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ABCA7 Genotype Moderates the Effect of Aerobic Exercise Intervention on Generalization of Prior Learning in Healthy Older African Americans

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Abstract. African Americans are at elevated risk for age-related cognitive decline, with double the prevalence of Alzheimer's disease (AD) compared to Caucasians Americans. Various behavioral, biological, and lifestyle factors may underlie this health disparity, but little is known about the relative importance and interactions among these different risk factors in African Americans. While the neuroprotective effects of aerobic exercise on biomarkers are well established, few studies have examined the differential benefits of exercise based on genetic risk for AD. Furthermore, evidence is limited regarding the potential moderating effects of *ABCA7*, a gene known to confer significantly greater AD risk in African Americans. In a case-control matched sample of 56 healthy older African Americans, we investigated the effect of an aerobic exercise intervention on a hippocampus-related assessment of generalization following rule learning, in individuals who were carriers of the *ABCA7* rs3764650 non-risk (TT) or high-risk (GG) genotype. Following the exercise-intervention, the non-risk group made significantly fewer generalization errors, while there was no improvement in generalization for the high-risk group. For the controls, no changes in generalization scores were observed regardless of genotype status. Our results indicate that the ongoing adverse effects of *ABCA7* high-risk genotype may diminish the benefits associated with aerobic exercise. As such, the potential disease-modifying effects of aerobic exercise on AD-related neuropathology may be limited to carriers of the *ABCA7* rs3764650 non-risk genotype.

Keywords: *ABCA7*, aerobic exercise, African American, Alzheimer's disease

INTRODUCTION

African Americans are at an increased risk for age-related cognitive decline and memory loss, with older African Americans being twice as likely to develop Alzheimer's disease (AD) and other dementias, compared to Caucasian Americans [1, 2]. The underlying cause of this health disparity is not sufficiently understood because it is influenced by a myriad of genetic, behavioral, and lifestyle factors. *APOE* and *ABCA7* genes are the strongest heritable contributors to AD in African Americans [3–6]. Modifiable lifestyle factors such as diet, exercise, and aerobic fitness also contribute to AD risk. In particular, higher levels of aerobic fitness are associated with decreased cognitive decline and reduced risk of AD [7, 8].

In the medial temporal lobe (MTL), one of the earliest brain regions impacted by the disease process, the hippocampus is a major site of neuroplasticity that is sensitive to the effects of physical exercise. Higher levels of aerobic fitness correspond to larger hip-

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pocampal volume in older adults [9, 10]. Six to twelve months of aerobic exercise can increase hippocampal volume [11, 12], cerebral blood flow [13], and improve cognition and memory [14, 15] in healthy older adults, as well as those with mild cognitive impairment (MCI). Taken together, these results suggest that aerobic exercise may have neuroprotective effects on hippocampal structure and function.

However, little is known about the interactive effects of exercise with other risk factors. Specifically, few studies have examined the differential effects of an aerobic exercise intervention in those with varying degrees of genetic risk for AD. One such study in non-demented elderly found improvements in the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) following a home-based physical activity intervention, only in *APOE* ε4 non-carriers [15]. Furthermore, following a six-month exercise intervention, individuals diagnosed with MCI showed an exercise-induced increase in brain-derived neurotrophic factor (BDNF) expression—associated with neuroplasticity and survival—in ε4 non-carriers but not in carriers [16]. Conversely, in individuals with either a family history of AD [17] or a personal history of stroke [18], improvements in cognition were associated with participation in exercise training irrespective of *APOE* ε4 carrier status. Outside of *APOE*, *ABCA7* is the strongest genetic risk factor, conferring significantly higher AD risk in African Americans [4]. Despite this, no studies have examined whether the effect of an aerobic exercise intervention varies based on *ABCA7* genotype.

As a member of the superfamily of ATP-binding cassette (ABC) transporters, *ABCA7* functions to regulate the homeostasis of cholesterol and phospholipids in the central nervous system and peripheral tissues. Research suggests that the contribution of *ABCA7* to AD risk is mediated by dysfunctional *ABCA7* expression [19], such that, increased level of *ABCA7* expression has been associated with more severe cognitive deficits in AD patients [20]. One *ABCA7* single nucleotide polymorphism (SNP) rs3764650 has been found to influence *ABCA7* expression levels in the brain [21] and is linked to 10–20% increased risk of AD in Caucasians [5, 6]. This *ABCA7* variant has also been found to exacerbate cognitive decline in subjects with a final diagnosis of MCI or AD [22] due to its association with a later age of onset and shorter disease process [20, 23].

An association between *ABCA7* variant rs3764650 and AD has not been found in genome wide association studies (GWAS) in African American cohorts. However, the minor allele frequency (MAF) of the risk "G" allele is higher in African Americans (0.25) than in Caucasians (0.1) [24]. In a recent cross-sectional case-control study of 100 healthy older African Americans, we demonstrated that *ABCA7* rs3764650 genotype modulates the association between aerobic fitness and a cognitive assessment of generalization following rule learning [25]. During this two-phased concurrent discrimination and generalization task, participants learned a series of visual discriminations and then had their generalization skills tested after the stimulus information changed. This task selectively engages the hippocampus [26], and unlike other standard cognitive assessments, performance can differentiate hippocampal-atrophied from non-atrophied individuals who are otherwise non-demented and apparently cognitively intact [27]. In our study [25], higher levels of aerobic fitness (VO_2 max) were significantly associated with fewer generalization errors in carriers of the non-risk (TT) genotype, whereas there was no relationship between aerobic fitness and generalization for carriers of the high-risk (GG) genotype. These results suggest differing risk patterns between cognitive decline and aerobic fitness by *ABCA7* rs3764650 genotype across individuals.

Using the same concurrent discrimination and generalization paradigm described earlier, the present study investigated the effect of a 20-week aerobic exercise intervention, compared with "treatment as usual," on hippocampal function and potential AD risk in a group of healthy older African Americans, who were either carriers of the *ABCA7* rs3764650 non-risk (TT) or high-risk (GG) genotype. Based on our previous findings [25], we hypothesized that following the intervention, aerobic exercise-related improvement in generalization performance will selectively be observed in carriers of the non-risk *ABCA7* rs3764650 genotype.

MATERIALS AND METHODS

Participants in this study were recruited through longstanding partnerships with local churches; senior centers; city, county, and state offices for health and aging; as well as from outreach to public housing and other federally subsidized low-income housing sites. For additional details on our community engagement, outreach, and recruitment strategies, see http://www.brainhealth.rutgers.edu.

Table 1
Characteristics for carriers of the *ABCA7* rs3764650 non-risk (TT) and high-risk (GG) genotype within the exercise-intervention and control groups

Characteristic	Aerobic Exercise		Control	
	Non-Risk	High-Risk	Non-Risk	High-Risk
Sample Size	14	14	14	14
Sex (Females)	13	14	11	13
Age (years)	70.79 (5.08)	71.71 (7.69)	68.93 (6.83)	68 (4.56)
Education (years)	14.11 (2.31)	14.28 (2.46)	13.71 (1.48)	13.25 (1.72)
Attendance (%)	83 (7.45)	83.7 (7.99)		

Individuals were eligible for participation if they identified as African American and were at least 55 years old. All subjects completed a battery of standardized neuropsychological and cognitive tests, as well as, an aerobic fitness and physical health assessment. Following the initial testing battery, participants in the exercise intervention group enrolled in a 20-week dance-based aerobic exercise program. With this type of community-based research, a randomized control design would pose unacceptable ethical issues; hence, we recruited "treatment as usual" controls that were matched on baseline body mass index (BMI) and aerobic fitness level. Participants in the "treatment as usual" control group underwent all the assessments but had no additional contact with us during intervention period. Considering that we did not match subjects on age and education, we controlled for these factors in all analyses (see below). At the end of the intervention period, all participants were re-tested on the cognitive and fitness assessments. The protocol was approved by the Rutgers University–Newark Institutional Review Board.

Participants

56 individuals participated in our present study with a case-control matched design. 28 subjects completed the exercise intervention, half of whom were homozygous for the *ABCA7* rs3764650 non-risk "T" allele, while the other half were homozygous for the high-risk "G" allele. We then matched the exercise intervention group with "treatment as usual" controls based on baseline BMI, aerobic fitness, and *ABCA7* rs3764650 genotype. Overall, the current study included 5 males and 51 females, with an average age of 69 years (Table 1).

Participants exhibiting signs of dementia, evident from the standardized neuropsychological assessments (see below) or who were taking medication(s) known to affect cognition were excluded from the study. Other exclusion criteria included: excessive alcohol and/or drug use, psychiatric disorders (including bipolar disease and schizophrenia), seizure disorders (such as epilepsy), and significant cerebrovascular or cardiovascular diseases. Participants were required to be independently ambulatory (no wheelchair, walker, or cane) and have no other contraindications for exercise; this was confirmed by written physician approval before the start of the study. All participants were fluent English speakers and completed written informed consent prior to participation.

Standardized neuropsychological assessments and self-report measures

In order to assess cognition and exclude anyone showing signs of cognitive impairment consistent with early dementia or other age-related disorders, we administered a series of neuropsychological tests. The neuropsychological battery consisted of the Mini-Mental State Examination (MMSE) (broad assay of cognitive impairment), Rey Auditory Verbal Learning Test (RAVLT) Delayed Recall (verbal memory), and Wechsler Adult Intelligence Scale (WAIS-IV) Digit Span (working memory) (Table 2).

Aerobic fitness assessment

The Six Minute Walk was used to determine aerobic fitness. Participants were instructed to walk a premeasured length on a flat surface for 6 min, with the goal of covering as much ground as possible [28]. At the completion of the 6 min, total walking distance was recorded in meters. To approximate participants' maximal oxygen consumption, we utilized the equation determined by Ross et al. (2010): VO_2 max = [4.948 + (0.023 * Distance)]. This protocol to predict maximal oxygen consumption (VO_2 max) is widely recognized as both a representation of the functional limitations of the cardiovascular system as well as a measure of aerobic fitness [30]. In addition,

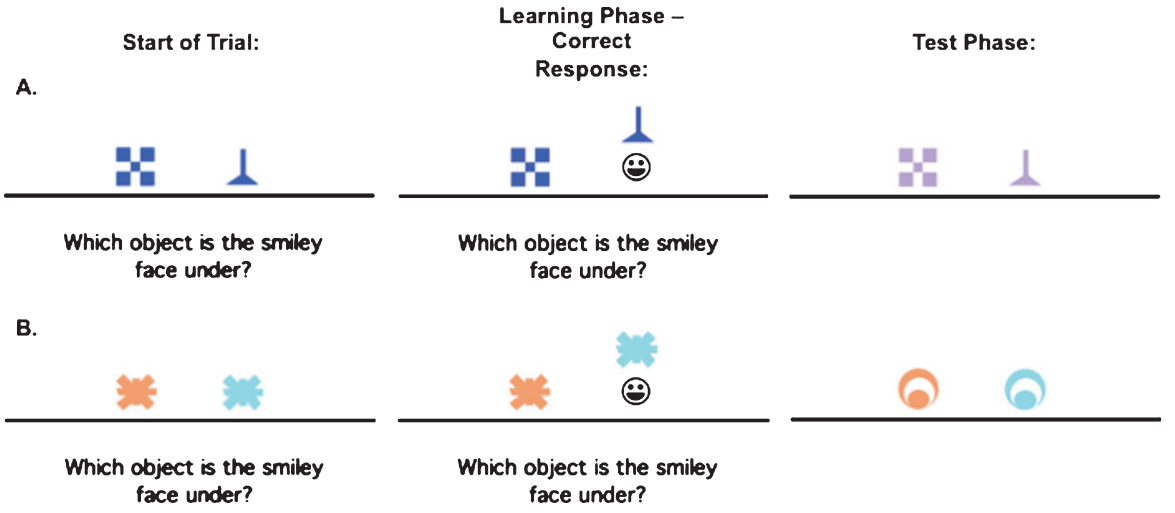

Fig. 1. An example of the concurrent discrimination and generalization task. On each trial of initial learning (acquisition), the discrimination pair is presented and if the participant responds correctly, the chosen object is raised to reveal a smiley face icon underneath. During test phase (generalization), events are similar to the acquisition phase, but the objects are changed so that the relevant feature remains the same, but the irrelevant feature is novel. Here (A) is an example of a trial where the relevant feature is shape, but not color, while (B) is an example of a trial where the relevant feature is color, but not shape.

participants' BMI was computed as a broad measure of physical health.

Behavioral paradigm: concurrent discrimination and generalization task

We have previously described the concurrent discrimination and generalization task in Myers et al. [27]. To summarize, it is a two-phase task in which participants learn a series of visual discriminations and are then tested on their ability to generalize when the stimulus information changes. For each discrimination pair, either the shape or color is relevant to the correct choice, but not both. During both the initial learning (acquisition) and test (generalization) phases of the task, each pair of shapes is presented sequentially and pseudo-randomly. Onscreen, the chosen object rises and if the choice was correct, a smiley face is revealed underneath (Fig. 1). No information about the correct object is given ahead of time, making this an incrementally acquired, feedback-based learning task, in which participants have to learn which object was correct. After reaching criterion performance on the acquisition phase, without warning, subjects are presented with reconfigured stimuli during the generalization phase. For example, the blue checkerboard versus blue funnel might change to lavender checkerboard versus lavender funnel as shown in Fig. 1A, first row, third column; the shapes remain the same, but the irrelevant attribute (color) changes from blue to lavender. In the second discrimination learned, the orange versus blue spider discrimination might change to an orange versus blue circle; shape remains irrelevant, but color continues to be predictive (Fig. 1B).

Individuals who solved the concurrent discrimination by basing associations on the relevant features (funnel beats checkerboard and blue beats orange) could perform perfectly in the generalization phase, since the relevant features are still predictive. By contrast, individuals who had approached the concurrent discrimination phase by learning to respond to whole objects (blue funnel beats blue checkerboard), by treating all features equally, are effectively confronted with novel objects (lavender funnel and lavender checkerboard) in the generalization phase, and might perform near chance.

Exercise intervention

Following the initial assessments, exercise intervention participants enrolled in a 20-week dance-based aerobic exercise program, which met twice a week, for 60 min per session. Participants' heart rates were monitored throughout each class session. During the exercise sessions, led by a certified and professional trainer, all participants exercised at a moderate intensity level; all individual sessions were tailored to achieve an intensity of 65–80% of heart rate reserve among our study population. Each ses-

sion consisted of 10 min of warm-up, 45 min of aerobic exercise in a standard dance-based aerobics format, and 5 min of cool down and stretching. Records of adherence to the program (attended sessions) and any adverse events were kept for each exercise session. Attendance rates for the exercise intervention participants are reported in Table 1.

Genetic data collection and processing

Saliva samples were collected using Oragene kits during the neuropsychological testing visit. DNA extraction and genotyping were conducted at the Rutgers University Human Genetics Institute. *ABCA7* SNP rs3764650 genotyping was carried out by quantitative PCR on an Eppendorf Mastercycler thermal cycler, using a TaqMan Custom Genotyping assay.

Statistical and power analyses

Mean scores on the standardized measures of cognitive functioning (MMSE, Digit Span, RAVLT), concurrent discrimination and generalization task performance (acquisition and generalization errors), BMI, and aerobic fitness (VO_2 max) were submitted to mixed ANCOVAs (analysis of covariance), with Time (baseline versus post-intervention) as a within subject factor, and, Intervention (aerobic exercise versus "treatment as usual" control) and Genotype (GG high-risk versus TT non-risk) as between subject factors, with age and years of education as covariates. Each ANCOVA was adjusted using the Benjamini-Hochberg test and a Monte-Carlo simulation [31] of 20,000 resamples to account for the joint test of the 7 individual outcome variables being analyzed. Any significant main effects or interactions were explored further with *post-hoc* ANCOVAs and *t*-tests as described in the Results section below. *Post-hoc* tests were also corrected for multiple comparisons using the Benjamini-Hochberg test.

Of primary interest were the three-way interaction to detect the combined effects of exercise and genotype over time (Intervention × Genotype × Time), and, the two-way interactions to detect the effect of exercise (combined across genotype and vice-versa) over time (Intervention × Time; Genotype × Time). We used an R package [32] to simulate a mixed ANCOVA design and empirically compute *a-priori* power through 1000 simulations. An Intervention × Genotype-induced difference of 0.5 standard deviation (medium effect size) in the dependent variable means over Time (3-way interaction) was considered worthwhile to detect. As such, on each trial we simulated a dataset that had exactly the desired properties, performed an ANCOVA, and used the ANCOVA results to compute the statistical power. According to these power calculations, a sample size of $n = 52$ would provide 85% power to detect an Intervention × Genotype × Time interaction. A sample size of $n = 38$ would provide 85% power to detect an Intervention-induced (or Genotype-induced) difference of 0.5 standard deviation (medium effect size) in the dependent variable means over Time (2-way interactions). Our current sample of $n = 56$ was therefore deemed sufficient to support the evaluation of our hypotheses.

RESULTS

The assumptions of ANCOVA were checked for each outcome measure; detailed characterization of each assumption can be found in the Supplementary Material.

The participants in the exercise group showed a 6.9% increase in VO_2 max while the controls showed an increase of 1.3%; however, this difference was not significant (Time × Intervention: $F(1, 50) = 1.71$, $p = 0.197$, p-corrected = 0.285). On the

Table 2
Neuropsychological tests, BMI, and aerobic fitness measures at baseline and at the end of the 20-week intervention period

	Aerobic Exercise				Control			
	Non-Risk		High-Risk		Non-Risk		High-Risk	
Measures	Baseline	Post-Intervention	Baseline	Post-Intervention	Baseline	Post-Intervention	Baseline	Post-Intervention
MMSE	28.21 (1.12)	27.57 (1.34)	27.57 (2.0)	27.43 (1.83)	27.93 (1.86)	27.64 (2.24)	27.21 (1.72)	27.93 (1.94)
Digit Span	23.43 (4.83)	25.07 (3.79)	21.93 (4.08)	21.79 (3.91)	21.14 (4.35)	21.5 (3.16)	22.71 (5.01)	24.07 (5.28)
RAVLT-Delayed Recall	6.43 (3.82)	7.71 (3.81)	6.79 (3.33)	9.21 (3.26)	6.64 (3.34)	7.43 (2.98)	5.86 (3.48)	7.14 (3.39)
BMI	31.98 (4.55)	31.95 (4.68)	30.74 (4.65)	30.24 (4.82)	30.17 (6.32)	30.03 (6.58)	31.08 (7.22)	31.79 (7.17)
VO_2	14.7 (2.32)	15.63 (1.32)	14.61 (2.90)	14.94 (1.81)	14.51 (2.46)	14.86 (2.12)	14.32 (2.74)	14.21 (3.06)

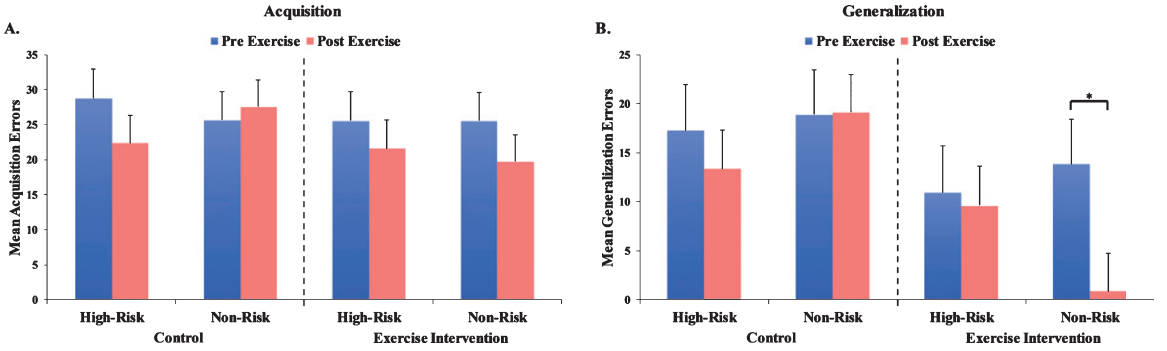

Fig. 2. Performance (total errors) on the concurrent discrimination and generalization task at baseline and post-intervention. On initial learning (acquisition), across groups, participants did not differ at baseline and did not show a significant change in performance during the intervention duration (A). On the test phase, carriers of the non-risk (TT) *ABCA7* genotype who underwent the exercise-intervention made significantly fewer generalization errors, while there was no improvement in generalization performance for any other group at the end of the intervention period (B).

three-way ANCOVA, for both BMI and VO_2 max, there were no significant interactions and no main effects of Time, Intervention, or Genotype (Table 2). Thus, we did not observe any significant exercise or genotype-related improvements in either physical health or aerobic fitness at the end of the 20-week intervention.

No main effects or interactions were observed for any of the standardized neuropsychological assessments, indicating that across groups, participants did not differ at baseline and did not show a significant change in performance during the intervention period (Table 2).

On the concurrent discrimination and generalization task, all participants reached the criterion of 16 consecutive correct responses on the acquisition phase, indicating that they successfully learned the task. No main effects or interactions were observed for acquisition errors, indicating that all groups learned the task equally well at baseline, and, did not show any significant differences in task acquisition following the intervention period (Fig. 2A). We therefore did not control for acquisition when analyzing performance on the generalization phase.

For generalization phase errors, there was a main effect of Intervention ($F(1, 50) = 3.99$, $p = 0.05$, p-corrected = 0.104) and a significant Time × Intervention × Genotype interaction ($F(1, 50) = 4.56$, $p = 0.038$, p-corrected = 0.057). To ensure that the main effect of Intervention was not due to baseline differences in generalization errors, we performed a two-way ANCOVA with Intervention and Genotype as fixed factors, and, age and level of education as covariates. There were no main effects or interactions, thereby confirming that pre-intervention generalization performance did not differ across groups. We then followed up on the Time × Intervention × Genotype interaction and examined each Intervention group (aerobic exercise and control) separately, performing a mixed ANCOVA with Time as a within-subject factor, Genotype as a between-subject factor, and, age and years of education as covariates. For the control group, there were no significant main effects or interactions, indicating that after the 20-week interval no changes in generalization were observed for carriers of either the high-risk or non-risk genotype (Fig. 2B). However for the exercise-intervention group, there was a significant Time × Genotype interaction ($F(1, 24) = 8.48$, $p = 0.008$, p-corrected = 0.016). Pairwise *t*-tests revealed that following the exercise-intervention, the non-risk group made significantly fewer generalization errors ($t(1, 13) = 4.1$, $p = 0.001$, p-corrected = 0.002), while there was no difference in generalization performance between baseline and post-intervention follow-up for the high-risk group ($t(1, 13) = 1.24$, $p = 0.238$, p-corrected = 0.476). Hence, *ABCA7* genotype moderates the effect of aerobic exercise on generalization, such that, the exercise-intervention improved generalization performance selectively for individuals who were carriers of the non-risk genotype (Fig. 2B).

DISCUSSION

In a sample of African American elderly, the present study investigated the effect of a 20-week aerobic exercise intervention using a behavioral paradigm known to be sensitive to hippocampal function: the concurrent discrimination and general-

ization task. Comparing individuals who were either carriers of the *ABCA7* rs3764650 non-risk (TT) or high-risk (GG) genotype, we observed that, following the exercise-intervention, the non-risk group made significantly fewer generalization errors. In contrast, there was no improvement in generalization performance for the high-risk group. Finally, no changes in generalization scores were observed for controls, regardless of genotype status.

The hippocampus is one of the major brain sites of neuroplasticity in adulthood, and several studies have demonstrated marked benefits of aerobic exercise on hippocampal structure and related cognitive function [11–15]. In a previous cross-sectional study [25], we demonstrated that *ABCA7* rs3764650 genotype modulates the association between aerobic fitness and a hippocampus-related cognitive assessment of generalization, such that, the benefit of aerobic fitness on generalization was observed only in carriers of the *ABCA7* non-risk TT genotype, but not in carriers of the high-risk GG genotype. The results of the current study significantly extend these prior findings by demonstrating analogous outcome longitudinally. Following a 20-week cardio-dance intervention, exercise-related improvements in generalization performance were selectively observed in carriers of the *ABCA7* rs3764650 protective TT genotype. This interaction likely indicates that preexisting or ongoing deleterious effects of the *ABCA7* high-risk genotype may have diminished the neural and cognitive benefits associated with aerobic exercise. Hence, our results suggest that *ABCA7* high-risk genotype may attenuate the neuroprotective effects of aerobic fitness and exercise in cognitively healthy older adults.

Consistent with our previous cross-sectional study [25], in the current study there were no genotype-related differences in generalization errors at baseline, as well as, no genotype-induced improvements in performance during the intervention period for the control group. Furthermore, GWAS studies in African Americans have found either none, or nominally significant associations of *ABCA7* rs3764650 and AD [4, 33, 34]; however, another variant, *ABCA7* rs115550680, has been linked to the development of late-onset AD in African Americans [4]. The findings of this study therefore indicate that in African Americans, *ABCA7* rs3764650 may not confer direct AD risk, but it may indirectly increase the risk of AD by moderating the protective effects of aerobic exercise. It remains a significant open question whether these results are specific to African Americans, and perhaps account for the higher incidence rates of dementia and AD in this population by compounding the overall *ABCA7*-related risk. Further investigation is required to elucidate the interracial generalizability of the interactive effects of *ABCA7* rs3764650 and aerobic exercise on AD-related neuropathology.

These important findings are not without limitations. There were no measurable exercise-induced improvements in aerobic fitness (VO_2 max). Even though the participants in the exercise group showed a greater increase in aerobic fitness than controls, this difference was not significant, which may be a result of the gender imbalance in our sample. Previous research has shown a diminished VO_2 max response to exercise training in women [35]. Furthermore, a recent study in African Americans found significant gender-based differences in exercise-induced alteration in VO_2 max, such that, an exercise intervention produced statistically significant increases in VO_2 max in men but not in women [16]. With just five male participants in the present study, we cannot infer anything about gender effects. Stratification by sex in future work is needed to elucidate whether *ABCA7*-related mechanisms differentially modulate the neurocognitive effects of aerobic exercise in men and women, and, how these differences may relate to gender-based variations in aerobic fitness improvements.

Conversely, despite the absence of a change in aerobic fitness, carriers of the non-risk genotype showed exercise-induced improvements in cognition, as measured by generalization. Notably, these healthy participants did not show any significant change in performance on the common standardized measures of declarative memory such as delayed recall of semantic or episodic memories. However, in studies with AD patients [36, 37], *ABCA7* risk variants were related to variations in episodic memory as measured by the standardized assessments. Furthermore, a similar exercise intervention program that met three times per week [38] found improvements on some standardized neuropsychological measures in a cohort of sedentary older women. As such, exercise-induced changes in standard neuropsychological measures may manifest with higher intensity and/or higher frequency interventions. Another possible underlying cause of this discrepancy could be that in cognitively healthy older adults, generalization of learning is the earliest hippocampus-related cognitive domain to be targeted by the causal mechanisms that are impacted by both exercise and *ABCA7* genotype (albeit in opposite directions), even before

improvements in aerobic fitness are discernible. Thus, the concurrent discrimination and generalization behavioral paradigm may be a more sensitive tool for assessing the efficacy of aerobic exercise-based interventions in remedying the mild cognitive deficits seen in the earliest phases of prodromal AD in otherwise cognitively healthy individuals, before the more severe and more commonly reported deficits in episodic memory arise.

Among the various modifiable lifestyle factors, physical inactivity is the greatest modifiable risk factor for dementia [39]. Individuals who engage in more physical exercise earlier in life show less cognitive decline [40, 41] and have a reduced risk of developing dementia later in life [42, 43]. However, it is imperative to understand whether the benefits of physical exercise are similar for those with and without a genetic risk for dementia and AD when designing interventions to mitigate risk at the individual level. Several population-based studies examining the interaction between *APOE* ε4, physical exercise, and dementia risk have yielded equivocal results; some studies reported that the protective effects of physical activity on future cognitive decline was specific to *APOE* ε4 carriers [44–46], while others have reported that physical activity reduces the risk for dementia only in non-carriers of the ε4 allele [47–49]. Consistent with our results, interventional studies in healthy older adults [15] and in those with MCI [16] have reported that physical exercise reduced dementia risk for *APOE* ε4 allele non-carriers but not for carriers. However, in individuals with a family history of AD [17] and stroke patients [18], exercise-induced improvements in memory were observed irrespective of *APOE* ε4 carrier status.

The results of the present study add to this emerging picture of a differing relationship between cognitive decline and exercise, based on genetic risk for AD: the potential disease-modifying effects of aerobic exercise on AD-related neuropathology may be limited to carriers of the non-risk *ABCA7* rs3764650 genotype. To our knowledge, this is the first study to demonstrate the interactive effect of an *ABCA7* variant and aerobic exercise on hippocampus-related cognitive functioning.

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Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/19-0723r2).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-190723.

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