.1	
Up to Bachelor's or Associate's degree.	28	51.9	
Up to Graduate degree	20	37.0	
Genotype			
Carrier	23	43%	
Noncarrier	31	57%	

BMI body mass index; *M* mean; *MMSE* Mini-Mental State Examination; *SD* standard deviation.

Table 2. Means and standard deviations for cognitive outcomes organized at each time point by cognitive domain

Cognitive Domain (Test)	Baseline	Pretest	Midtest	Posttest
Attention				
PASAT3	44.56 (11.30)	48.28 (11.26)	50.33 (9.52)	51.04 (9.38)
PASAT2	34.00 (9.50)	37.80 (10.76)	38.35 (10.16)	42.29 (9.61)
Memory				
AVLT T1	5.87 (1.85)	7.61 (2.02)	8.72 (2.20)	9.73 (2.27)
AVLT T6	9.94 (2.84)	11.04 (2.60)	11.54 (3.06)	12.38 (2.24)
AVLT delayed recall	9.41 (2.87)	11.20 (2.81)	11.63 (2.82)	12.31 (2.35)
AVLT recognition	13.57 (1.43)	13.91 (1.66)	14.19 (1.48)	14.42 (2.24)
CFT recognition	20.45 (1.79)	20.94 (1.93)	21.64 (1.46)	21.48 (1.91)
Recall	18.62 (6.61)	23.35 (6.64)	23.93 (5.47)	26.21 (6.87)
CFT delayed recall	18.36 (7.03)	22.82 (5.55)	23.69 (5.33)	25.93 (6.18)
DS forward	6.02 (1.22)	6.52 (1.23)	6.42 (1.51)	6.42 (1.18)
DS backward	4.72 (1.21)	4.80 (1.04)	4.98 (1.25)	5.20 (1.15)
Information processing				
CFT copy	33.94 (2.66)	34.03 (2.62)	34.10 (1.90)	34.12 (1.82)
WAIS-DS	51.59 (7.72)	53.67 (7.90)	54.44 (8.22)	54.53 (8.21)
TMT A	34.53 (7.61)	33.83 (8.21)	33.33 (10.68)	31.57 (7.12)
Stroop Color	65.85 (12.47)	64.45 (11.75)	65.01 (21.84)	63.79 (10.92)
Stroop Word	46.22 (6.85)	48.27 (10.17)	47.12 (8.91)	45.98 (7.80)
Executive function				
TMT B	55.24 (15.25)	56.55 (16.96)	53.45 (21.89)	52.39 (13.78)
TMT exec function	44.52 (15.29)	46.89 (15.41)	43.64 (21.29)	43.51 (13.05)
Stroop Color-Word	118.39 (27.92)	110.92 (22.55)	114.66 (29.31)	107.74 (25.26)
Stroop Interference	62.35 (22.71)	54.56 (16.15)	58.59 (27.38)	52.86 (23.01)
TOL total moves	82.08 (17.28)	74.47 (12.42)	74.23 (19.58)	73.36 (13.76)
TOL total time	363.89 (147.85)	312.92 (113.12)	312.45 (127.46)	302.20 (96.61)

AVLT Auditory Verbal Learning Test; *CFT* Complex Figure Test; *DS* digit span; *PASAT* Paced Auditory Serial Addition Test; *TMT* Trail-Making Test; *TOL* Tower of London; *WAIS-DS* Wechsler Adult Intelligence Scale III Digit Symbol Substitution Task.

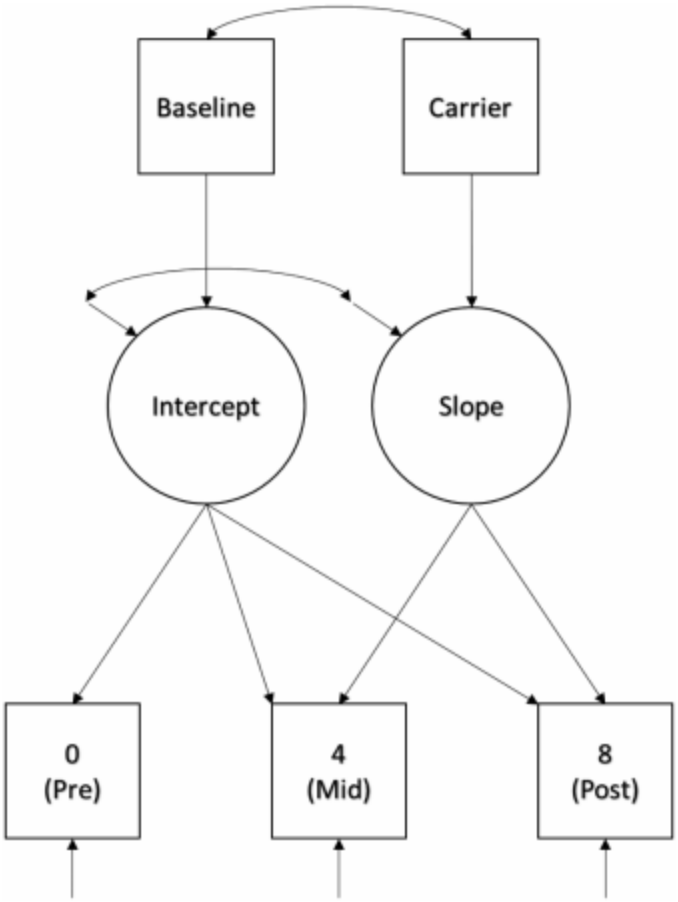

Fig. 3. Model representing the linear latent growth curve analyses.

There were two outcomes of primary interest in these models. One was the mean slope for each model, which was indicative of estimated monthly change in cognitive test performance. The other was the association of *APOE* ε4 carrier status with slope, which was indicative of whether test performance of *APOE* ε4 carriers changed at a rate different to noncarriers (i.e., moderation). Negative slopes and negative predictor associations were indicative of improvement for the TMT and the Stroop tasks, and for all measures of EF. For all other tasks, positive slopes and positive predictor associations with slope were indicative of improvement. Model fits were assessed by examining whether fit indices met commonly accepted criteria: chi-squared ($p \geq .05$), root mean square error of approximation (<.05), comparative fit index (CFI; > .95), and Tucker Lewis index (TLI; > .95) and are presented in Table 3. Sample size limitations ($n = 54$) prevented estimation of higher-order (domain-level) models. Bonferroni corrections for multiple comparisons were determined too conservative; however, a correction factor of 10 (i.e., $p < .005$) was applied to address concerns over Type I error inflation. Further, results were interpreted in terms of consistency within each domain, rather than simply focusing on individual cognitive outcomes for which statistical significance was achieved.

Table 3. Fit statistics for all latent growth models

Attention	X^2	*df*	*p*	RMSEA	CI_{90}	CFI	TLI
PASAT3	13.33	7	0.065	0.13	0.00–0.23	0.95	0.93
PASAT2	13.15	7	0.069	0.13	0.00–0.23	0.96	0.95

Attention	X^2	*df*	*p*	RMSEA	CI_{90}	CFI	TLI
Memory							
AVLT T1	4.59	5	0.469	0.00	0.00–0.18	1.00	1.00
AVLT T6	4.25	5	0.515	0.00	0.00–0.17	1.00	1.00
AVLT delayed recall	4.77	6	0.574	0.00	0.00–0.16	1.00	1.00
AVLT recognition	4.80	5	0.440	0.00	0.00–0.19	1.00	1.00
CFT delayed recognition	10.84	7	0.146	0.10	0.00–0.21	0.81	0.76
CFT immediate recall	14.59	7	0.042	0.14	0.03–0.25	0.94	0.93
CFT delayed recall	7.67	5	0.176	0.10	0.00–0.23	0.98	0.97
DS forward	7.13	5	0.211	0.09	0.00–0.22	0.94	0.90
DS backward	2.46	7	0.930	0.00	0.00–0.05	1.00	1.00
Information processing							
CFT copy	13.86	7	0.054	0.14	0.00–0.24	0.90	0.87
WAIS-DS	2.81	7	0.902	0.00	0.00–0.07	1.00	1.00
TMT A	5.96	7	0.544	0.00	0.00–0.15	1.00	1.00
Stroop Color	8.02	7	0.331	0.05	0.00–0.18	1.00	0.99
Stroop Word	4.92	5	0.426	0.00	0.00–0.19	1.00	1.00
Executive function							
TMT B	9.86	6	0.131	0.11	0.00–0.23	0.96	0.94
TMT set-switching	10.40	6	0.109	0.12	0.00–0.24	0.94	0.91
Stroop Color-Word	8.48	7	0.292	0.06	0.00–0.19	0.99	0.98
Stroop Interference	6.57	5	0.255	0.08	0.00–0.22	0.97	0.95
TOL total moves	11.91	6	0.064	0.14	0.00–0.25	0.93	0.89
TOL total time	11.57	6	0.072	0.13	0.00–0.25	0.95	0.92

AVLT Auditory Verbal Learning Test; *CFI* comparative fit index; *CFT* Complex Figure Test; *DS* digit span; *PASAT* Paced Auditory Serial Addition Test; *RMSEA* root mean square error of approximation; *TLI* Tucker Lewis index; *TMT* Trail-Making Test; *TOL* Tower of London; *WAIS-DS* Wechsler Adult Intelligence Scale III Digit Symbol Substitution Task.

Results

Results of the repeated measures ANOVA indicated that there was a significant effect of time on fitness, $F(1.79, 71.63) = 5.02$, $p = 0.01$, with follow-up tests showing that fitness improved significantly from pretest (mean [*M*] = 556.79 ft, standard error [*SE*] = 10.26) to posttest (*M* = 594.85 ft, *SE* = 11.22). LGCM results are presented in Table 4 and are described below.

Table 4. Results from linear growth curve models for each cognitive outcome organized by cognitive domain

	Intercept	*p*	Base (*β*)	*p*	Slope	*p*	Carrier	*p*
Attention								
PASAT3	18.171	0.000	0.676	0.000	0.256	0.239	-0.026	0.912
PASAT2	8.994	0.012	0.836	0.000	0.384	0.017	0.068	0.772
Memory								
AVLT Trial 1	4.029	0.000	0.608	0.000	0.287	0.000	-0.074	0.276
AVLT Trial 6	5.214	0.000	0.582	0.000	0.144	0.000	0.054	0.259
AVLT delayed recall	6.078	0.000	0.538	0.000	0.150	0.004	-0.016	0.795
AVLT delayed recognition	8.731	0.000	0.376	0.017	0.093	0.031	-0.036	0.478
CFT delayed recognition	15.142	0.000	0.293	0.001	0.024	0.597	0.094	0.140
CFT immediate recall	11.275	0.000	0.635	0.000	0.335	0.001	0.012	0.930
CFT delayed recall	12.379	0.000	0.567	0.000	0.389	0.000	-0.045	0.703
DS forward	4.350	0.000	0.357	0.007	-0.002	0.930	-0.042	0.341
DS backward	2.753	0.000	0.431	0.000	0.044	0.087	-0.002	0.951
Information processing								
CFT copy	20.894	0.000	0.385	0.000	0.057	0.165	-0.037	0.615

	Intercept	*p*	Base (*β*)	*p*	Slope	*p*	Carrier	*p*
WAIS-DS	6.943	0.022	0.907	0.000	0.141	0.114	-0.054	0.715
TMT A	8.786	0.019	0.725	0.000	-0.061	0.682	-0.322	0.118
Stroop Color	10.524	0.009	0.819	0.000	-0.007	0.949	-0.177	0.214
Stroop Word	-2.172	0.662	1.088	0.000	-0.218	0.009	-0.034	0.778
Executive function								
TMT B	18.747	0.020	0.680	0.000	-0.302	0.293	-0.050	0.902
TMT set-switching	21.038	0.000	0.576	0.000	-0.280	0.335	0.007	0.987
Stroop Color-Word	30.075	0.001	0.684	0.000	-0.343	0.245	0.819	0.330
Stroop interference	21.933	0.000	0.526	0.000	-0.253	0.508	0.839	0.271
TOL total moves	38.297	0.001	0.441	0.003	-0.050	0.878	-0.156	0.687
TOL total time	137.183	0.000	0.511	0.000	-0.906	0.835	-2.156	0.401

AVLT Auditory Verbal Learning Test; Base baseline; *CFT* Complex Figures Test; *DS* digit span; *n/a* indicates that the parameter was fixed to 0; *PASAT* Paced Auditory Serial Addition Test; *TMT* Trail-Making Test; *TOL* Tower of London.

Attention

Attention was assessed using two cognitive outcomes (PASAT2, PASAT3). Fit indices suggested poor-to-mediocre fit for both the PASAT2 and the PASAT3 models. Baseline performance was significantly positively predictive of the intercept for both measures of attention ($p < .005$) indicating that scores at baseline were associated with scores at pretest. Participants failed to demonstrate improvement across time on either the PASAT2 ($p = .017$) or the PASAT3 ($p = .24$) Carrier status was not significantly predictive of slope for either of the PASAT tasks (p's = .77-.91).

Memory

Memory was assessed using nine cognitive outcomes: AVLT (Trial 1 & Trial 6, delayed recall, delayed recognition), CFT (immediate recall, delayed recall, delayed recognition), and Digit Span (Forward, Backward). Fit indices suggested good-to-excellent fit for AVLT Trial 1 and Trial 6, AVLT and CFT-delayed recall, AVLT delayed recognition, and Digit Span Backward models, poor-to-mediocre fit for the Digit Span Forward model, and poor fit for the CFT-delayed recognition and immediate recall models. Baseline performance was a significant positive predictor of intercept in all memory models ($p < .001$) with the exception of AVLT delayed recognition ($p = .017$), and Digit Span Forward ($p = .007$). Participants demonstrated significant improvement (i.e., significant slope factors) for AVLT Trial 1, Trial 6, delayed recall ($p < .005$) and for CFT immediate and delayed recall ($p < .001$). Slope factors did not reach significance for the AVLT delayed recognition model ($p = .031$), the CFT-delayed recognition model ($p = .597$), or either the Digit Span Forward ($p = .930$) or Backward ($p = .087$) models. Carrier status was again not significantly associated with the slope factors in any of the memory outcome models.

Information Processing

Information processing was assessed using five cognitive outcomes: CFT copy, WAIS-DS, TMT A, Stroop Color, and Stroop Word. Fit indices suggested excellent fit for all models except CFT copy, for which fit was poor. Baseline performance was significantly, positively predictive of intercept for all information processing outcomes ($p < .001$). Participants failed to demonstrate significant improvement for any of the information processing outcomes. Carrier status was

again not significantly predictive of slope for any information processing outcomes (p = .12–.78).

Executive Function

EF was assessed using six cognitive outcomes: TMT B, TMT set-switching (TMT B-TMT A), Stroop Color-Word time, and Stroop
interference Stroop CW−Stroop C + Stroop W2Stroop CW−Stroop C + Stroop W2 scores, and TOL total moves and total time to complete. Fit indices suggested good-to-excellent fit for Stroop Color-Word and Stroop interference models, mediocre fit for the TMT B and TOL total moves models; and, poor fit for the TMT set-switching and TOL total time models. Baseline performance was significantly, positively predictive of intercept for all EF outcomes ($p < .005$). However, participants did not demonstrate significant change in performance (p = .24 – .99), and carrier status was not significantly predictive of slope for any EF outcomes (p = .27 – .99).

Discussion

The cognitive reserve hypothesis and evidence from past research support the expectation that participation in a PA program will benefit cognitive performance by older adults. There is also cross-sectional and prospective evidence suggesting that the effects of PA on cognitive performance are moderated by *APOE* ε4 carrier status. The purpose of this study was to assess the extent to which benefits that are associated with participation in an 8-month exercise program can be observed in persons with a FHxAD and to assess the extent to which these benefits differ as a function of one's genetic risk for Alzheimer's disease.

Results from this study partially support past research showing that PA by older adults improves cognitive performance [10]. In particular, in association with their participation in an 8-month PA program consisting of aerobic exercise and strength training, older cognitively normal adults improved on multiple measures of memory. It is important to point out that study participants all had a FHxAD, yet the sample achieved cognitive benefits from pretest to posttest that are similar to what has been observed in previous samples that do not have this familial risk of AD. This is an important finding because of the fact that a FHxAD is associated with a heightened risk of AD [11, 12] and there is no known cure for AD. Further, if PA helps to maintain cognitive performance over time in persons with an increased risk of AD due to their familial history, this could have important public health implications. This is because delaying the onset of AD by as little as 6 months can reduce the prevalence of AD by 100,000 people after 10 years [44].

Of additional importance is the fact that these improvements were generally not influenced by *APOE* ε4 carrier status. That is, these results suggest that cognitively normal older adults with a FHxAD can achieve cognitive benefits to memory that are associated with participation in a PA program and that these benefits are evident irrespective of whether or not they carry the *APOE* ε4 allele which also heightens their genetic risk for AD. Importantly, it must be emphasized that because of the lack of a control group, it is not possible to know for certain if these improvements over time are causally related to the PA program or if they reflect practice effects [45]. Although we used a dual-baseline method to minimize practice effects across the PA intervention, past research has shown that practice effects can occur with repeated trials on

cognitive measures like those used in this study. Hence, the lack of a control group and the potential for practice effects is a primary limitation of this study.

As previously mentioned, the primary limitation of this study is the lack of a control group. However, the decision was made *a priori* to focus resources on a case–control study specifically aimed at exploring the differential effects of an 8-month PA intervention on cognitive performance relative to *APOE* ε4 status. While this design precludes our ability to determine causality, findings will facilitate the design of future randomized control trials (RCTs). Interpreting these results relative to previous literature is challenging because this is the first study in which PA was manipulated so that associated changes in cognitive performance could be observed. The most relevant previous literature consists exclusively of nonexperimental prospective studies in which researchers typically compared active individuals to inactive individuals by assessing changes in global cognitive performance (e.g., MMSE) or clinical cognitive impairment over several years. Although most of these studies suggest that the benefits of PA are greater for carriers of the *APOE* ε4 allele than for noncarriers, we do not believe our results to be inconsistent with this past literature. It is our interpretation that amongst cognitively normal inactive adults aged 50–65 years and with a FHxAD, both those with and without a heightened genetic risk for AD can achieve similar behavioral cognitive benefits from exercise. Subsequent research will be needed to assess the extent to which these cognitive gains slow age-related declines in cognitive performance and lessen the risk for clinical cognitive impairment, both of which would be expected to be greater for the carriers than for the noncarriers [46], as they progress past the age range observed in the present study.

One surprising finding in this study that should be acknowledged was the failure to observe improvements in EF in response to PA. In a meta-analytic review of RCTs with adults aged 50 years and over, Colcombe and Kramer [10] reported the largest effects for measures of EF (g = 0.68). Thus, we expected to see improvements in EF associated with participation in PA. However, Smith et al. [47]. meta-analytically reviewed RCTs with adults and reported that the average effect size for measures of EF was substantially smaller (g = 0.12). They suggested that Colcombe and Kramer's report might have been inflated because of the inclusion of two studies with relatively large positive effects that were not actually RCTs. It is also possible that setting the upper age limit at 65 in the present study made detection of changes in EF and other cognitive domains more difficult. In the aforementioned meta-analysis, the reported effect sizes for studies with participants ranging in age from 50 to 65 years were significantly lower than those reported for studies with older participants [10]. This pattern is not surprising given the observation that the average age of onset for AD or age-related cognitive decline ranges from the late 60's to 70's depending upon *APOE* ε4 carrier status [17, 19].

In sum, this study provides initial evidence that participation in a PA program is associated with cognitive performance benefits to memory in older cognitively normal adults with a FHxAD and regardless of their *APOE* ε4 carrier status. This is consistent with past RCTs which have shown that PA results in improvements in cognitive performance as compared to control conditions [10, 47, 48], but also extends our understanding to an appreciation that these benefits can be obtained by persons with a FHxAD and that *APOE* ε4 carrier status does not moderate behavioral outcomes within this age range. Given that both persons with a FHxAD [11, 12] and *APOE* ε4 carriers are at a heightened risk for AD [14–19], this is important because

increased cognitive reserves (as might be achieved through PA) may be protective against clinical cognitive impairment [4]. Further, prospective evidence indicates that *APOE* ε4 carriers who are physically active have a reduced risk of cognitive decline, dementia, and AD [25, 27, 28, 49]. If previously sedentary, older individuals can improve cognitive function through PA, the typical progression of cognitive decline may be sufficiently delayed to dramatically reduce an individual's risk of AD and, at a population level, this could have an impact on world-wide prevalence [44]. Given that there is at this time no known cure for AD, further experimental research exploring the potential of PA as a preventive strategy is clearly warranted.

Conflict of interest. The authors declare that they have no conflict of interest.

Informed consent. Informed consent was obtained from all individuals included in the study.

Ethical Approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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