

RESEARCH ARTICLE

Lower CD8+ T-cell senescence partially mediates the neuroprotection of higher aerobic fitness

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Abstract

INTRODUCTION: Immunosenescence – age-related changes in immunity – may exacerbate the pathologic processes of Alzheimer's disease (AD), a condition that disproportionately affects African Americans. Fortunately, a higher level of aerobic fitness is linked to both reduced immunosenescence and lower AD risk. However, it remains unclear whether higher aerobic fitness and decreased AD is mediated by lower proportions of T-cell senescence. In a cohort of older African Americans, we aimed to (1) examine the relationship between aerobic fitness and generalization (a cognitive indicator of AD risk) and (2) investigate whether T-cell senescence mediated this relationship.

METHODS: A total of 231 older African American participants from the Aging & Brain Health Alliance ($M_{\text{age}} = 70.74$ years, $SD = 6.40$; $M_{\text{education}} = 14.02$ years, $SD = 2.25$; $M_{\text{MoCA}} = 23.16$, $SD = 2.63$) responded to demographic, health, and lifestyle questionnaires; completed a cognitive battery including a generalization task (stimulus differentiation and transfer task); underwent anthropometric and physical performance measures; and provided a blood sample for T-cell senescence characterization. Peripheral blood mononuclear cells were isolated and analyzed for senescence-associated beta-galactosidase activity as a measure of proportions of cytotoxic CD8+ T-cell senescence. Aerobic fitness ($VO_2\text{peak}$) was estimated from the six-minute walk test. Covariates included age, sex, education, and waist-to-hip ratio.

RESULTS: Higher aerobic fitness was significantly associated with fewer generalization errors. Furthermore, higher aerobic fitness was associated with lower CD8+ T-cell senescence ($\beta = -0.15$, $p = 0.02$), which was associated with fewer generalization errors ($\beta = -0.17$, $p = 0.01$). Overall, 15% of the effect of higher aerobic fitness on fewer generalization errors was mediated by lower CD8+ T-cell senescence.

Bernadette A. Fausto, Elizabeth Akbulut, and Mustafa Sheikh contributed equally to this work.

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DISCUSSION: One pathway by which higher aerobic fitness is associated with lower AD risk in older African Americans is through lower proportions of CD8+ T-cell senescence. These results highlight the immune and cognitive function benefits of a physically active lifestyle, particularly in a demographic that faces a higher risk for AD.

KEYWORDS

aerobic fitness, African American, generalization, immunosenescence, mediation

Highlights

- Immunosenescence may exacerbate the pathologic processes of AD.
- Higher levels of aerobic fitness are linked to reduced immunosenescence.
- Higher levels of aerobic fitness are also associated with reduced AD risk.
- The neuroprotective effect of aerobic fitness is mediated by CD8+ T-cell senescence.
- Aerobic fitness has both immune and cognitive health benefits in later life.

1 | BACKGROUND

African Americans have over twice the risk of Alzheimer's disease (AD) compared to non-Hispanic White Americans, a disparity rooted in complex socio-environmental factors.^{1,2} These factors, such as limited access to quality healthcare and exposure to harmful conditions in the built environment, can exacerbate adverse cognitive health outcomes.¹ Such barriers may also influence physical activity levels and concomitant changes in aerobic fitness, as accessibility to safe exercise environments may impact engagement in aerobic exercise.² These multifaceted considerations warrant a focused investigation into the physical and cognitive health experiences of older African Americans.

Fortunately, aerobic fitness and aerobic exercise are neuroprotective.³⁻⁵ Several observational studies and clinical trials indicate that higher levels of aerobic fitness correlate with a reduced risk of developing AD and/or attenuated AD-related cognitive and brain changes.^{3,6,7} Regions crucial for memory, such as the medial temporal lobe (MTL) and hippocampus, are particularly sensitive to aerobic fitness-related volumetric changes in aging,⁷ leading to better preservation of cognitive functions like episodic memory and generalization of prior learning in aerobically fit older adults.^{8,9} Despite these findings, there are insufficient data on the underlying mechanisms linking aerobic fitness and reduced AD risk, especially among older African American cohorts.

One potential pathway is immune function.¹⁰ The accumulation of senescent cells in aging is linked to weakened immune systems and age-related diseases, including AD.^{11,12} T-cell senescence, particularly in CD8+ T cells,¹³ has been implicated in AD due to its proinflammatory nature and diminished immunosurveillance capabilities,^{14,15} with Black and African American adults exhibiting elevated levels of T-cell senescence.^{16,17} These immunological alterations have been associated with higher chronic disease burden and may contribute to the elevated risk of neurodegenerative diseases in this population.¹⁷

Fortunately, aerobic exercise and aerobic fitness may help maintain an aging immune system.^{18,19} For example, master athletes exhibit lower T-cell senescence percentages compared to individuals who had no regular exercise training in the last 20 years, indicating that sustained aerobic fitness during aging may prevent senescent T-cell accumulation.²⁰ As such, exercise and aerobic fitness may be neuroprotective for AD, potentially via immune regulation, and we aimed to verify this in African Americans who have an elevated risk of developing AD.

1.1 | Purpose of this study

In a cohort of older African Americans, this study aimed to (1) examine the relationship between aerobic fitness and cognitive function, including generalization, a sensitive cognitive marker of Alzheimer's risk,²¹ and (2) investigate whether CD8+ T-cell senescence mediated fitness-cognitive function relationships. We hypothesized that (H1) higher aerobic fitness would be associated with better cognitive function, consistent with previous studies,²² and (H2) CD8+ T-cell senescence would mediate the relationship between aerobic fitness and cognitive function, suggesting that the neuroprotective effects of fitness are partially explained by variations in T-cell senescence.

2 | METHODS

Participants were drawn from the Aging & Brain Health Alliance (ABHA), a university-community partnership established in 2006 to assist with ongoing community engagement and recruitment of local residents into biomedical research studies at Rutgers University-Newark. The ABHA investigates risk and resilience factors for AD among older African American adults ages 60 years and over.

RESEARCH IN CONTEXT

- 1. Systematic review:** PubMed, PsycINFO, Crossref, and Web of Science databases were searched using terms related to immunosenescence, aerobic fitness, cognitive changes in preclinical AD, and Alzheimer's risk. All relevant sources are properly cited.
- 2. Interpretation:** Current findings highlight the importance of aerobic exercise and exercise-related fitness improvements in African Americans aged 60 and older. One mechanism by which fitness may attenuate AD risk is through reduced accumulation of senescent CD8+ T cells.
- 3. Future directions:** Exercise and concomitant improvements in aerobic fitness, therefore, present a cost-effective and safe non-pharmacological alternative to delay immune aging and, in turn, pathological cognitive aging. Creative and culturally appealing exercise interventions should be tailored to different subpopulations, especially those who are at greatest risk for AD, including African American communities.

Participants respond to demographic, lifestyle, and health questionnaires; undergo cognitive testing (with a subset completing neuroimaging sessions if medically eligible); complete anthropometric measurements and a physical fitness protocol; and provide a blood sample for various AD and health biomarkers. For detailed recruitment strategies and engagement methods by ABHA see Gluck et al.²³

For the current analyses, eligible participants were required to be 60 years of age or older; identify as African American or Black; speak, read, and understand English; and be willing to provide a blood sample for immunological markers. Individuals were excluded from the current analyses if they: had a Montreal Cognitive Assessment (MoCA) score of 18 or lower²⁴; had a diagnosis of any neurodegenerative disorder or learning disability; had a major stroke or serious brain injury; were taking medications typically prescribed for dementia (e.g., Aricept, Exelon, Namzaric); self-reported excessive alcohol and/or recreational drug use; underwent a medical procedure requiring general anesthesia in the past 3 months; were color blind (as some cognitive tasks require color discrimination); and were unable to see a computer screen from a normal viewing distance. At the time of data extraction, we included 252 participants. However, 21 participants were missing one or more values for key variables in the current analyses, resulting in a final analytic *N* of 231. A missing value analysis revealed that the analytic sample of 231 did not significantly differ from the 21 participants with one or more missing data points on age, sex composition, or education, *p* > 0.05, suggesting that the analytic sample is representative of the overall sample. See Table 1 for demographics of the analytic sample (*N* = 231).

TABLE 1 Descriptive statistics for the analytic sample (*N* = 231).

Variables	Mean (<i>n</i>)	Standard deviation (%)
Age (years)	70.74	6.40
Education (years)	14.02	2.25
Sex (female)	(178)	(77.10)
Montreal Cognitive Assessment (points)	23.16	2.63
Geriatric Depression Scale–Short form (points)	1.77	2.15
Waist-to-hip ratio	0.92	0.08
VO ₂ peak estimate (mL/kg/min)	12.58	1.57
SA-βGal activity in CD8+ T cells	65.90	20.34
RAVLT–delayed recall	0.25	0.17
Digit span total	22.94	5.08
Concurrent discrimination and transfer task	–	–
Training errors	27.02	16.27
Generalization errors	17.78	17.92

Abbreviations: RAVLT, Rey Auditory Verbal Learning Test, SA-βGal, Senescence-associated β-galactosidase activity in CD8+ T-cell populations.

2.1 | Procedure

Interested candidates were telephone-screened to determine initial eligibility. Potentially eligible candidates were then invited to attend an in-person screening visit (MoCA screening and colorblindness testing) and, if eligible, signed an informed consent form and proceeded with the full laboratory protocol, including a blood draw and a 2-h cognitive and physical function assessment. All research protocols were approved by the Rutgers University Institutional Review Board.

2.2 | Measures**2.2.1 | Outcomes***Stimulus differentiation and transfer task (generalization)*

The stimulus differentiation and transfer task indexes generalization of prior learning. A measure of AD risk, this two-phase task measures (1) the ability to learn rules (training phase) and (2) the ability to flexibly apply those rules to new contexts (generalization phase).²⁵ In brief, during each trial of the training phase, participants are presented with a pair of stimuli and asked, "Which object is the smiley face under?" to which they respond via a left or right button press to select the correct object. Upon selecting the correct object, the object moves up to reveal a smiley face. Participants learn via trial-and-error feedback which object is the correct object among eight object pairs. Correctness is based on either shape or color. Once participants reach the criterion (i.e., 16 consecutive correct responses or a maximum of 96 trials), participants proceed to the generalization phase. During the generalization phase, participants are confronted with novel but

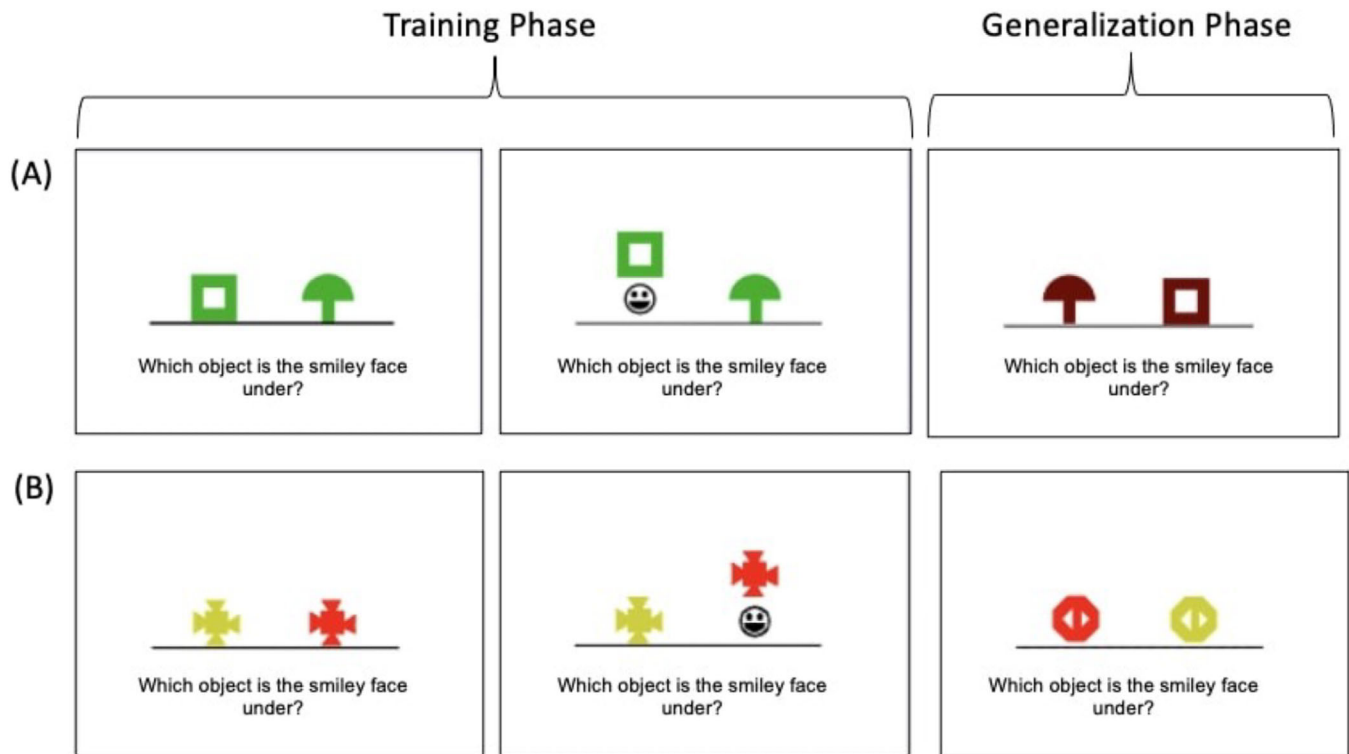


FIGURE 1 Stimulus differentiation and transfer task examples. (A) In this example, participants learn to choose the green box in preference to the green mushroom during the training phase. Thus, shape is predictive (relevant), but color is not (irrelevant). In the generalization phase, participants are presented with a brown box and a brown mushroom; the brown box is the correct object, so the shape is still predictive, but the irrelevant feature (color) has been altered. (B) In this example, color is predictive (relevant), but shape is not (irrelevant).

similar object pairs and are asked again to indicate the correct object, taking into consideration the rules they learned in the training phase to discriminate between incorrect and correct objects. See Figure 1, for example, training and generalization trials. Performance is recorded as the number of training and generalization phase errors committed, with higher scores indicating worse generalization performance.

Rey auditory verbal learning test (episodic memory) and digit span (working memory)

The Rey Auditory Verbal Learning Test (RAVLT) is a measure of verbal episodic memory.²⁶ The digit span subtest of the Wechsler Adult Intelligence Scale-Fourth edition is a measure of short-term and working memory as well as attention.²⁷ Normative performance data in African American adults are available from Mayo's Older African American Normative Studies (MOAANS)²⁸ and the National Alzheimer's Coordinating Center Uniform Dataset,²⁹ respectively.

2.2.2 | Key predictor

Aerobic fitness

We used a modified 6-min walk test as a proxy for aerobic fitness.³⁰ Participants are asked to walk back and forth along a premeasured distance of 27 m (approximately 90 feet) for 6 min at their normal walking speed. Participants' distance walked is then converted to peak aerobic

capacity expressed as milliliters of oxygen consumed in a minute per kilogram of body weight as per the formula from Ross and colleagues³¹: $VO_{2peak} = 4.948 + 0.023 \times \text{distance walked}$. Higher VO_{2peak} scores indicate better aerobic fitness.

2.2.3 | Mediator

CD8+ T-cell senescence

Senescence-associated β -galactosidase (SA- β Gal) activity is a hallmark of senescent cells. SA- β Gal activity of CD8+ T cells was characterized as per a small modification of a recently published novel protocol; for more details, see Martínez-Zamudio et al.¹³ In brief, peripheral blood mononuclear cells (PBMCs) were obtained from heparinized peripheral blood using ficoll-hypaque gradient centrifugation. PBMCs were counted and analyzed for cellular senescence using the SPiDER- β Gal kit from Dojindo Molecular Technologies. PBMCs were incubated with a 1:500 dilution of bafilomycin A-1 for 1 h, which neutralizes non-senescent β Gal activity. A 1:500 dilution of SPiDER- β Gal (Dojindo Molecular Technologies), a cell-permeable, self-immobilizing, fluorogenic SA- β Gal substrate, was then added to the cells for 30 min. This substrate is acted upon by the SA- β Gal enzyme within the cells, causing it to emit a fluorescent signal when interrogated by the laser in the flow cytometer. Next, PBMCs were labeled with antibodies to CD3, CD4, and CD8. The cells were then washed and analyzed using

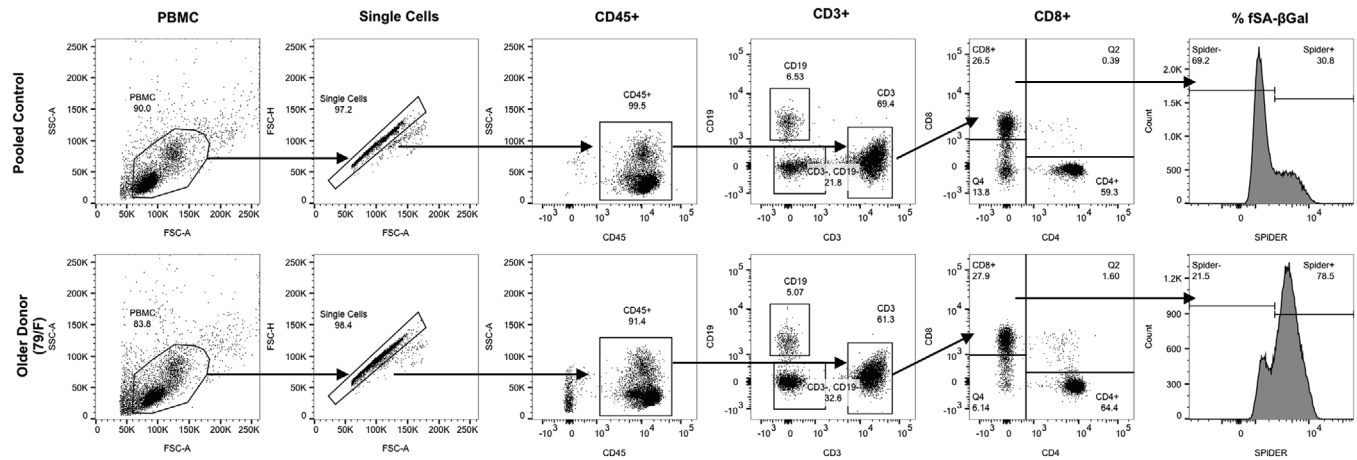


FIGURE 2 Gating strategy for senescence-associated β -galactosidase activity of CD8+ T cells. Peripheral blood mononuclear cells (PBMCs) from study donors and a control donor pool (included in each assay) were incubated with bafilomycin A for 1 h followed by the SPiDER reagent for 30 min, then washed and surface-stained with antibodies to CD45, CD3, CD4, CD8, and CD19. After fixation, cells were acquired by flow cytometry and analyzed with FloJo software. Cells are gated for PBMCs, then single cells, CD45 (to detect leukocytes), then CD3 (all T cells), and then CD8+ T cells. (B) Cells (CD19 B cell marker) and CD4+ T cells were excluded from the analysis. The CD8+ cells were further gated for SPiDER+, representing percentage of SA-bGal activity positive cells. The SPiDER-positive cells were determined using our internal control of three pooled younger donors (top panels), and the same gate was applied for a representative older donor (75-year-old female) in the lower panels. Numbers below descriptors in the histograms or quadrants are the percentage of the parent population.

multiparameter flow cytometry (BD Biosciences LSRFortessa) to measure the fluorescence intensity of individual cells. The CD8+ T-cell subset was analyzed in the PBMC population using FloJo software (BD Biosciences). A frozen sample of stored PBMC from three combined donors was used as an internal control in each assay to help identify the CD8+ T cells with high SA- β Gal activity. The flow cytometric gating strategy is shown in Figure 2. The value is expressed as a percentage of CD8+ T cells with high SA- β Gal activity. Hereafter, we refer to this variable as CD8+ T-cell senescence.

2.2.4 | Covariates

Age, sex as a biological variable, education, and waist-to-hip ratio (WHR) were treated as covariates in all adjusted analyses, given previous literature linking these factors with either cognitive function and/or aerobic fitness.^{32–35}

2.3 | Statistical analyses

Descriptive statistics were calculated for all continuous and categorical-ordinal variables. Parametric and non-parametric bivariate correlations, depending on variable scaling, were also examined. Then, a series of hierarchical linear regressions was run to determine the relationships between aerobic fitness (VO_{2peak}) and cognitive function (generalization, episodic memory, and working memory scores as outcomes). For each hierarchical linear regression, covariates (age, sex, education, and WHR) were entered in Step 1, and VO_{2peak} was added in Step 2, allowing us to examine the independent contribution of

VO_{2peak} to cognitive outcomes after considering covariates. Change in R^2 from Step 1 to Step 2 was used to determine whether VO_{2peak} accounted for significant variance in cognitive function after accounting for covariates.

We also explored whether the relationships between VO_{2peak} and cognitive function were mediated by immune function (CD8+ T-cell senescence) using bootstrapped mediation procedures included in the PROCESS SPSS macro.³⁶ The simple mediation model (Model 4) with 5000 bootstrapping simulations for each model was computed to derive the total, direct, and indirect effects. As per Preacher and Hayes,³⁶ statistical mediation was assumed when the bootstrapped confidence intervals did not overlap zero. The percentage mediated was derived by computing the ratio of the indirect effect to the total effect. Data were analyzed using the IBM SPSS Statistics for Mac software, version 29.0.2.0 (IBM Corp., Armonk, NY, USA).

3 | RESULTS

Descriptive statistics for the analytic sample ($N = 231$ participants) are included in Table 1. Participants were on average about 71 years old and completed 14 years of education ($SD = 2.25$). The majority of participants were female (77.1%). Figure 2 shows the gating strategy for the CD8+ senescent T cells, and Figure 3 shows the violin plots for the key variables: (A) VO_{2peak} , (B) CD8+ T-cell senescence, and (C) generalization of prior learning errors. Table 2 provides the bivariate intercorrelations for the variables included in the present analyses. The analytic dataset, data codebook, and statistical analysis code are publicly available on Open Science Framework.³⁷

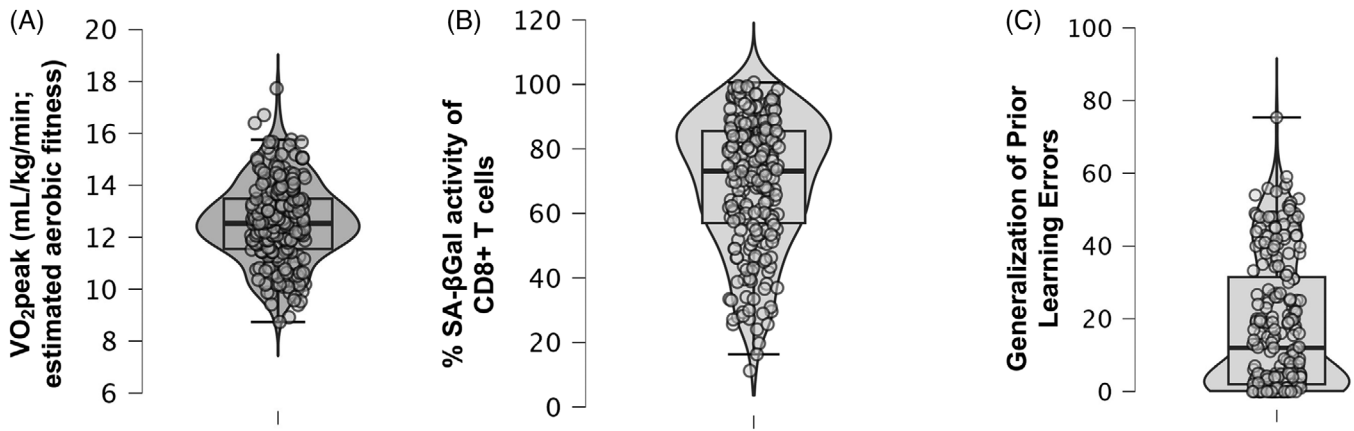


FIGURE 3 Violin box plots for (A) VO_2 peak, (B) percentage of senescence-associated β -galactosidase (SA- β Gal) activity of CD8+ T-cells, and (C) generalization of prior learning errors.

TABLE 2 Intercorrelation coefficients among demographic, predictor, and dependent variables.

	Age	Edu	MoCA	GDS-SF	WHR	VO_2 peak	SA- β Gal CD8+	RAVLT R	Digit span total	Training errors	Generalization errors
1. Age	-										
2. Education	0.06 (0.40)	-									
3. MoCA	-0.13 (0.05)	0.13 (0.05)	-								
4. GDS-SF	-0.16* (0.02)	-0.19** (0.003)	-0.17* (0.01)	-							
5. WHR	-0.10 (0.12)	-0.11 (0.09)	0.01 (0.88)	0.09 (0.17)	-						
6. VO_2 peak	-0.10 (0.12)	0.16* (0.02)	0.06 (0.35)	-0.18** (0.006)	0.05 (0.43)	-					
7. SA- β Gal CD8+	0.11 (0.11)	-0.05 (0.41)	-0.05 (0.44)	0.08 (0.23)	0.23** (0.001)	-0.15* (0.03)	-				
8. RAVLT-DR	0.04 (0.59)	0.21** (0.002)	0.35** (0.001)	-0.10 (0.15)	-0.12 (0.07)	-0.06 (0.35)	-0.09 (0.16)	-			
9. Digit span total	-0.10 (0.14)	0.22** (0.001)	0.37** (0.001)	-0.11 (0.10)	-0.08 (0.22)	0.16* (0.02)	-0.10 (0.14)	0.17* (0.01)	-		
10. Training errors	0.10 (0.15)	-0.29** (.001)	-0.23** (0.002)	0.14* (0.03)	0.04 (.56)	-0.20** (0.002)	0.15* (0.02)	-0.14* (0.04)	-0.16* (0.01)	-	
11. Gener- alization errors	0.01 (0.98)	-0.24** (0.001)	-0.21** (0.002)	0.17* (0.01)	0.05 (0.48)	-0.17* (0.01)	0.19** (0.004)	-0.10 (0.13)	-0.20** (0.002)	0.72** (0.001)	-

Note: Correlation coefficients for each bivariate correlation. *p* values are in parentheses.

Abbreviations: GDS-SF, Geriatric Depression Scale–Short form; MoCA, Montreal Cognitive Assessment; RAVLT, Rey Auditory Verbal Learning Test, SA- β Gal, senescence-associated β -galactosidase activity in CD8+ T-cell populations, WHR, waist-to-hip ratio.

**p* < 0.05.

***p* < 0.01.

Here, we investigated relationships between VO_2 peak and cognitive function (generalization, episodic memory, and working memory

and (2) explored CD8+ T-cell senescence as a mediator of the relationships between VO_2 peak and cognitive function.

3.1 | Hierarchical regressions between VO₂ peak and cognitive function

3.1.1 | Stimulus differentiation and transfer task (generalization)

In Step 1, with all covariates entered as independent variables, education was the sole covariate significantly associated with generalization errors, $\beta = -0.22$, $p < 0.001$. The linear combination of age, sex, education, and WHR indicated good model fit with generalization errors, $F(4, 230) = 3.65$, $p = 0.01$. In step 2, VO₂ peak contributed significant additional variance in generalization errors; as VO₂ peak increases, generalization errors decrease, $\beta = -0.13$, $p = 0.04$, $R^2 = 0.08$, sig F change = 0.04.

3.1.2 | RAVLT (episodic memory)

In Step 1, only education significantly emerged as a significant covariate for RAVLT delayed recall, $\beta = 0.17$, $p = 0.01$. There was a good overall model fit, $F(4, 230) = 10.46$, $p < 0.001$. Adding VO₂ peak in Step 2 revealed that VO₂ peak was not an independent predictor of RAVLT ($\beta = -0.02$, $p = 0.81$), nor did it contribute significant variance to the model, $R^2 = 0.16$, sig F change = 0.81.

3.1.3 | Digit span (working memory)

In Step 1, education ($\beta = 0.20$, $p < 0.01$) was a significant covariate for digit span with good overall fit, $F(4, 226) = 4.07$, $p = 0.003$. Adding VO₂ peak shows that both were independently associated with digit span ($\beta = 0.13$, $p = 0.05$) and contributed significant variance to the fully adjusted model, sig F change = 0.05.

3.2 | Mediation analyses

Mediation analyses were performed to test whether CD8+ T-cell senescence mediates the association between aerobic fitness (independent variable) and cognitive function (dependent variables of generalization, episodic memory, and working memory). All mediation analyses were adjusted for age, sex, education, and WHR.

Figure 4 depicts the total, indirect, and direct effects of the association between aerobic fitness and generalization with CD8+ T-cell senescence as a mediator. The mediation model revealed that there was a significant indirect effect of CD8+ T-cell senescence on the relationship between aerobic fitness and generalization (total indirect effect $\beta = -0.03$, 95% CI $[-0.06, -0.01]$, $p < 0.05$). Furthermore, the direction of the paths indicated that higher aerobic fitness was associated with lower CD8+ T-cell senescence ($\beta = -0.15$, $p = 0.02$), which was associated with fewer generalization errors ($\beta = 0.17$, $p = 0.01$). Overall, 15% of the effect of higher aerobic fitness on fewer generalization errors was mediated by lower CD8+ T-cell senescence.

There were no significant mediation effects of CD8+ T-cell senescence for episodic memory or working memory.

4 | DISCUSSION

The present study aimed to (1) examine the relationship between aerobic fitness and cognitive function, including generalization (a sensitive cognitive marker of AD risk), and (2) investigate whether CD8+ T-cell senescence mediates any fitness-cognitive function relationships. Higher aerobic fitness was significantly associated with better working memory and generalization, but not episodic memory, in this cohort of older African Americans. Furthermore, we found that one pathway by which higher aerobic fitness is associated with generalization (AD risk) in older African Americans is through lower proportions of CD8+ T-cell senescence. Meanwhile, CD8+ T-cell senescence did not mediate any other fitness-cognitive function relationships. Overall, these results highlight the immune and cognitive function benefits of a physically active lifestyle.

These results are consistent with prior works demonstrating the neuroprotective benefits of aerobic fitness in older age.^{22,38} Fitness-associated cognitive improvements often occur in the episodic memory and working memory domains.^{39,40} Our results revealed cross-sectional fitness and cognitive function relationships in working memory and generalization domains. Interestingly, however, episodic memory was not related to aerobic fitness. This discrepancy may be due to the suitability of generalization to better capture variability in aerobic fitness levels (compared to episodic memory) in this particular cohort of cognitively unimpaired but demographically at-risk older African Americans. Growing research suggests that traditional episodic memory tests are relevant in the more overt stages of progressive cognitive decline associated with AD and are influenced by cognitive reserve factors like education quality and quantity. Generalization, on the other hand, is rather resistant to cognitive reserve confounds, given that its paradigm originated from non-verbal tasks in animal studies.⁴¹ Additionally, changes in generalization may precede episodic memory declines.²⁵ As such, varying levels of aerobic fitness may be commensurate with variations in generalization but not with episodic memory at this preclinical stage of AD.

We also identified a partial mediation of the aerobic fitness-generalization relationship through CD8+ T-cell senescence. That is, 15% of the neuroprotective value of fitness is through healthier immune function. Indeed, the infiltration of peripheral immune cells through the blood-brain barrier and the influence of systemic inflammation on the function of central nervous system microglia could be involved in this mediated pathway.^{42,43} While the blood-brain barrier restricts the passage of many immune cells and molecules, senescence-related proinflammatory secretions (included in the senescence-associated secretory phenotype) including cytokines can still exert effects on the brain by interacting with receptors on endothelial cells and other cells at the barrier.⁴³ Maintaining aerobic fitness in aging may help stall the accumulation of senescent cells,¹⁸ preventing proinflammatory states and protecting against blood-brain barrier

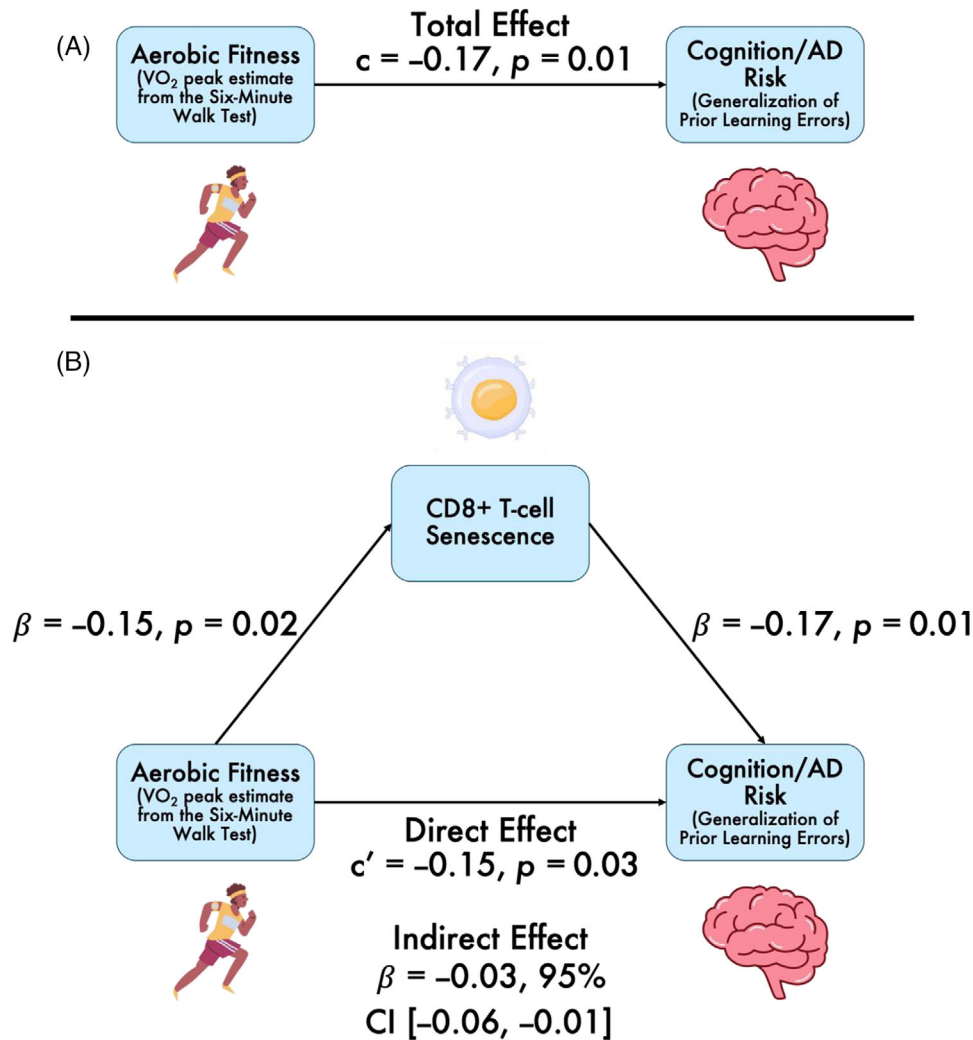


FIGURE 4 Mediation model of the neuroprotection of higher aerobic fitness through lower CD8+ T-cell senescence. (A) Top panel: significant total effect of aerobic fitness and generalization of prior learning errors. (B) Bottom panel: significant direct effect (denoted by c'), which measures the relationship between aerobic fitness and generalization of prior learning errors while controlling for the mediator, CD8+ T-cell senescence. The overall analysis revealed that the total effect of higher aerobic fitness (X) on lower generalization errors (Y) is significant. This effect includes a significant direct path, indicating that increased fitness levels are associated with fewer generalization errors. Additionally, there is a significant indirect effect mediated by T-cell senescence, suggesting that the influence of fitness on generalization partly operates through its effect on CD8+ T-cell senescence. Approximately 15% of the effect of aerobic fitness on generalization errors is mediated by CD8+ T-cell senescence.

intrusions. Animals that engage in exercise exhibit reduced activation of microglia, decreased levels of proinflammatory proteins in the hippocampus, and increased microglial proliferation along with higher expression of neuroprotective factors.⁴⁴ Here, we found that aerobic fitness may reduce AD risk through lower CD8+ T-cell senescence. Taken together, these findings hint at the cost-effective, protective effects of aerobic exercise on both AD risk and aging immune function.

While these are promising results for implications in exercise intervention development, the limitations of the current study include: (1) analyses of fitness, immune function, and cognitive function links were cross-sectional in nature; (2) effects may not generalize to other cohorts of older African Americans and other subsets of the population; and (3) some confounds may have been omitted. Directionality of observed relationships cannot be inferred. Importantly, specific mech-

anisms of how aerobic fitness influences immunosenescence, which in turn affects cognitive function, have yet to be elucidated.

Future longitudinal and interventional studies can help elucidate the temporality and underlying mechanisms of fitness, cognitive function, and immune function relationships. Additionally, it may be beneficial to explore not only VO₂ estimates but also raw 6-min walk test distance data⁴⁵ and the energetic cost of walking,⁴⁶ as these measures can complement our understanding of aerobic fitness in relation to cognitive/AD risk outcomes.

Furthermore, the sample was recruited from only the greater Newark area, so findings may not generalize to other African American communities. There was an underrepresentation of male participants (22.9%) relative to the sex ratio in greater Newark (2:1 women to men [33.3% men]⁴⁷). Contrary to some extant research,¹⁷ there were no

significant differences between women and men on T-cell senescence or generalization performance in the current study. Future studies should strive for a balanced or representative ratio of women to men, allowing for a more comprehensive examination of sex as a biological variable.

Finally, there is a growing appreciation of metabolic conditions such as diabetes² that may contribute to AD risk and are related to fitness and immune function. The association of diabetes with dementia may also be mediated by several pathways leading to increased vascular contributions to impairment and dementia (VCID), including via vasoconstriction affecting cerebrovasculature and via neuroinflammation.⁴⁸ While other such factors were outside the scope of the current analysis (we only controlled for age, sex, education, and WHR), future studies may consider adding medical comorbidities to analyses. Despite these limitations, the study also had the following strengths: (1) data were from the ABHA study, one of the largest, most deeply phenotyped studies of older African Americans; (2) *post hoc* achieved statistical power was excellent at 99%; (3) the use of a non-invasive field test of aerobic fitness via the 6-min walk test; and (4) the use of newer age CD8+ T-cell senescence and cognitive markers that may be more sensitive to fitness variations.

The novel CD8+ T-cell senescence marker we used here has both biological significance and practical applicability. Unlike other markers often associated with senescence or exhaustion (e.g., CD57, PD1), CD8+ T cells with high SA- β Gal activity do not overlap significantly with these markers, establishing a unique cellular state distinct from traditional T-cell exhaustion.¹³ Furthermore, CD8+ T cells exhibit a dramatic increase in high SA- β Gal activity with age (from 30% in younger donors in their 20s to 64% in older participants 60+), making this marker a clear and quantifiable indicator of senescence in aging populations¹³ (while other senescence markers show little variation with chronological or biological aging⁴⁹). Given its role in cytotoxic immunity and biological aging, strategies to monitor and modulate CD8+ T-cell senescence could hold promise for improving health outcomes – including fitness and cognitive health – in aging populations.⁵⁰ Nevertheless, future studies may still consider including canonical markers of senescence (e.g., *p16^{INK4a}*) to provide a more comprehensive view of the senescence landscape in CD8+ T cells.

5 | CONCLUSION

Current findings highlight the importance of aerobic exercise and exercise-related fitness improvements in African Americans ages 60 and older. One mechanism by which fitness may attenuate AD risk is through reduced accumulation of senescent CD8+ T cells. Exercise presents a cost-effective and safe non-pharmacological strategy to delay immune aging and, in turn, pathological cognitive aging. However, exercise interventions should be designed to fit various subpopulations in diverse socio-environmental contexts, particularly targeting those at higher risk for AD, including African American communities.

AUTHOR CONTRIBUTIONS

Bernadette A. Fausto: Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Validation, Formal Analysis, Visualization, Writing – original draft. **Elizabeth Akbulut:** Conceptualization, Data Curation, Investigation, Methodology, Project Administration, Supervision, Validation, Formal Analysis, Visualization, Writing – original draft. **Mustafa Z. Sheikh:** Conceptualization, Data Curation, Investigation, Methodology, Project Administration, Supervision, Validation, Formal Analysis, Visualization, Writing – original draft. **Diana Grass:** Investigation, Methodology, Supervision, Formal Analysis, Validation, Writing – review and editing. **Nica Aquino:** Data Curation, Investigation, Methodology, Formal Analysis, Supervision, Validation, Writing – review and editing. **Luis Garza-Martinez:** Data Curation, Investigation, Methodology, Formal Analysis, Supervision, Validation, Writing – review and editing. **Fanyu Hercules-Tawe:** Investigation, Methodology, Writing – review and editing. **Stephanie Ghaly:** Investigation, Methodology, Writing – review and editing. **Alicia Codrington:** Investigation, Methodology, Project Administration, Supervision, Validation, Writing – review and editing. **Andrew Gamil:** Investigation, Methodology, Writing – review and editing. **Imran Arshad:** Investigation, Methodology, Writing – review and editing. **Darian Napoleon:** Investigation, Methodology, Writing – review and editing. **Robert Perna:** Investigation, Methodology, Writing – review and editing. **Victoria Paruzel:** Investigation, Methodology, Software, Writing – review and editing. **Mark A. Gluck:** Investigation, Methodology, Project administration, Software, Supervision, Validation, Resources, Funding Acquisition, Writing – review and editing. **Patricia Fitzgerald-Bocarsly:** Investigation, Methodology, Project Administration, Supervision, Validation, Writing – original draft

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the [supporting information](#)

DATA AVAILABILITY STATEMENT

The dataset, codebook, and statistical codes are publicly available for download at the following Open Science Framework repository: https://osf.io/453un/?view_only=76a8c8e261a646f099b5ae03f2df9069.

CONSENT STATEMENT

All human subjects provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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