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Original Research

Relations Between Cardiorespiratory Fitness and Cognition in Older Adults With Amnestic Mild Cognitive Impairment From the Aerobic Exercise and Cognitive Training (ACT) Trial: Sex Differences

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KEYWORDS
Alzheimer disease;
Cardiorespiratory fitness;
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Abstract *Objective:* To examine the associations of cardiorespiratory fitness with executive function, episodic memory, and global cognition and sex differences in these associations in community-dwelling older adults with amnestic mild cognitive impairment.
Design: A cross-sectional study using baseline data from the aerobic exercise and cognitive training (ACT) trial.
Setting: The ACT trial conducted exercise testing in an exercise laboratory and data collections in a research facility.
Participants: ACT trial participants were recruited through referrals, registries, exhibits, flyers, media, and advertisements and screened for eligibility. To be eligible for this study, ACT enrollees needed complete data on all study variables. Among 146 ACT enrollees, 142 met eligibility for this study (N=142).
Interventions: None.

List of abbreviations: ACSM, American College of Sports Medicine; ACT, aerobic exercise and cognitive training; AD, Alzheimer disease; CRF, cardiorespiratory fitness; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; SE, standard error; Vo_{2peak}, peak oxygen consumption.

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Main Outcome Measures: Cardiorespiratory fitness was measured as peak oxygen consumption (Vo_{2peak}) with a peak cycle-ergometer test, executive function with the EXAMINER, episodic memory with the Brief Visuospatial Memory Test-Revised, and global cognition with Montreal Cognitive Assessment.
Results: The average age of the sample was 73.8±5.8 years with 16.9±2.9 years of education, with 87.3% White, 51.4% men, and 69.7% married. After controlling for covariates, Vo_{2peak} was significantly related to executive function (*b*=.037, standard error [SE]=0.015, *P*=.0154, semipartial [*sr*] correlation coefficient=.239) and episodic memory (*b*=.590, SE=0.226, *P*=.0102, *sr*=.216), but not global cognition (*b*=.074, SE=0.055, *P*=.1837, *sr*=.125). For men, Vo_{2peak} was significantly associated with executive function (*b*=.063, SE=0.024, *P*=.0099, *r*=.430) and episodic memory (*b*=1.088, SE=0.312, *P*=.0009, *r*=.382).
Conclusions: Our findings show that Vo_{2peak} was associated with executive function and episodic memory in the overall sample and in men. Future studies can examine the longitudinal relations between cardiorespiratory fitness and cognition.

Alzheimer disease (AD) and related dementias affect 6.3 million Americans and will inflict 14 million Americans and cost >$1.1 trillion by 2050. Extensive epidemiologic evidence has linked physical activity and exercise to reduced risk of AD.[1,2] A potential mechanism underpinning the cognitive benefits from physical activity and exercise is cardiorespiratory fitness (CRF). Greater CRF was associated with better cognition,[3] executive function,[4] and short-term memory[5] in healthy older adults. Moreover, greater CRF was linked to reduced hippocampal volume loss measured with magnetic resonance imaging (MRI) among healthy older adults.[6] Among older adults with amnestic mild cognitive impairment (MCI), higher CRF was associated with higher gray matter volume, mostly in the frontal superior cortex, and fewer white matter abnormalities.[7] A recent study divided a sample of 649,605 U.S. veterans into 5 fitness groups; incident AD and related dementias rank the highest in the least-fit group and reduce as CRF increases for the low-fit, moderate-fit, fit, and high-fit groups at 0.87, 0.80, 0.74, and 0.67 person-years, respectively.[8]

Understanding the role of CRF in cognitive changes in older adults with MCI and by sex are critical areas of research. Interindividual differences in CRF responses to exercise interventions have been established in younger adults[9] and reported recently in older adults with AD dementia.[10] Moreover, in other populations such as young and middle-aged adults and conditions such as cancer, human immunodeficiency virus infection, and obesity, CRF has been proposed and, in some cases, tested as a tailoring variable to personalize exercise prescription in the precision exercise approach to maximize exercise's effects on identified outcomes.[11]

Sex differences in CRF and AD have been well established. Women differ from men in their CRF levels; for example, CRF values of elite female athletes are ~10% lower than those seen in men of similar elite status expressed as maximum oxygen consumption in mL/kg/min.[12] Women are also at a greater risk of AD than men and experience a greater deterioration of cognition than men at the same stage of AD across a broad range of cognition including episodic, verbal, and visuospatial memory.[13] In contrast, some studies showed a processing or executive function advantage for healthy women. These differences may be attributable to differences in cognitive reserve, resilience, genetics, and functional and structural brain changes in women in comparison with men.[14] However, sex differences have not been well integrated into precision exercise approaches.

The purpose of this study was to examine the associations of CRF with executive function, episodic memory, and global cognition and sex differences in these associations in community-dwelling older adults with amnestic MCI. Baseline data from the aerobic exercise and cognitive training (ACT) trial that tests the cognitive effects and mechanisms of 6-month combined aerobic exercise and cognitive training were used. We hypothesized that higher CRF is associated with greater executive function, episodic memory, and global cognition and that these associations are stronger in women than in men.

Methods

Design

This study used a cross-sectional design of baseline data from the ACT trial, which tests the efficacy and mechanisms of a 6-month ACT intervention in older adults with amnestic MCI (ClinicalTrials.gov Identifier: NCT03313895; date of registration: October 18, 2017). The ACT trial was approved by the institutional review board at each site. Details of the trial protocol were previously published.[15]

Setting

Over-the-phone screening and medical clearance were conducted at research offices. In-person interviews and data collections occurred in a private room at the clinical research facility. CRF testing was performed in exercise laboratories and supervised by a physician or nurse practitioner.

Participants

A comprehensive recruitment plan was implemented to proactively recruit participants, including referrals by community partners such as YMCAs, clinics, and senior facilities; research registries; presentations; exhibits at local events; media outreach such as Facebook; press release; and newspaper advertisement.

The inclusion criteria were education-corrected Montreal Cognitive Assessment (MoCA) score of 18-26, >1 SD below age- and/or education-corrected population norms on Rey Auditory Verbal Learning test, preserved activities of daily living, absence of dementia, community-dwelling, age of ≥65 years, English-speaking, adequate visual acuity, verified exercise safety by health care providers, >3 months on drugs affecting cognition, verified MRI safety, and capacity to give consent. The exclusion criteria were Geriatric Depression Scale score of >5 with contextual evidence suggesting unstable major depression or psychiatric disorders; resting heart rate of ≤50 or ≥100 beats/min; neurologic, psychiatric, or substance dependency in the past 5 years; American College of Sports Medicine (ACSM) contraindications to exercise; new symptoms or diseases; abnormal electrocardiogram findings during exercise testing; current enrollment in an intervention study; and abnormal MRI findings.

Of the 1149 respondents, we were able to reach 707 to complete over-the-phone screening, and 146 met the eligibility criteria for enrollment in the ACT trial. To be included in this study, ACT enrollees must have complete data on all study variables, resulting in a final sample size of 142.

Variables and measures

The independent variable was CRF. The dependent variables included executive function, episodic memory, and global cognition. Potential covariates included demographics, body mass index, comorbidities, AD medications, activities of daily living, depression, and premorbid intellect. Data were collected by trained staff blinded to the study aims to reduce bias.

Independent variable

CRF was measured by peak oxygen consumption (Vo_{2peak}) in a symptom-limited peak cycle-ergometer test that was initially developed based on the ACSM protocol and tested in our previous studies of older adults with AD.[16,17] After sitting quiet for 5 minutes, the participant began to cycle on a recumbent stationary cycle at 40-60 rpm. The intensity was increased at 1 metabolic equivalent (3.5 mL oxygen/kg body weight/min) every 3 minutes until the participant fatigued or met >2 ACSM maximum test criteria. Peak Vo_2 and hemodynamic responses such as heart rate were continuously monitored via electrocardiogram and indirect calorimetry. Borg Rating of Perceived Exertion was administered, and it assessed blood pressure checked during the last minute of each stage and at peak exercise.

Dependent variables

Executive function was measured using the EXAMINER (Joel H. Kramer at UCSF), a computerized test package designed for randomized controlled trials. It calculates 3 subdomain composite scores on working memory, cognitive control, and fluency and an overall composite score for executive function.[18] Test-retest reliabilities are 0.78-0.93.[19]

Episodic memory was assessed using the Brief Visuospatial Memory Test-Revised. The Brief Visuospatial Memory Test-Revised is a visual test of learning and episodic memory. Participants were shown 6 figures for 10 seconds and asked to draw the figures from memory afterward. Participants repeated viewing and drawing for a total of 3 times. A learning score was calculated by summing the total number of figures accurately drawn by participants. Next, participants were asked to recall and redraw the figures after a 25-minute delay, and a delayed recall score was also calculated based on the number of figures accurately recalled. Interform reliability and the construct and criterion-related validity have been supported in studies using various samples.[20]

Global cognition was measured using MoCA. MoCA assesses different cognitive domains including attention and concentration, executive functions, language, visuoconstructional skills, conceptual thinking, orientation, and calculations. It is scored 0-30, adjusted by educational level. MoCA's inter-rater reliability was 0.96.[21]

Potential covariates

Demographics included age, sex, race, and education. Body mass index was a participant's weight in kilograms divided by the square of height in meters. Comorbidities reflected the sum of all chronic conditions. Use of AD medications was dichotomized as yes or no. Daily functioning was assessed by Activities of Daily Living-Prevention Instrument. Depression was measured by the Geriatric Depression Scale. Premorbid intellect was assessed using the Wechsler Test of Adult Reading.[22]

Power and data analysis plan

Given α=0.05 and 10% of outcome variation due to covariates, a sample size of 140 achieved >0.80 power to detect a small proportion of outcome variation uniquely because of Vo_{2peak} (ie, ΔR^2=0.049). We first examined basic descriptive statistics, frequencies, and various plots. No excessive multicollinearity was present.

Differences between women and men on all study variables were assessed by Satterthwaite's (ie, unequal variance) independent-samples *t* test and Fisher exact test, respectively. For each cognitive outcome, we estimated 2 regression models: the first model included Vo_{2peak} only, and the second model further included the covariates for the overall sample and each sex. Consistent with study hypotheses, the primary statistics of interest were the estimate and significance test of the regression coefficient for Vo_{2peak} as well as corresponding measures of effect, specifically Pearson (*r*) and the semipartial (*sr*) correlation coefficients. Exploratory analyses were performed similarly for the subdomains of executive function. SAS, version 9.4, was used for all analyses, and the regression models were estimated with a robust standard error (SE) method (known as HC3).[23-25]

Results

Participant characteristics

The sample had a mean age ± SD of 73.8±5.8 years, education of 16.9±2.9 years, and Vo_{2peak} of 17.09±4.96 mL/kg/min, with 87.3% White non-Hispanic and 51.4% men. More men were married (83.6% vs 55.1%) and older (74.8 vs 72.7y), with more years of formal education (17.5 vs 16.2) and greater Vo_{2peak} (18.4 vs 15.8mL/kg/min) than women (table 1).

Relations of Vo_{2peak} with executive function

With no covariates in the model, Vo_{2peak} was positively related to executive function for the overall sample (*b*=.022, SE=0.008, *P*=.0108, *r*=.195) and for men (*b*=.043, SE=0.013, *P*=.0021, *r*=.377) but not for women (*b*=.015, SE=0.011, *P*=.1904, *r*=.126; table 2). With covariates in the model, Vo_{2peak} was positively related to executive function for the entire sample (*b*=.037, SE=0.015, *P*=.0154, *sr*=.239) and for male participants (*b*=.063, SE=0.024, *P*=.0099, *sr*=.430) but not for female participants (*b*=.006, SE=0.015, *P*=.6895, *sr*=.038; table 3). With the covariates in the model, women had greater executive function than men (*b*=.284, SE=0.137, *P*=.0400; table 3).

Relation of Vo_{2peak} with episodic memory

With no covariates in the model, Vo_{2peak} was not related to episodic memory for the entire sample (*b*=.255, SE=0.157, *P*=.1072, *r*=.126), women (*b*=.152, SE=0.207, *P*=.4655, *r*=.077), or men (*b*=.322, SE=0.263, *P*=.2258, *r*=.146; table 2). However, when the covariates were included, Vo_{2peak} was positively related to episodic memory for the entire sample (*b*=.590, SE=0.226, *P*=.0102, *sr*=.216) and for men (*b*=1.008, SE=0.312, *P*=.0009, *sr*=.382) but not for women (*b*=.085, SE=0.283, *P*=.7640, *sr*=.032; table 3).

Relations of Vo_{2peak} with global cognition

With no covariates in the model, Vo_{2peak} was not related to global cognition for the entire sample (*b*=.036, SE=0.037, *P*=.3198, *r*=.084), women (*b*=.036, SE=0.045, *P*=.4341,

Table 1 Characteristics of the sample

Variable	Overall (N=142) Mean ± SD or n (%)	Female (n=69) Mean ± SD or n (%)	Male (n=73) Mean ± SD or n (%)	*P*‡
Covariates				
Age (y)	73.77±5.79	72.67±5.84	74.82±5.58	.026
Race				1.00
White non-Hispanic	124 (87.3)	60 (87.0)	64 (87.7)	
Other*	18 (12.7)	9 (13.0)	9 (12.3)	
Marital status				<.001
Married	99 (69.7)	38 (55.1)	61 (83.6)	
Other†	43 (30.3)	31 (44.9)	12 (16.4)	
Education (y)	16.86±2.90	16.18±2.73	17.50±2.93	.006
BMI	27.47 (5.15)	26.72 (5.68)	28.19 (4.53)	.093
AD medications				.305
Yes	17 (12.0)	6 (8.7)	11 (15.1)	
No	125 (88.0)	63 (91.3)	62 (84.9)	
Psychological/emotional medications				.137
Yes	39 (27.5)	23 (33.3)	16 (21.9)	
No	103 (72.5)	46 (66.7)	57 (78.1)	
Activities of daily living	17.98±2.86	18.17±3.31	17.79±2.37	.437
GDS	1.88±1.90	1.99±2.07	1.78±1.73	.525
Premorbid intellect	41.14±7.34	41.29±7.67	41.00±7.06	.815
No. of comorbidities	2.87±1.75	2.93±1.53	2.81±1.95	.684
Independent variable				
Vo_{2peak}	17.09±4.96	15.76±4.94	18.35±4.66	.002
Dependent variables				
Executive composite	−0.003±0.56	0.08±.58	−0.08±.53	.073
Episodic memory	46.07±9.99	45.37±7.92	46.74±10.26	.415
Global cognition	23.56±2.15	23.71±2.00	23.41±2.29	.408
Fluency	0.28±0.69	0.44±.65	0.12±.69	.005
Cognitive control	−0.16±0.53	−0.13±.53	−0.18±.52	.563
Working memory	0.11±0.67	0.10±.72	.12±.62	.871

Abbreviations: BMI, body mass index; GDS, Geriatric Depression Scale.

* The other category for the overall sample includes Asian (n=4), Black non-Hispanic (n=7), Hispanic (n=5), and unknown (n=2).

† The other category for the overall sample includes divorced (n=18), widowed (n=14), never married (n=10), and other (n=2).

‡ *P* value for the Satterthwaite (ie, unequal variance) independent-samples *t* test, for numeric variables, or Fisher exact test, for categorical variables, assessing differences between females and males.

Table 2 Simple linear regression results for all outcomes with predictor Vo_{2peak}

Outcomes	All (N=142)			Females (n=69)			Males (n=73)		
	b	SE	*r*	*b*	SE	*r*	*b*	SE	*r*
Vo_{2peak}									
Executive function	.022*	0.008	.195	.015	0.011	.126	.043†	0.013	.377
Episodic memory	.255	0.157	.126	.152	0.207	.077	.322	0.263	.146
Global cognition	.036	0.037	.084	.036	0.045	.088	.060	0.064	.123
Fluency	.021	0.011	.152	.016	0.014	.119	.049†	0.018	.331
Cognitive control	.017*	0.008	.161	.019	0.011	.173	.021	0.013	.188
Working memory	.021*	0.011	.156	.005	0.014	.037	.040*	0.015	.297

NOTE. *b* is the raw score regression coefficient, and *r* is the Pearson correlation coefficient.
* *P*<.05.
† *P*<.01.

r=.088), or men (*b*=.060, SE=0.064, *P*=.3494, *r*=.123; table 2). After the inclusion of covariates, Vo_{2peak} was not related to global cognition for the entire sample (*b*=.074, SE=0.055, *P*=.1837, *sr*=.125), women (*b*=.018, SE=0.094, *P*=.8456, *sr*=.033), or men (*b*=.117, SE=0.090, *P*=.1990, *sr*=.185; table 3).

Relations of Vo_{2peak} with fluency, cognitive control, and working memory

With no covariates in the model, Vo_{2peak} was not related to fluency (*b*=.021, SE=0.011, *P*=.0585, *r*=.152) for the entire sample and for women (*b*=.016, SE=0.014, *P*=.2762, *r*=.119) but was related to fluency for men (*b*=.049, SE=0.018, *P*=.0084, *r*=.331; table 2). When covariates were included, Vo_{2peak} was positively related to fluency for the entire sample (*b*=.053, SE=0.016, *P*=.0015, *sr*=.282) and for male participants (*b*=.083, SE=0.025, *P*=.0019, *sr*=.432), but not for female participants (*b*=.024, SE=0.018, *P*=.1770, *sr*=.135; appendix 1). Women had greater fluency than men (*b*=.528, SE=0.146, *P*=.0004; appendix 1).

With no covariates in the model, Vo_{2peak} was positively related to cognitive control for the overall sample (*b*=.017, SE=0.008, *P*=.0415, *r*=.161) but not for women (*b*=.019, SE=0.011, *P*=.1032, *r*=.173) or men (*b*=.021, SE=0.013, *P*=.1247, *r*=.188; table 2). When covariates were included, Vo_{2peak} was not related to cognitive control for the entire sample or either sex (appendix 1).

With no covariates in the model, Vo_{2peak} was positively related to working memory for the overall sample (*b*=.021, SE=0.01, *P*=.0309, *r*=.156) and for men (*b*=.040, SE=0.015, *P*=.0107, *r*=.297) but not for women (*b*=.005, SE=0.014, *P*=.6972, *r*=.037; table 2). When covariates were included, Vo_{2peak} was not related to working memory for the entire sample or either sex (appendix 1).

Discussion

We examined the relations of CRF with cognition in community-dwelling older adults with amnestic MCI and the effects of sex on these relations. Our findings showed that CRF measured as Vo_{2peak} was associated with executive function and episodic memory after controlling for covariates, and these associations were significant in men but not in women.

Aging-related decline in CRF has long been established. Nationally representative normative data suggest that it decreases at ~1% per year or 10% over 10 years.[26] However, a recent study of the Wisconsin Registry for Alzheimer's Prevention found that Vo_{2peak} declined at ~3% per year or 14.2% over a 5-year period specifically in mid-to-late aged adults who were cognitively unimpaired, although the Vo_{2peak} values of their participants were similar to national normative data (28.26mL/kg/min) at baseline.[27] This finding of accelerated decline in Vo_{2peak} in mid-to-late aged adults could be clinically and scientifically significant in the context of AD, indicating accelerated decline in Vo_{2peak} as a potential early physiological marker of cognitive decline. Our study showed that the Vo_{2peak} levels in our participants who were older adults with amnestic MCI was 17.9±2.72 mL/kg/min. Even after considering that Vo_{2peak} measured on a cycle-ergometer is typically 10%-20% lower than that measured on a treadmill,[28] the Vo_{2peak} levels in our participants were drastically lower than those in the Wisconsin Registry and expected normative values from nationally representative samples. These findings collectively indicate the possibility that older adults with AD may experience a faster decline in Vo_{2peak} during or before the long preclinical phase of AD, which in turn contributes to great cognitive decline, a hypothesis that needs to be tested in future longitudinal studies.

Our findings of the associations of Vo_{2peak} with executive function and episodic memory are likely mediated through changes in brain structure and function. Adults with unimpaired cognition with higher Vo_{2peak} at baseline were found to experience a slower annual decline in total gray matter volume and cognition, but not hippocampal volume, over 3-5 years of follow-up.[29] Moreover, increased CRF was associated with increased brain activations in the left inferior frontal and precentral gyri in older adults with MCI.[30] These brain regions are important for executive function and memory encoding, which may explain the associations of Vo_{2peak} with executive function and episodic memory that we observed in our study.

The associations of CRF with executive function and episodic memory were significant in men only in our study. It has been well established that women have lower CRF[12] and a greater risk of AD than men.[14] Although some studies reported that women also suffer from a greater deterioration of cognition than men at the same stage of AD across a

Table 3 Regression results for the primary outcomes

Predictors	All (N=142)			Females (n=69)			Males (n=73)		
	b	SE	*sr*	*b*	SE	*sr*	*b*	SE	*sr*
Executive function									
Vo_{2peak}	.037*	0.015	.239	.006	0.015	.038	.063*	0.024	.430
Age	−.018	0.012	−.157	−.033	0.017	−.276	−.005	0.017	−.047
Race/ethnicity†	−.055	0.177	−.031	−.085	0.263	−.045	−.032	0.279	−.019
Female‡	.284*	0.137	.200	-	-	-	-	-	-
Married§	.003	0.098	.002	−.044	0.139	−.036	.169	0.148	.112
Education (y)	.023	0.018	.104	.010	0.030	.038	.038	0.028	.193
BMI	.022	0.012	.172	.006	0.015	.039	.025	0.016	.189
AD medications‖	−.311	0.159	−.171	−.909#	0.208	−.420	.036	0.184	.023
Psychological/emotional medications¶	−.146	0.101	−.112	−.299	0.159	−.223	−.052	0.140	−.038
Activities of daily living	−.026	0.016	−.122	−.018	0.021	−.086	−.035	0.027	−.150
GDS	.017	0.023	.051	.021	0.029	.061	.036	0.040	.108
Premorbid intellect	.010	0.006	.115	.015	0.009	.144	.004	0.009	.044
No. of comorbidities	.030	0.025	.086	.005	0.049	.011	.065*	0.031	.204
Intercept	−.384	1.210	-	1.978	1.363	-	−2.101	1.879	-
R^2	.259*	-	-	.427#			.308#	-	-
Episodic memory									
Vo_{2peak}	.590*	0.226	.216	.085	0.283	.032	1.088#	0.312	.382
Age	.078	0.177	.038	−.055	0.248	−.027	.253	0.234	.115
Race/ethnicity†	−1.465	2.876	−.046	−.016	4.007	−.001	−2.660	4.422	−.080
Female‡	1.801	2.245	.071	-	-	-	-	-	-
Married§	1.427	2.052	.060	1.804	2.842	.087	2.422	3.426	.083
Education (y)	.457	0.334	.117	.510	0.680	.114	.718	0.489	.187
BMI	.522¶	0.185	.223	.238	0.286	.101	.732*	0.292	.285
AD medications‖	−2.917	2.640	−.090	−13.876#	3.480	−.380	3.205	2.827	.105
Psychological/emotional medications¶	−.323	1.831	−.014	.574	2.746	.025	−1.728	2.468	−.066
Activities of daily living	−.041	0.303	−.011	.833*	0.367	.241	−1.003	0.539	−.219
GDS	−.013	0.524	−.002	−.670	0.713	−.118	.285	0.953	.044
Premorbid intellect	.098	0.114	.063	−.032	0.203	−.018	.100	0.178	.061
No. of comorbidities	1.060	0.562	.170	−.315	1.010	−.045	1.760*	0.672	.286
Intercept	1.746	18.824	-	21.845	27.903	-	−16.882	22.821	-
R^2	.147	-	-	.246#			.329#	-	-
Global cognition									
Vo_{2peak}	.074	0.055	.125	.018	0.094	.033	.117	0.090	.185
Age	.004	0.044	.008	−.045	0.065	−.109	.054	0.063	.110
Race/ethnicity†	.736	0.630	.107	.514	1.048	.079	.832	1.069	.112
Female‡	.589	0.470	.108	-	-	-	-	-	-
Married§	−.005	0.388	−.001	.310	0.578	.073	−.147	0.544	−.023
Education (y)	.048	0.083	.057	−.053	0.140	−.057	.138	0.116	.161
BMI	.081	0.046	.161	.077	0.074	.159	.051	0.068	.088
AD medications‖	−.785	0.552	−.112	−2.566#	0.802	−.342	.269	0.699	.039
Psycholological/emotional medications¶	.329	0.457	.065	−.067	0.633	−.014	.748	0.714	.127
Activities of daily living	−.059	0.070	−.073	.021	0.100	.029	−.197	0.111	−.192
GDS	.012	0.096	.009	.026	0.180	.022	.004	0.141	.003
Premorbid intellect	.089#	0.028	.265	.104	0.058	.287	.086*	0.040	.236
No. of comorbidities	.005	0.103	.004	−.038	0.218	−.026	.015	0.141	.011
Intercept	15.423	4.573	-	20.523	6.590	-	12.507	7.071	-
R^2	.179*	-	-	.270*			.281	-	-

NOTE. *b* is the raw score regression coefficient. *sr* is the semipartial correlation coefficient.
Abbreviations: BMI, body mass index; GDS, Geriatric Depression Scale.
* *P*<.05.
† Coded as 1=White non-Hispanic, 0=other.
‡ Coded as 1=female, 0=male.
§ Coded as 1=married, 0=not married.
‖ Coded as 1=currently reports taking AD medication, 0=otherwise.
¶ Coded as 1=currently reports taking medication for psychological/emotional problems, 0=otherwise.
# *P*<.01.

broad range of cognition including episodic, verbal, and visuospatial memory,[13] others found that healthy women had an executive function advantage over men. In our study, women showed lower CRF than men, similar episodic memory and global cognition to men, and an advantage over men in fluency with the executive function composite approaching significance (table 1). The lack of associations of CRF with executive function and episodic memory in women in our study may be caused by differences in cognitive reserve, resilience, genetics, and functional and structural brain changes in women in comparison with men.[14] Our findings have significant clinical and research implications regarding the mechanisms of aerobic exercise interventions for men and women, suggesting that sex-specific interventions may be necessary or CRF as a less sensitive measure of exercise effects for understanding exercise's cognitive effects in women with amnestic MCI. Future studies are needed to replicate our findings.

It remains unknown if the association of Vo_{2peak} with executive function was mainly driven by specific executive function domains. In our study, 3 domains of executive function were measured, including working memory, cognitive flexibility, and fluency, but Vo_{2peak} was associated only with fluency. Although the structure and function of the brain are interconnected and CRF likely affects the whole brain, differential sensitivity of various brain regions to CRF's effects has been postulated.[27,30] These findings have a methodologic implication for clinical practice and future research regarding the use of domain-specific or global measures. For example, a clinical trial of 52-week aerobic exercise improved CRF by 11% but did not show a benefit on amyloid load, brain volume, and cognition in adults with unimpaired cognition. Considering the differential cognitive effects of aerobic exercise in trial design may help improve the trial's power in detecting cognitive effects and is scalable for clinical implementation by reducing personnel and resource needs.

Study limitations

There are several strengths to our study, including a well-designed and implemented CRF and cognitive testing protocol with high adherence (1 participant did not complete exercise testing because of an incidental finding of arrhythmia on resting electrocardiogram, 2 participants had difficulty with computerized cognitive tests, and 1 participant did not complete a covariate measure of premorbid intellect). Both domain-specific and global cognition were measured. Data were analyzed with methods that reduced biases. Although we used the 0.05 alpha level to preserve power and promote discovery, a Bonferroni adjusted alpha level of 0.05/3 (ie, 0.0167) could have been applied to assess the association between CRF and each of the 3 primary outcomes. We note that each significant association, in the model including covariates, between CRF and a given primary outcome is also significant with use of this more stringent alpha level, indicating that primary study conclusions are the same with the use of either alpha level. Our findings were limited by the cross-sectional nature of the study. Our sample was relatively more educated than the U.S. general population and did not achieve the diversity seen in the general population.

Conclusions

Our findings show that CRF was associated with executive function and episodic memory in the overall sample and in men. Older adults with amnestic MCI had lower CRF than representative of national normative data. Future studies need to examine the longitudinal changes in CRF across the AD spectrum from preclinical AD phase to MCI to dementia to understand the inflection points in CRF changes that contribute to cognitive decline.

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