



Effects of an Exercise Intervention and APOE-ε4 on Executive Function in Midlife Adults at Risk for Alzheimer’s Disease: The PAAD-2 Trial



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Introduction

- Executive functions (EFs) such as working memory, planning, switching, categories generation, and inhibitory control decline with advancing age and are predictive of progression along the continuum of cognitive decline to dementia.¹
- Apolipoprotein E (APOE) is a genetic risk factor for Alzheimer’s disease (AD) with the epsilon 4 allele (ε4) increasing risk and the epsilon 2 (ε2) allele decreasing risk.²
- Meta-analyses support that physical activity (PA) interventions significantly improve EF performance in older adults (>55 yrs; Hedges’ g=0.21³; >60 yrs; Hedges’ g = 0.13-0.51⁴)
- Prospective studies show that PA is protective against AD (HR=0.72) even after controlling for APOE-ε4 and other confounders (adjusted HR=0.85)⁵
- Only a few interventions have tested the potential benefits of PA relative to APOE-ε4 carrier status and none have tested this question in middle-aged adults.
- The purpose of this study was to examine the moderating role of APOE-ε4 on the effects of a one-year exercise intervention on EF in midlife.

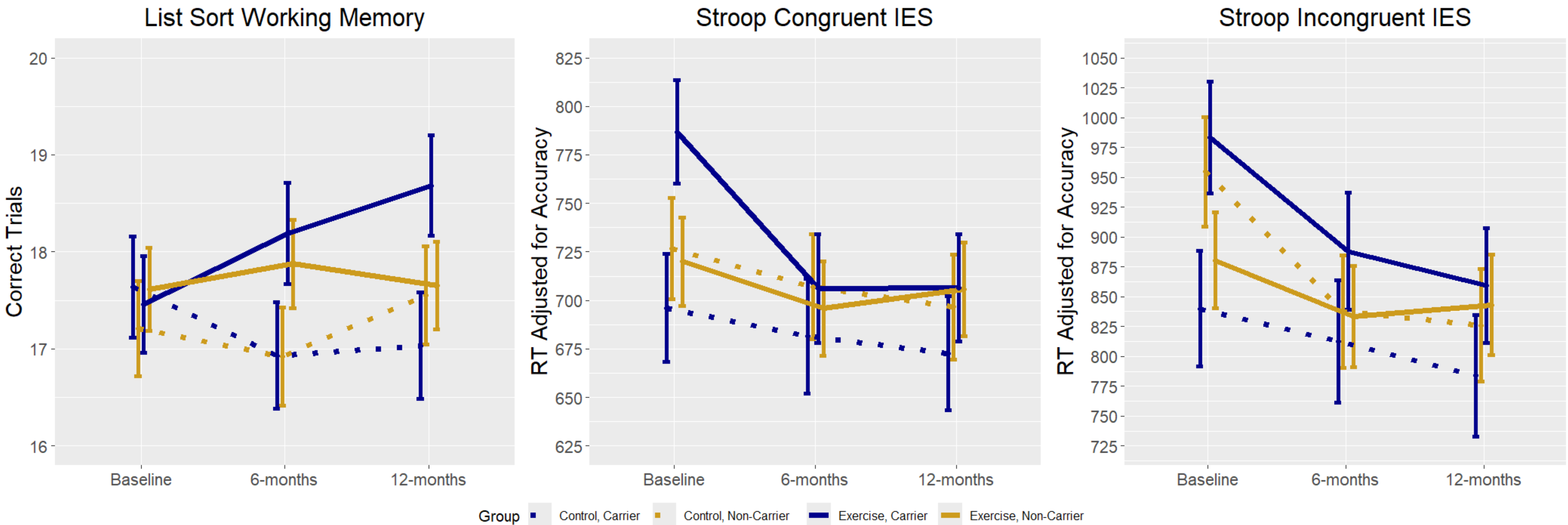
Methods

- Baseline, mid-test (~6-month), and post-test (~12-month) EF performance data from the PAAD-2 clinical trial (NIH-R01AG058919)^{6,8} were analyzed.
- Cognitively normal adults (N=180, Age=56.4±6.42 years) with a family history of AD (FH+) were randomized to an exercise group (group strength training and individual moderate-intensity walking 3x/week) or a usual care control (UCC) group (received educational materials every 2 weeks) for 12 months.
- APOE alleles were determined from saliva samples, and participants were categorized as carriers (ε3/ε4, ε4/ε4) or non-carriers (ε2/ε3, ε2/ε4, ε3/ε3).*
- Working memory was assessed with list sort working memory (LSWM, correct trials). Inhibitory control was assessed with the Stroop incongruent condition and processing speed was assessed with the Stroop congruent condition. Inverse efficiency scores (IES) were calculated to simultaneously consider speed and accuracy [IES = reaction time/(1-error rate), lower score=better].
- Multilevel linear mixed effects modeling was used to estimate the effects of group (referent=UCC), APOE-ε4 status (referent=non-carriers), time (referent=pre-test), and their interaction on EF at pre-, mid- and post-test controlling for first-degree relative FH+ and relevant demographic factors.

Results

	Full Sample	Exercise	UCC
Sample size	180	98	82
Age, years	56.41±6.42	56.35±6.65	56.48±6.16
Education, years	16.75±2.34	16.72±2.35	16.79±2.39
BMI (body mass index), kg/m ²	28.63±5.93	29.35±6.50	27.76±5.07
% Female	89%	90%	88%
% APOE-ε4 carriers	38%	39%	38%

- For LSWM, the three-way interaction of Group x APOE-ε4 x Time was not significant at mid-test (B=0.89, p>.22) but was significant at post-test (B=2.13, p<.01): exercise carriers improved from baseline (M=1.23, p<.01).
- For Stroop Congruent IES, the three-way interaction was not significant at mid-test (B= -61.71, p>.13) but approached significance at post-test (B= -72.35, p<.09). Although not significant overall, pairwise comparisons showed a significant improvement for exercise carriers from baseline to mid-test (M= -80.74, p<.001) and from baseline to post-test (M = -80.13, p<.001).
- For Stroop Incongruent IES, the three-way interaction was significant at mid-test (B= -138.41, p<.04) and post-test (B= -159.40, p<.02): control non-carriers improved from baseline to mid- (M= -117.19, p<.001) and post-test (M= -128.75, p<.001); exercise carriers improved from baseline to mid- (M= -95.4, p<.02) and post-test (M= -124.03, p<.001).
- *Results did not differ with e2/e4 exclusion (relevant because e2 may be protective, but responses may also be unique).



Discussion / Conclusion

- Benefits of exercise were observed across all EF outcomes for APOE-ε4 carriers, with effects reaching or approaching significance depending on the measure. Performance of participants in the control condition did not change significantly with the exception of improvements in Stroop Incongruent IES for the non-carriers.
- Given the status of participants—cognitively unimpaired middle-aged adults with a FH+ — and that EF declines are early markers of MCI and predict progression along the AD continuum, these results may offer critical insight for AD prevention in middle-age and in older ages.
- This window of time (midlife) may provide an important opportunity for exercise interventions to deliver benefits for cognitive health, particularly in those with a genetic risk for AD.
- Limitations of this study include that EF at baseline was not equivalent across groups and that generalizability is limited due to the homogeneity of the sample with respect to race and sex.

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