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RESEARCH ARTICLE

Cardiorespiratory fitness and cognition in persons at risk for Alzheimer's disease

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Abstract

Introduction: This study examined the relationship between cardiorespiratory fitness (CRF) and longitudinal cognitive functioning in a cohort enriched with risk factors for Alzheimer's disease (AD).

Methods: A total of 155 enrollees in the Wisconsin Registry for Alzheimer's Prevention completed repeat comprehensive neuropsychological evaluations that assessed six cognitive domains. Peak oxygen consumption (VO₂peak) was the primary measure of CRF. Random effects regression was used to investigate the effect of CRF on cognitive trajectories.

Results: Higher CRF was associated with slower decline in the cognitive domains of verbal learning and memory ($P < .01$) and visual learning and memory ($P < .042$). Secondary analyses indicated that these effects were stronger among men than women, and for noncarriers of the apolipoprotein E $\epsilon 4$ allele.

Discussion: Higher CRF was associated with a slower rate of the decline in episodic memory that occurs as a natural consequence of aging in a cohort enriched with risk factors for AD.

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KEYWORDS

aging, cognition, episodic memory, exercise test, humans, neuropsychological tests

1 | BACKGROUND

The aging of populations around the world has led to an increase in the prevalence of Alzheimer's disease (AD). In the United States alone, the number of people expected to have AD may reach 13.8 million by 2050.¹ This projection has led to an intensification of research aimed at investigating modifiable factors that may delay the onset of symptoms related to the progression of AD.

Cognition is known to decline with normal cognitive aging and even more so in those with AD.²⁻⁴ Although decreases in performance across cognitive domains such as memory, processing speed, attention, language, executive function, and visuospatial ability have been observed in normal cognitive aging, these are not necessarily indicative of a neurodegenerative process.^{2,5,6}

Whereas physical activity is any bodily movement that results in energy expenditure, cardiorespiratory fitness (CRF) is the ability of the circulatory and respiratory systems to supply oxygen to the musculoskeletal system during sustained physical activity, and has been found to be associated with cognitive benefits in older populations.⁷⁻¹² Lower CRF in older populations has also been associated with greater cognitive decline over time.^{11,13} However, not all studies have come to the same conclusion. One review of studies involving aerobic activities aimed at improving CRF failed to find cognitive benefits in healthy older adults.¹⁴ Others have shown that aerobic exercise interventions may indeed slow cognitive decline in individuals with AD.¹ This discrepancy between the potential benefits of CRF on cognition may become clearer with additional longitudinal research on cognitive change. With the expected rise in AD prevalence, strategies to alter the prospective course of cognitive change in those at risk for developing AD have become a critical focus for research. Further insights into early cognitive change may highlight points of intervention to slow the progression of AD-related cognitive decline.

When investigating the impact of CRF on cognition in a population at risk for AD, it is important to consider individual differences that may impact cognition and CRF. There is strong evidence that CRF differs between sexes, with males showing higher CRF on average.^{15,16} Additionally, sex-dependent differences have been observed when investigating the linkage between CRF and cognition.^{8,17} Although carriage of the apolipoprotein E (APOE) ϵ 4 allele is associated with increased risk of cognitive impairment and decline,¹⁸ this impact of APOE ϵ 4 carriage has been shown to potentially be altered by behavioral choices.¹⁶ Together, these present an opportunity to investigate how lifestyle strategies may differentially impact certain subpopulations.

Accordingly, the objective of this study was to investigate the impact of CRF on cognition over time, in a population with heightened risk for AD.¹⁹ Peak oxygen consumption (VO_{2peak} , ml/kg/min), the "gold standard" for measuring CRF, was used as our fitness metric.¹² Consis-

tent with the principles of cognitive reserve and resistance to AD, we hypothesized that individuals with higher CRF would exhibit preserved cognitive function over time compared to their less fit peers.^{20,21} As secondary analyses, we also investigated the extent to which our initial findings differed across strata defined by sex and carriage of the APOE ϵ 4 allele.

2 | METHODS

2.1 | Participants

One hundred fifty-five participants enrolled in the Wisconsin Registry for Alzheimer's Prevention (WRAP) were included in this study. WRAP is a longitudinal, observational study established in 2001 and currently includes >1500 individuals who were cognitively normal and between the ages of 40 and 65 at study entry.^{19,22} WRAP participants undergo their first follow-up visit 4 years after the baseline visit, with subsequent visits occurring every 2 years thereafter. All participants are diagnostically characterized in standardized, multidisciplinary, consensus conference wherein cognitive normalcy is determined on the basis of intact performance (typically above -1.5 standard deviation [SD] normative thresholds) on a battery of cognitive tests, absence of neurologic/psychiatric conditions that might impair cognition as determined by a licensed clinician, and preserved functional abilities based on self or informant reports.²² The WRAP cohort is enriched with risk factors for AD including family history of AD and/or APOE ϵ 4 carriage. APOE ϵ 4 genotype was determined using competitive polymerase chain reaction-based assays (LGC Genomics).²² APOE ϵ 4+ status was defined as carrying one or two copies of the ϵ 4 allele.

Participants for this report were selected based on completion of repeated neuropsychological evaluation and a valid graded exercise test (GXT). All study procedures were approved by the University of Wisconsin Institutional Review Board and each participant provided informed consent prior to study participation.

2.2 | Graded exercise test

A continuous GXT was performed on a treadmill (Trackmaster TMX428CP, Full Vision Inc.), using a modified Balke protocol, to assess CRF after a 12-hour fast from nicotine caffeine, alcohol, and medication (prescription and over the counter).²³ Participants refrained from exercise on the day of the test. The GXT was administered by a certified exercise physiologist and supervised by a physician. During a short warm-up period at 0% incline, a quick, yet comfortable, walking speed was determined prior to exercise testing as a safety measure. For

RESEARCH IN CONTEXT

- Systematic Review:** The authors reviewed current literature using commonly used databases (PubMed, etc.), publications, and print resources. This search indicated a dearth of information on cardiorespiratory fitness (CRF) and longitudinal cognitive change in cohorts at risk for Alzheimer's disease (AD). Relevant sources are discussed and cited.
- Interpretation:** Our findings contribute to the literature that suggests that efforts aimed at improving CRF may potentially be a point of intervention to promote cognitive health and potentially protect against future development of AD.
- Future Directions:** The article outlines limitations of the current study that may serve as the foundation for additional studies in the future. These include the need for a more diverse population, longitudinal measurements of CRF, and investigating possible early cognitive changes that may be incipiently altering lifestyle choices.

HIGHLIGHTS

- Longitudinal evaluation of cognition.
- Higher cardiorespiratory (peak oxygen consumption) fitness slowed age-related cognitive decline.
- Cohort with heightened risk for Alzheimer's disease was examined.

those able to, a walking speed of 3.5 miles per hour was used throughout the test. Every 2 minutes, the treadmill incline was increased by 2.5% until the participant reached volitional exhaustion or the exercise physiologist stopped the test due to safety concerns. Continuous measurements of oxygen uptake (VO_2), carbon dioxide production, minute ventilation (VE), work rate, and heart rate were obtained using a metabolic cart and two-way non-rebreathing valve (TrueOne® 2400; ParvoMedics). The metabolic cart was calibrated prior to each test using standard gases with known concentrations within a calibrated three-liter syringe. Heart rate was continuously measured through a twelve-channel electrocardiogram device (Schiller CS-200; Exercise Stress System) and rating of perceived exertion (RPE) was assessed during the last 30 seconds of each stage. After volitional exhaustion, treadmill speed was reduced to 2 miles per hour at 0% incline for a 3-minute cool down period. Given that WRAP is a longstanding study with rolling enrollment, and that GXT was implemented as part of an ancillary study, participants completed their GXT at different points in time in their WRAP participation, not necessarily at their baseline WRAP visit.

TABLE 1 Cognitive factors and their component tests

Cognitive factor	Cognitive tests
Immediate memory	Rey Auditory Verbal Learning Test—trials 1 and 2 ⁴⁷
Verbal learning and memory	Rey Auditory Verbal Learning Test—trials 3–5, and delayed recall ⁴⁷
Speed and flexibility	Trails A time, Trails B time, number named for Stroop Color-Word ^{48,49}
Working memory	Digit span forward, digit span backward, and letter-number sequencing subsets of Wechsler Adult Intelligence Scale III ⁵⁰
Visual learning and memory	Brief visuospatial memory test—total learning and delayed recall ⁵¹
Story recall	Logical memory test I (immediate recall) and II (delayed recall) ⁵²

Peak effort was determined using criteria set by the American College of Sports Medicine.¹² Specifically, peak effort was reached if the participant met two of the following criteria: respiratory exchange rate ≥ 1.15 , change in $\text{VO}_2 < 200$ ml with an increase in work, RPE ≥ 17 , and achieving at least 90% of age-predicted maximal heart rate. CRF was indexed as the peak VO_2 (i.e., $\text{VO}_{2\text{peak}}$) when criteria were met. These criteria were used to avoid potential age-driven relationships when volitional effort was not met.²⁴

2.3 | Cognitive evaluation

At each WRAP visit, participants undergo a comprehensive battery of cognitive tests.²² As described in prior publications from our group^{25–28} factor analyses using promax rotation and maximum likelihood estimation²⁹ were used to reduce the set of cognitive measures to a smaller number of factors and obtain weights used to combine the measures within each factor. The six resulting weighted factor scores were then standardized ($\sim N[0, 1]$) into z-scores, using means and standard deviations obtained from the whole baseline sample. The cognitive factors are presented in Table 1.

2.4 | Statistical analyses

Random effects regression was used to investigate whether CRF impacted cognitive performance across visits.³⁰ Random intercept and slope were used with an unstructured covariance structure. The implementation of random effects for the intercept and slope allowed for the fact that each person might have a different “starting point” and a different “rate of change” as is typically the case in longitudinal studies. The “fixed effects” in the model included time (in years since cognitive baseline), $\text{VO}_{2\text{peak}}$, $\text{VO}_{2\text{peak}} \times \text{time}$ interaction, and the following covariates: age, sex, education, beta blocker usage (usage slows down the heart, impacting the readings during the GXT), number of study visits (to adjust for potential practice effects), history of diabetes, and history of depression to account for individual differences in their effects.¹ Our primary term of interest was the $\text{VO}_{2\text{peak}} \times \text{time}$

TABLE 2 Demographic characteristics (N = 155)

Characteristic	Value ^a
Age at baseline (years)	53.7 (6.3)
Female (%)	67.7
Education (years)	16.34 (2.16)
Family history of Alzheimer's disease (%)	69.7
APOE ε4 carriage (%)	37.4
Diabetes (%)	4.5
Depression (%)	28.4
Beta blocker usage (%)	4.5
Body mass index (kg/m ²)	27.54 (5.36)
VO ₂ peak, ml kg ⁻¹ min ⁻¹	26.09 (6.36)
Number of study visits (median) (range)	5.00 (2-6)
Number of Individuals with 2/3/4/5/6 study visits	2/5/14/58/76
Years of follow-up	12.16 (2.39)

^aValues indicate mean (SD), unless otherwise indicated.

Abbreviations: APOE, apolipoprotein E; SD, standard deviation; VO₂peak, peak oxygen consumption.

interaction. A significant interaction would indicate that CRF impacts the rate of change in cognition over time. Last, as secondary analyses, we refitted our original model after stratifying the study sample by APOE ε4 status and sex to investigate the extent to which our findings differed between subgroups of interest.^{17,18,31} All statistical tests were run in IBM SPSS version 26 and findings were considered significant at $P < .05$.

3 | RESULTS

3.1 | Participant characteristics

Most participants had a family history of AD (69.7%) and slightly more than a third were APOE ε4 carriers (37.4%). The sample was 67.7% female, with mean age of 53.7 ± 6.3 . Participants in this study have been enrolled in WRAP for between 4 and 16 years, with a mean of

12.16 years. The median number of visits attended was 5 (range, 2–6). Further demographic characteristics can be found in Table 2.

3.2 | CRF and cognitive trajectories

As summarized in Table 3, a significant VO₂peak x time interaction was detected in the cognitive domains of verbal learning and memory (B [standard error (SE)] = 0.0032 [0.0012], $P < .01$) and visual learning and memory (B [SE] = 0.0028 [0.0014], $P < .042$). To further investigate these findings, we divided the sample into tertiles based on their VO₂peak. The mean (SD) VO₂peak, in ml/kg/min, for the tertiles are as follows: low CRF = 19.89 (2.76), moderate CRF = 25.22 (1.41), high CRF = 33.29 (4.6). Table 4 and Figure 1A and B show the model-predicted longitudinal decline trajectories in each cognitive function for the CRF tertiles. Those with higher CRF had a slower annual decline in their test scores compared to those with lower CRF for both verbal learning and memory (–0.18, –0.16, –0.13 unit change per year for low, moderate, and high CRF, respectively) and visual learning and memory (–0.071, –0.055, –0.034 unit change per year for low, moderate, and high CRF, respectively). No significant CRF effect was found on the longitudinal change rate for the other cognitive domains (Table S1 in supporting information).

3.3 | Secondary analyses

Table 5 displays the results from the stratified analyses. For the APOE ε4 stratification, the VO₂peak x time interaction reached the prespecified 0.05 threshold within the APOE ε4– group for the verbal learning and memory domain ($P = .043$). When stratifying by sex, the only significant VO₂peak x time interaction was found among male participants for verbal learning and memory domain ($P = .009$).

4 | DISCUSSION

In this study, we found that in a middle-aged cohort enriched with risk factors for AD, higher CRF was associated with a slower decline in

TABLE 3 Association between CRF and prospective cognitive functioning

Effect	Time		VO ₂ peak		Time x VO ₂ peak		R ² (%)
	B (SE)	P	B (SE)	P	B (SE)	P	
Immediate memory	–0.14 (0.083)	.088	–0.00034 (0.016)	.983	0.00028 (0.0017)	.871	0.2
Verbal learning and memory	–0.24 (0.063)	.001	–0.030 (0.013)	.021	0.0032 (0.0012)	.010	22.2
Speed and flexibility	–0.085 (0.058)	.147	0.0043 (0.013)	.737	0.0011 (0.0011)	.298	3.3
Working memory	0.012 (0.053)	.813	–0.0029 (0.016)	.855	–0.000006 (0.00093)	.995	0
Visual learning and memory	–0.13 (0.072)	.079	–0.030 (0.015)	.046	0.0028 (0.0014)	.042	15.3
Story recall	–0.078 (0.072)	.279	–0.0016 (0.015)	.917	0.00008 (0.00014)	.954	0

Abbreviations: CRF, cardiorespiratory fitness; SE, standard error VO₂peak, peak oxygen consumption.

†In addition to time, VO₂peak, and time x VO₂peak, the models included the following covariates: age, sex, education, beta blocker usage, number of study visits, history of diabetes, and history of depression.

TABLE 4 Model-predicted longitudinal decline trajectories in verbal and visual learning and memory at low, moderate, and high levels of CRF

Cognitive outcome	CRF level	Intercept (baseline scores)			Slope (rate of change per year)		
		B	SE	P	B	SE	P
Verbal learning and memory	Low	1.17	0.61	.057	-0.18	0.056	.002
	Moderate	1.00	0.60	.095	-0.16	0.055	.005
	High	0.76	0.59	.202	-0.13	0.057	.021
Visual learning and memory	Low	1.78	0.72	.015	-0.071	0.065	.272
	Moderate	1.61	0.71	.023	-0.055	0.064	.387
	High	1.38	0.70	.050	-0.034	0.066	.609

Abbreviations: CRF, cardiorespiratory fitness; SE, standard error; VO₂peak, peak oxygen consumption.

†The table presents model-predicted longitudinal cognitive trajectories at low, moderate, and high tertile levels of VO₂peak, respectively. The covariates included age, sex, education, beta blocker usage, number of study visits, history of diabetes, and history of depression.

cognition over time. This finding was specifically within the cognitive domains of verbal learning and memory and visual learning and memory. Given that increased physical activity is a key means of favorably altering CRF,³² these findings help contribute to the literature that suggests that physical activity aimed at improving CRF may potentially be a point of intervention to delay symptoms common to AD.

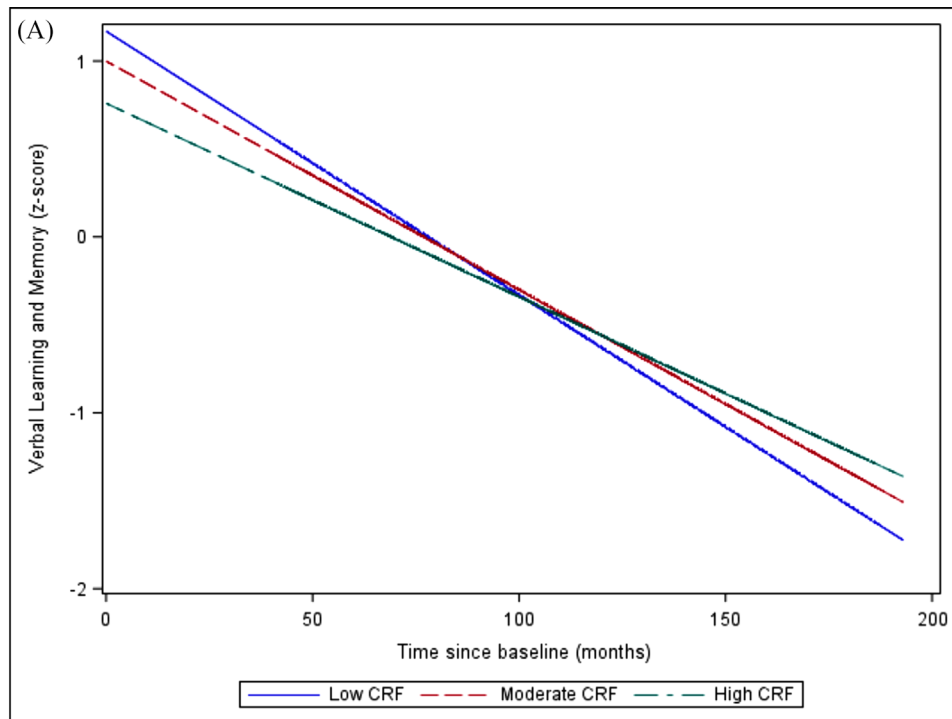
Graphical exploration of our findings revealed that individuals with higher CRF exhibited a slower decrease in their test scores for the two significant cognitive domains of verbal and visual learning and memory (see Figure 1A,B). Specifically, the rate of change in both verbal learning and memory (low CRF = -0.18, moderate CRF = -0.16, high CRF = -0.13) and visual learning and memory (low CRF = -0.071, moderate CRF = -0.055, high CRF = -0.034), shows that more physically fit individuals saw a lower yearly decrease in cognitive performance. One interpretation of this finding may be that individuals with higher CRF may retain the ability to benefit from practice across repeated exposures, unlike their less fit peers. Previous studies have found evidence that absence of practice effects may be a possible marker of early cognitive changes.^{33,34} In our study, we found that the number of repeat exposures to the testing occasion was a significant predictor of performance on both verbal learning and memory (B [SE] = 0.49 [0.14], $P < .001$) and visual learning and memory (B [SE] = 0.32 [0.16], $P = .044$). The observation that the low fit individuals had a faster decrease on these two cognitive domains therefore potentially indicates an absence of benefits from practice. However, given that we controlled for interindividual differences in repeat exposure in our analyses, it is possible that our findings are not fully explained by repeat exposure to the test material, but through alternative means in which CRF is involved. This conclusion is further supported by the fact that the CRF tertiles did not differ in number of study visits attended (mean number of visits = 5.35 for low CRF, 5.37 for moderate CRF, and 5.22 for high CRF).

Our results are consistent with previous studies that documented the benefits of higher CRF on cognitive outcomes.^{13,35-37} For example, Barnes et al. found that in an older population (mean age of 69 years), higher CRF at baseline was associated with less cognitive decline over 6 years.¹³ Zhu et al. found that CRF in young adulthood was predictive of cognitive function 25 years later.³⁶ Our sample was younger

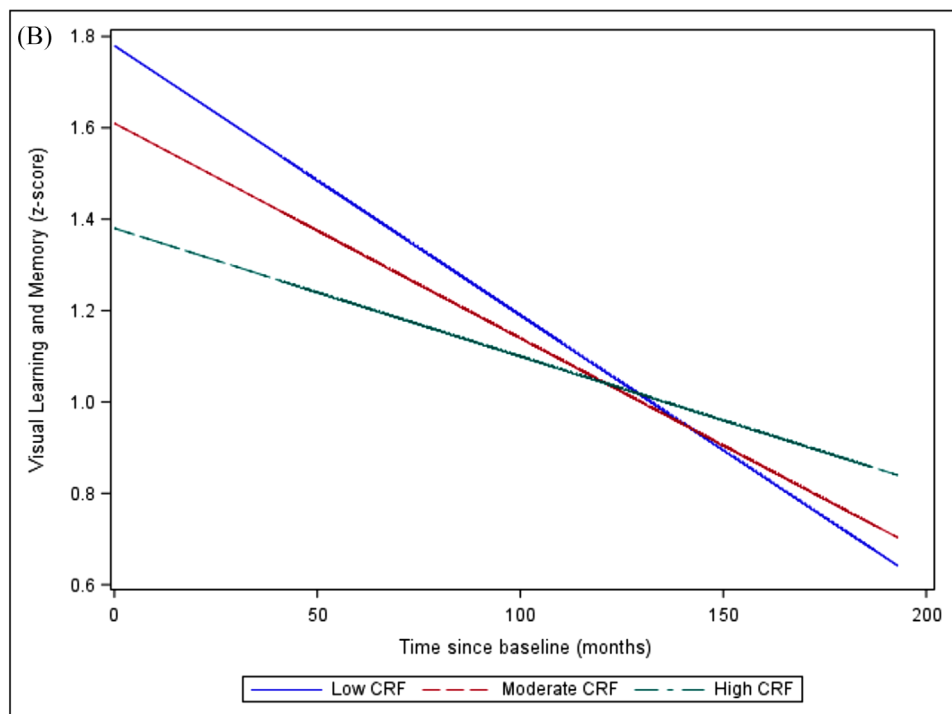
than that of Barnes et al. but older than Zhu et al., and the cohort our participants were drawn from are selected for heightened risk of AD, based on family history and APOE $\epsilon 4$ carriage, compared to the general population. Nonetheless our findings are in line with these prior works and underscore the beneficial role that CRF has with respect to clinically relevant cognitive outcomes. Our results are also consistent with our group's recent study that found WRAP participants with higher baseline CRF showed slower annual decline in total gray matter and cognitive function.³⁷ Interestingly, our findings are only limited to episodic memory, which is the earliest cognitive domain to be impacted by AD.¹ Perhaps longer periods of observation may be needed to witness changes in other cognitive domains.

In our stratified analyses further exploring the two significant cognitive factors, we found a significant VO₂peak x time interaction on verbal learning and memory for APOE $\epsilon 4$ - individuals, when stratifying by APOE $\epsilon 4$ status. When stratifying by sex, men retained a significant interaction for verbal learning and memory. Specifically, among men, there was a heightened positive effect of having higher CRF on the rate of change for verbal learning and memory over time. These findings suggest that there may be potentially different effects of CRF on longitudinal cognition between the sexes and based on carriage of the APOE $\epsilon 4$ allele.^{16,37} That said, it should be noted that the APOE $\epsilon 4$ - group was about twice the size of the APOE $\epsilon 4$ + group, which may have played a role in the differential APOE $\epsilon 4$ effect. Further studies are necessary for more fully understanding these preliminary findings.

Some potential mechanisms behind our findings may involve improved cerebrovascular health. Higher CRF is associated with many cerebrovascular benefits including improved arterial compliance, cerebral blood flow, and white matter integrity.³⁸⁻⁴² Additionally, arterial stiffness has been found to be associated with faster cognitive decline and risk of developing dementia in older populations.⁴³ Vascular risk factors, such as hypertension and diabetes, also contribute to the structure and integrity of the brain itself, potentially impacting cognition.^{44,45} Together, these suggest a cascade through which efforts to improve CRF may enhance vascular health and ultimately confer cognitive benefits. Future research in a larger cohort with a broader array of vascular abnormalities is needed to test this potential linkage through formal mediation analyses.



CRF=Cardiorespiratory fitness



CRF=Cardiorespiratory fitness

FIGURE 1 A and B, Higher aerobic fitness was associated with slower decline in prospective memory functioning

TABLE 5 Sex- and APOE ϵ 4-stratified examination of the association between CRF and prospective episodic memory

Effect	Time		VO ₂ peak		Time x VO ₂ peak		R ² (%)
	B (SE)	P	B (SE)	P	B (SE)	P	
Verbal learning and memory (male)	-0.40 (0.11)	.001	-0.070 (0.022)	.003	0.0058 (0.0021)	.009	—§
Verbal learning and memory (female)	-0.18 (0.079)	.024	-0.009 (0.018)	.606	0.0022 (0.0017)	.205	8.02
Visual learning and memory (male)	-0.11 (0.14)	.448	-0.030 (0.027)	.286	0.0023 (0.0028)	.41	13.2
Visual learning and memory (female)	-0.13 (0.086)	.121	-0.024 (0.019)	.197	0.0025 (0.0017)	.154	22.3
Verbal learning and memory (APOE ϵ 4+)	-0.25 (0.096)	.01	-0.038 (0.018)	.041	0.0031 (0.0018)	.093	16.4
Verbal learning and memory (APOE ϵ 4-)	-0.23 (0.085)	.007	-0.029 (0.019)	.127	0.0035 (0.0017)	.043	35.4
Visual learning and memory (APOE ϵ 4+)	-0.26 (0.12)	.028	-0.020 (0.019)	.304	0.0014 (0.002)	.491	36.9
Visual learning and memory (APOE ϵ 4-)	-0.045 (0.097)	.641	-0.036 (0.021)	.088	0.0036 (0.0019)	.071	10.5

Abbreviations: APOE, apolipoprotein E4; CRF, cardiorespiratory fitness; SE, standard error; VO₂peak, peak oxygen consumption.

†In addition to time, VO₂peak, and time x VO₂peak, the models included the following covariates: age, sex, education, beta blocker usage, number of study visits, history of diabetes, and history of depression. Following Singer and Willett,³⁰ R² was calculated as the proportional reduction in the estimated variance of the random slope (i.e., change rate over time) between the models with versus without the time x VO₂peak interaction term. It indicates the percentage of variance in the change rate explained by the interaction.

‡For verbal learning and memory (male), the variance estimate of the random slope was zero, and thus random intercept model was instead selected as the final model. Correspondingly, R² was not calculated.

Our study is not without limitations. Chiefly, the WRAP cohort is largely composed of highly educated, non-Hispanic White individuals harboring specific risk factors for AD; therefore, there is a potential restriction of the generalizability of our results to the larger population. Selection criteria also limits generalizability of the results as only those who were physically able to complete the GXT were included in analyses. Second, the more formal approach to testing sex and APOE ϵ 4 differences on the effects of CRF on cognitive changes would entail fitting three-way interactions (e.g., sex x VO₂peak x time), which would have been underpowered given the study sample size. Therefore, we instead performed stratified analyses, which are a statistically acceptable workaround.⁴⁶ However, stratified analysis might not completely resolve the power issue, given only part of the sample is included in the analysis at any point. Future research with increased sample sizes would be needed for thoroughly evaluating the sex and APOE differences. Also, our CRF measure was from one point in time and may not necessarily represent CRF over the entire duration of observation. Therefore, it would be of interest to collect repeat measurements of CRF to help shed light on whether, and to what extent, changes in CRF track with changes in cognition. In addition, given the number of cognitive measures tested, our analyses are potentially vulnerable to Type I error. Applying a conventional Bonferroni correction would set alpha at 0.008, rendering all associations nonsignificant. Such a correction was deemed overly restrictive but, that said, our findings should be interpreted cautiously. In addition, it is plausible that the cognitive domains not found to have significant VO₂peak x time interactions simply had lesser variability over time in our sample compared to the domains of visual and verbal memory, suggesting possible psychometric limitations within our sample. Last, it is important to acknowledge the alternative possibility that the individuals with low CRF may already be experiencing the sequelae of incipient cognitive decline. In other words, rather than low CRF being the driver of poorer cognition, it is possible that awareness of very subtle cognitive changes might lead

some individuals to gradually refrain from certain lifestyle behaviors (such as physical activity) that are beneficial for CRF and cognition.

5 | CONCLUSION

We found that in a middle-aged cohort enriched with risk factors for AD, higher CRF was associated with slower decline in cognitive performance in the domain of episodic memory. These findings contribute to the literature that suggests that efforts aimed at improving CRF may potentially be a point of intervention to promote cognitive health and potentially protect against future development of AD.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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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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