

# Cardiorespiratory Fitness in Early-stage Alzheimer Disease

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**Abstract:** There is an increasing interest in exercise and fitness in Alzheimer disease (AD) given evidence suggesting a role in the maintenance of cognitive health. There is, however, little data on the objective measure of cardiorespiratory fitness in individuals with AD. Thus, we assessed cardiorespiratory fitness in early AD and its relationship with physical activity levels, health markers, and cognitive performance in nondemented (Clinical Dementia Rating 0, n = 31) and early-stage AD (Clinical Dementia Rating 0.5 and 1, n = 31) participants. Cardiorespiratory fitness was assessed with maximal exercise testing to determine peak oxygen consumption ( $VO_2^{\text{peak}}$ ). Additionally, dual emission x-ray absorptiometry scanning for body composition and glucose tolerance tests were conducted. Despite reductions in physical performance and habitual physical activity levels in early AD, cardiorespiratory fitness ( $VO_2^{\text{peak}}$ ) was comparable in the 2 groups (19.8 in early AD vs. 21.2 mL/kg/min in nondemented,  $P = 0.26$ ). AD participants performed well on treadmill tests with similar levels of perceived exertion, maximal heart rate, and respiratory exchange ratio compared with nondemented individuals. After controlling for age and sex,  $VO_2^{\text{peak}}$  was associated with a beneficial gluoregulatory profile and inversely associated with percent body fat, body mass index, and triglycerides. A relationship between cognitive performance measures and  $VO_2^{\text{peak}}$  was not apparent. These results suggest that individuals in the early stages of AD have the capacity for maximal exercise testing and have comparable levels of cardiorespiratory fitness as nondemented individuals. Reduced physical activity associated with early AD underscores the need for further defining the role of exercise as a potential therapeutic intervention in the early stages of AD.

**Key Words:** Alzheimer disease, cardiorespiratory fitness, physical activity

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## BACKGROUND

There is an increasing interest in using exercise as a therapeutic intervention in the treatment of Alzheimer disease (AD). This interest has largely been stimulated by studies in nondemented older adults demonstrating a positive relationship between physical activity and cognitive health markers.<sup>1–7</sup> A relative paucity of exercise data exists in individuals with AD, particularly in the early stages when the greatest potential for therapeutic benefit exists. Importantly, physical activity and exercise studies are limited by a lack of standardized criteria for defining degree of physical activity and most rely on self-reported activity measures.<sup>8</sup> Few studies have used objective measures such as cardiorespiratory fitness, which is considered the standard measure of fitness.<sup>9</sup> Cardiorespiratory fitness is closely related to physical activity level<sup>9</sup> and may be stronger than self-reported physical activity as a predictor of many health outcomes.<sup>10</sup>

To our knowledge, no studies have assessed cardiorespiratory fitness in individuals with AD although studies of nondemented older adults suggest that reduced fitness may represent a risk factor for cognitive decline<sup>11</sup> and AD.<sup>2,7</sup> A prospective study of nondemented individuals demonstrated that lower fitness at baseline was associated with greater cognitive decline 6 years later.<sup>11</sup> Additionally, neuroimaging evidence suggests that individuals with higher fitness have less age-related loss of gray matter than those with lower levels of fitness,<sup>12</sup> whereas cardiovascular training to increase fitness was associated with improvements in executive function and corresponding alterations in functional imaging activity in prefrontal and parietal cortices.<sup>13</sup>

Despite the evidence that enhancing cardiorespiratory fitness may be a strategy for preventing cognitive decline in nondemented older adults, its role in AD is not well-defined. Additionally, evidence necessary to create guidelines for the prescription of exercise in AD is lacking.<sup>14</sup> Characterizing fitness in the early stages of AD is an important initial step toward more precisely defining the role of exercise in AD. Thus, we examined the objective measure of cardiorespiratory fitness, peak oxygen consumption ( $VO_2^{\text{peak}}$ ) with maximal exercise

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testing, in a cohort of nondemented and early-stage AD participants. Our study objectives were to test the feasibility of maximal exercise testing in the early AD population, to characterize cardiorespiratory fitness in early AD and its relationship with physical activity levels and other health markers, and to explore the cross-sectional relationship between fitness and cognitive performance. We expected individuals with AD to have reductions in habitual physical activity levels and corresponding reductions in cardiorespiratory fitness. We also expected reduced fitness levels to be associated with worse cognitive performance and greater dementia severity.

## METHODS

### Sample and Recruitment

Nondemented [Clinical Dementia Rating (CDR) 0,  $n = 31$ ] and early-stage AD subjects (CDR 0.5 and 1,  $n = 31$ ) aged 65 and over were enrolled in the University of Kansas Brain Aging Project. Participants were recruited from a referral-based memory clinic and by media appeals. The CDR 0.5 ( $n = 23$ ) and CDR 1 ( $n = 8$ ) participants together represent early-stage AD. Study exclusions include neurologic disease other than AD, diabetes mellitus (defined as a clinical diagnosis and use of an antidiabetic agent), history of ischemic heart disease (acute coronary artery event, angina), schizophrenia, clinically significant depressive symptoms, abnormalities in B12, rapid plasma regain, or thyroid function, use of psychoactive and investigational medications, and significant visual or auditory impairment, systemic illness that may impair completion of the study.

### Clinical Assessment

The clinical assessment included a semistructured interview with the participant and with a collateral source knowledgeable about the participant. Diagnostic criteria for AD require the gradual onset and progression of impairment in memory and in at least one other cognitive and functional domain.<sup>15</sup> The presence or absence of dementia, and its severity if present, was determined using the CDR.<sup>16,17</sup> These methods have a diagnostic accuracy for AD of 93%.<sup>18</sup> The CDR assesses cognitive function along 5 levels of impairment from none to maximal (rated as 0, 0.5, 1, 2, or 3) in each of 6 domains: memory, orientation, judgment and problem solving, function in community affairs, home and hobbies, and personal care. On the basis of the collateral source and participant interviews, a global CDR score was derived from individual ratings in each domain such that CDR 0 indicates no dementia and CDR 0.5, 1, 2, and 3 represent very mild, mild, moderate, and severe dementia, respectively. The ratings in each of the 6 domains can be summed (“sum of boxes,”) to expand the CDR scale<sup>19</sup> with a range extending from 0 (no impairment) to 18 (maximum impairment).

Medications, past medical history, education, demographic information, and family history were collected

from the collateral source by the nurse clinician. Blood pressure was the average of 2 measurements using a manual cuff on the left arm. A standard physical and neurologic examination was performed to assess abnormalities in visual fields, cranial nerves, motor strength, sensation, reflexes, plantar responses, coordination, praxis, and gait. To assess symptoms of depression, the Geriatric Depression Scale<sup>20</sup> was administered to the collateral source for all participants (nondemented and demented). The Neuropsychiatric Inventory<sup>21</sup> was administered to the collateral source to assess the presence and severity of neuropsychiatric symptoms. Functional activity level was estimated using the Mild Cognitive Impairment Activities of Daily Living Scale (MCI-ADL) with information collected from the collateral source.

### Neuropsychologic Assessment

A trained psychometrician administered a psychometric battery, including standard measures of memory (WMS-R Logical Memory I and II,<sup>22</sup> Free and Cued Selective Reminding Task<sup>23</sup>), language (Boston Naming Test—5 item<sup>24</sup>), working memory (WMS III Digit Span Forwards and Backwards,<sup>22</sup> WAIS Letter-number sequencing<sup>25</sup>), executive function [Trailmaking A and B,<sup>26</sup> Verbal Fluency<sup>27</sup> (animals, fruits and vegetables), and Stroop Color-Word Test<sup>28</sup>], and visuospatial ability (WAIS Block Design<sup>25</sup>). The mini-mental status examination (MMSE)<sup>29</sup> was administered as a measure of global cognition. Additionally, all cognitive performance scores were converted to z-scores (with higher scores representing better performance) based on the mean and standard deviation of all nondemented and early AD subjects. The mean of each participant’s performance z-scores was determined to create an index of global cognitive performance.

### Cardiorespiratory Fitness

$VO_2^{\text{peak}}$  is an objective measure of cardiorespiratory fitness.<sup>30</sup>  $VO_2^{\text{peak}}$  provides a quantitative measure that reflects physical activity in addition to other factors such as age and heredity.  $VO_2^{\text{peak}}$  was measured during a symptom-limited graded treadmill test in the presence of a physician. Subjects were attached to a 12-lead electrocardiograph to monitor cardiac stability and wore a nonbreathing face mask. Subjects began walking at a pace of 1.7 miles/h at 0% grade. Every 2 minutes, the speed or grade was increased according to a protocol designed for a geriatric population.<sup>31</sup> Blood pressure and the participant’s self-assessment of exertion using the 15-point Borg Rating of Perceived Exertion scale<sup>32</sup> were acquired during the last 30 seconds of each 2-minute stage. Heart rates were recorded every 15 seconds. Expired air was measured for oxygen and carbon dioxide at 15-second intervals using a Parvomedics system. Gas calibrations were performed on the metabolic cart before each test according to the specifications of the manufacturer. American College of Sports Medicine (ACSM) guidelines<sup>9</sup> were used to determine whether the exercise test should be terminated early and included ST-segment

depression more than 2 mm, increasing nervous system symptoms (ie, ataxia, dizziness), sustained ventricular tachycardia, and chest discomfort.  $\text{VO}_2^{\text{peak}}$  was considered the highest observed value during the test.<sup>33,34</sup> To our knowledge, test-retest reliability of  $\text{VO}_2^{\text{peak}}$  determination by treadmill exercise testing has not been assessed in the AD population although the reliability of treadmill testing to determine peak oxygen consumption has been demonstrated in individuals with brain injury or cognitive impairments, including traumatic brain injury,<sup>35</sup> stroke,<sup>36</sup> and mental retardation.<sup>37–39</sup> Participant effort during the treadmill test was assessed with measures of the respiratory exchange ratio (RER) (the ratio of carbon dioxide produced to oxygen consumed; value  $\geq 1.0$  considered near-maximal effort<sup>40</sup>), maximum heart rate, and the maximum score on the Rating of Perceived Exertion. We also examined the frequency that subjects attained an RER  $\geq 1.0$ , 90% of predicted maximum heart rate ( $220 - \text{age}$ ), and a Rating of Perceived Exertion  $\geq 17$  (“very hard” or greater).

### Other Clinical Data

The participant’s level of habitual physical activity was estimated using the Physical Activity Scale in the Elderly (PASE). The PASE is a reliable and valid measure of physical activity and physical function developed specifically for older individuals.<sup>41</sup> The PASE assesses an individual’s level of physical activity within the last 7 days as an estimate of habitual physical activity. We modified the PASE by administering it to the subject’s study partner for both nondemented and AD subjects. The Physical Performance Test is a short battery of timed physical tasks that serves as a composite measure of physical performance. The modified Physical Performance Test<sup>42</sup> includes (1) writing a sentence, (2) simulated eating, (3) lifting a book and placing it on a shelf above shoulder height, (4) putting on and removing a jacket, (5) picking up a penny from the floor, (6) turning 360 degrees, (7) walking 50 feet, (8) chair rises, and (9) a progressive Romberg test.

A 14-sample intravenous glucose tolerance test was performed at 8:30 AM after a 12-hour overnight fast. An intravenous glucose bolus of 0.3 g/kg body weight was delivered at time 0. Venous blood samples were collected at  $-5$ , 1, 3, 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, and 180 minutes for determination of glucose (enzymatic assay, YSI 2300 STAT PLUS) and insulin (insulin radioimmunoassay kit, Diagnostic Systems Laboratory Inc) levels. The total areas under the curve (AUC) for insulin and glucose levels were determined by the trapezoidal rule. Total AUC, fasting, and 3-hour postglucose load levels for both insulin and glucose were used in analyses. Fasting venous blood samples were also assessed using commercial enzymatic assays for total and high-density lipoprotein cholesterol (Diagnostic Chemicals, Ltd) and triglycerides (Roche Diagnostic Systems). Highly sensitive C-reactive protein was determined in fasting blood by turbidimetric assay (Roche Diagnostics Systems). Low-density lipoprotein cholesterol was calculated by the

Friedewald calculation.<sup>43</sup> Hemoglobin A1C was determined using high performance liquid chromatography (Primus Corporation).

Dual energy x-ray absorptiometry (DEXA, Lunar Corp) was used to determine fat-free mass, fat mass, percent body fat, and total body mass. DEXA is able to detect changes in body composition in the order of 1.6% to 3.8%.<sup>44,45</sup> The coefficient of variation for the measurement of total body fat percent is 1.89% and for lean mass 0.63%.<sup>46</sup> Height was measured to the nearest 0.1 cm using a standard stadiometer (Harpender). Body mass index (BMI) was calculated as total body mass in kilograms divided by the square of height in meters.

### Statistical Analyses

Analyses were conducted using SPSS 13.0. Continuous variables are summarized by means and standard deviations, whereas categorical variables are summarized by frequency and percent. Continuous demographic and imaging variables were compared in early AD and nondemented groups using Student *t* test. A  $\chi^2$  test was used to compare categorical variables between groups. Linear regression analyses were used to determine the influence of cardiorespiratory fitness (independent variable) after controlling for the influence of age and sex on the dependent variables (cognitive performance, laboratory data, and body composition). Additional linear regression models were used to examine the role of behavioral measures (as independent variable) in predicting cardiorespiratory fitness (dependent variable) controlling for age and sex. Additionally, to examine the possibility that the relationship between  $\text{VO}_2^{\text{peak}}$  and health markers may be different in early AD and nondemented aging, linear regression analyses for all models were performed to examine for the presence of group  $\times$   $\text{VO}_2^{\text{peak}}$  interactions.

## RESULTS

### Sample Characteristics (Table 1)

The mean age of the entire cohort ( $n = 62$ ) was 75.9 years (SD 6.2) and there was no difference between nondemented ( $n = 31$ ) and early-stage AD ( $n = 31$ ) groups. Additionally, sex, education, and the use of antihypertensives, cholesterol-lowering agents, or  $\beta$ -blockers were not different across groups. Three individuals in the early AD group and 1 in the nondemented group were using  $\beta$ -blockers ( $P = 0.31$ ).

The cognitive and behavioral data (Table 2) in the demented group are consistent with that expected in the early stages of AD. Individuals in the early AD group had mild global cognitive dysfunction, as evidenced by their MMSE score of 25.2, comparable with mild cognitive impairment. Despite the mild level of global dysfunction, the early AD group demonstrated significant deficits in memory performance and executive function. Additionally, individuals with early-stage AD had evident functional impairment as demonstrated by a reduction in activities of daily living. Neuropsychiatric symptoms were

**TABLE 1.** Sample Characteristics

	Nondemented (n = 31)	Early AD (n = 31)	P
Age, y (SD)	76.1 (6.1)	75.8 (6.3)	0.84
Female, n (%)	19 (61.3)	16 (51.6)	0.44
Education, y (SD)	16.8 (2.6)	15.8 (3.4)	0.19
Antihypertensive use, n (%)	9 (29.0)	10 (32.3)	0.78
Cholesterol agent use, n (%)	9 (29.0)	9 (29.0)	1.0
β-Blocker use, n (%)	1 (3.2)	3 (9.7)	0.30
Ever smoked, n (%)	12 (38.7)	8 (25.8)	0.28
Pack years (SD)	41.5 (44.1)	38.3 (28.4)	0.86
Current smoker, n (%)	0 (0.0)	1 (3.2)	0.31
MMSE	29.5 (0.7)	25.2 (3.9)	< 0.001
Logical Memory II	19.8 (8.5)	4.5 (6.3)	< 0.001
Selective Reminding Task	16.0 (0.0)	12.7 (3.9)	< 0.001
Fluency	35.7 (7.4)	23.3 (10.0)	< 0.001
Stroop-Interference	33.2 (8.6)	20.5 (9.2)	< 0.001
Trailmaking B*	92.1 (23.0)	148.3 (38.0)	< 0.001
Activities of Daily Living	48.4 (3.5)	38.4 (9.3)	< 0.001
Geriatric Depression Scale*	0.3 (0.6)	3.7 (2.8)	< 0.001
Neuropsychiatric Inventory*	0.0 (0.0)	3.7 (5.4)	< 0.001

Unless noted, all data represent means (SD).

\*Lower scores represent better performance/function.

more common in the early AD group as evidenced by increased mean scores on both the geriatric depression scale and the neuropsychiatric inventory.

### Body Composition and Laboratory Characteristics

There were no significant group differences in body composition with similar BMI [24.4 (3.3 SD) in nondemented vs. 24.6 (4.1) in early AD,  $P = 0.77$ ], lean mass [44.0 kg (10.7 SD) vs. 42.5 kg (9.1) in early AD,  $P = 0.56$ ], and percent body fat [36.3% (9.2 SD) vs. 37.0% (10.4) in early AD,  $P = 0.79$ ]. Although total glucose AUC during the course of the 3-hour intravenous glucose tolerance test was not different across groups ( $P = 0.95$ ), 3-hour postload glucose levels were increased in early AD participants [83.4 mg/dL (6.6 SD) vs. 92.4 mg/dL (15.2) in early AD,  $P = 0.004$ ] and a trend to increased fasting glucose was present in early AD [95.0 mg/dL (11.2 SD) vs. 101.9 mg/dL (15.9) in early AD,  $P = 0.055$ ]. There were no group differences in fasting insulin [7.4  $\mu$ IU/mL (5.3 SD) vs. 7.8  $\mu$ IU/mL (5.6) in early AD,  $P = 0.78$ ], 3-hour postload insulin [5.6  $\mu$ IU/mL (4.9) vs. 7.3  $\mu$ IU/mL (6.3) in early AD,  $P = 0.27$ ], and total insulin AUC ( $P = 0.78$ ).

### Cardiorespiratory Fitness, Physical Performance, and Physical Activity (Table 2)

The objective measure of cardiorespiratory fitness,  $VO_2^{\text{peak}}$  during maximal exercise testing, was similar in the 2 groups (19.8 mL/kg/min in early AD vs. 21.2 mL/kg/min in the nondemented subjects,  $P = 0.26$ ). Measures of fitness were not different across groups when normalizing  $VO_2^{\text{peak}}$  by total lean mass determined by DEXA

( $P = 0.35$ ) and when assessing total peak oxygen consumption not accounting for body mass ( $P = 0.30$ ). Additionally, these analyses were unchanged when excluding the 4 individuals receiving  $\beta$ -blockers [21.4 mL/kg/min (5.3 SD) in nondemented vs. 19.8 (4.3) in early AD participants,  $P = 0.22$ ]. Cardiorespiratory fitness in the 8 CDR 1 AD subjects [20.8 mL/kg/min (4.5 SD)] was not different than that of the nondemented controls (21.2 mL/kg/min,  $P = 0.86$ ). Age was correlated with cardiorespiratory fitness ( $r = -0.22$ ,  $P = 0.009$ ) in the overall group and men had higher cardiorespiratory fitness than women [23.5 mL/kg/min (4.8 SD) vs. 18.2 (3.5),  $P < 0.001$ ]. Further analyses thus controlled for these important covariates.

To assess effort and performance on the maximal exercise test, we examined physiologic performance data and ratings of perceived exertion. Nondemented and early AD participants had similar levels of perceived exertion (16.9 vs. 17.3 in early AD,  $P = 0.52$ ). There was no difference across groups in the mean of the maximum heart rate achieved and maximum RER, a physiologic measure of exertion (Table 2). Additionally, 90% (n = 28) of the nondemented subjects and 84% (n = 26) in the early AD group achieved an RER  $\geq 1.0$  ( $P = 0.45$ ). A maximal Rating of Perceived Exertion of very hard or higher (17 or higher out of 20) was obtained on 71% (n = 22) of the AD subjects and 65% (n = 20) of the nondemented ( $P = 0.59$ ). A maximum heart rate of 90% predicted maximum value was obtained in 68% (n = 21) of AD subjects and 87% (n = 27) of nondemented ( $P = 0.07$ ). Forty-two percent (n = 13) of AD and 52% (n = 16) of the nondemented subjects achieved all 3 criteria [Rating of Perceived Exertion  $\geq 17$ , RER  $\geq 1.0$ , and a maximum heart rate  $\geq 90\%$  predicted ( $P = 0.45$ )]. Despite similar exercise intensity and  $VO_2^{\text{peak}}$ , individuals with early AD performed on the treadmill for an average of 150 seconds less than the nondemented cohort.

**TABLE 2.** Fitness Characteristics

	Nondemented (n = 31)	Early AD (n = 31)	P
Peak O <sub>2</sub> consumption (mL/kg/min)	21.2 (5.4)	19.8 (4.2)	0.26
Peak O <sub>2</sub> consumption by lean mass (mL/kg/min)	35.2 (5.8)	33.8 (5.9)	0.35
Total O <sub>2</sub> consumption (L/min)	1.6 (0.6)	1.4 (0.4)	0.3
Perceived exertion (6-20)	16.9 (1.9)	17.3 (2.4)	0.52
Maximum heart rate (beats/s)	144.4 (17.1)	138.6 (21.5)	0.24
Exercise duration (s)	665.7 (233.2)	513.8 (161.8)	<b>0.004</b>
RER	1.10 (0.1)	1.08 (0.08)	0.46
Physical Performance Test	30.1 (3.7)	26.7 (4.6)	<b>0.002</b>
Physical Activity Scale in elderly	129.1 (72.8)	77.8 (53.1)	<b>0.002</b>

All data represent means (SD).

Bold characters identify variables with  $P$  values less than 0.05.

Individuals with early AD demonstrated reductions in physical function as measured on the Physical Performance Test, generally considered a measure of frailty. Additionally, individuals with early AD had reductions in habitual physical activity levels (Table 2) compared with nondemented participants.

### Fitness Associations (Table 3)

$VO_2^{\text{peak}} \times$  dementia group interactions were absent for all analyses assessing the relationship of  $VO_2^{\text{peak}}$  with laboratory and body composition measures. This suggests that the relationship between fitness and health markers is not different across groups (early AD vs. nondemented). Thus, further analyses assessing the relationship of fitness with health markers were conducted using the combined cohort of early AD and nondemented participants ( $n = 62$ ). After controlling for age and sex,  $VO_2^{\text{peak}}$  was a significant predictor of lower percent body fat and BMI. Although cholesterol levels were not associated with  $VO_2^{\text{peak}}$ , increased levels of  $VO_2^{\text{peak}}$  were associated with reduced triglycerides.  $VO_2^{\text{peak}}$  was associated with lower fasting glucose, 3-hour insulin level, and total insulin AUC (over 3 h), suggesting an enhanced glucoregulatory profile with increased fitness.

### Behavioral Predictors of Cardiorespiratory Fitness (Table 4)

To assess what behavioral factors predict  $VO_2^{\text{peak}}$ , we conducted linear regression analyses controlling for age and sex. Significant predictors of  $VO_2^{\text{peak}}$  included physical activity level, physical performance, and symptoms of depression (Table 4). There were no predictor  $\times$  dementia group interactions in predicting  $VO_2^{\text{peak}}$ . Global cognition, MMSE performance, and dementia severity

**TABLE 3.** Cardiorespiratory Fitness as a Predictor of Health Markers

Dependent Variable	Standardized $\beta$	<i>P</i>
Systolic blood pressure	−0.24	0.18
Diastolic blood pressure	−0.04	0.82
Total cholesterol	−0.13	0.4
Triglycerides	−0.35	<b>0.03</b>
HDL	0.21	0.22
LDL	−0.1	0.56
C-reactive protein	−0.08	0.64
BMI	−0.51	<b>0.003</b>
Body fat %	−0.61	< <b>0.001</b>
Lean mass	0.17	0.07
Glucose AUC	−0.25	0.16
Fasting glucose	−0.44	<b>0.01</b>
3-h glucose	−0.31	0.07
Hemoglobin A1c	−0.33	0.06
Insulin AUC	−0.42	<b>0.02</b>
Fasting insulin	−0.2	0.25
3-h insulin	−0.36	<b>0.04</b>

Standardized  $\beta$ s represent the correlation between cardiorespiratory fitness [peak oxygen consumption (mL/kg/min)] and each dependent variable after controlling for age and sex.

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein. Bold characters identify variables with *P* values less than 0.05.

**TABLE 4.** Behavioral Predictors of Cardiorespiratory Fitness

Predictor	$\beta$	<i>P</i>
Global cognition	0.07	0.47
MMSE	0.08	0.4
CDR box score*	−0.13	0.19
Physical activity level	0.22	<b>0.02</b>
Physical Performance Test	0.24	<b>0.02</b>
Geriatric Depression Scale*	−0.24	<b>0.01</b>
Activities of Daily Living	0.13	0.19
Neuropsychiatric Inventory*	−0.13	0.2

Standardized  $\beta$ s represent the correlation between each predictor variable and cardiorespiratory fitness [peak oxygen consumption (mL/kg body mass/min)] after controlling for age and sex.

\*Lower scores represent better functioning.

Bold characters identify variables with *P* values less than 0.05.

(CDR box score) were not significant predictors of  $VO_2^{\text{peak}}$ .

### Fitness and Cognition

The relationship of  $VO_2^{\text{peak}}$  with cognitive performance was examined in the overall cohort ( $n = 62$ ) and in the individual groups after controlling for age. There was no apparent relationship between cognitive performance measures and  $VO_2^{\text{peak}}$ . The global cognitive performance measure was not associated with  $VO_2^{\text{peak}}$  in nondemented participants (standardized  $\beta = 0.09$ ,  $P = 0.62$ ) and early AD (standardized  $\beta = -0.07$ ,  $P = 0.71$ ) and  $VO_2^{\text{peak}}$  was not associated with performance on any of the specific neuropsychologic tasks. We also examined the relationship between habitual physical activity (PASE) and cognitive performance after controlling for age. There was no association between global cognitive performance and physical activity in nondemented (standardized  $\beta = -0.13$ ,  $P = 0.42$ ) and AD subjects (standardized  $\beta = 0.31$ ,  $P = 0.12$ ). In AD subjects, only verbal fluency performance was associated with physical activity (standardized  $\beta = 0.46$ ,  $P = 0.015$ ). Additionally, a trend to higher MMSE performance was apparent in AD subjects with increased physical activity (standardized  $\beta = 0.36$ ,  $P = 0.06$ ). In nondemented subjects, there was no association between physical activity and cognitive performance although a trend to increased performance on the Stroop interference task was evident (standardized  $\beta = 0.32$ ,  $P = 0.07$ ). Global cognitive function was not associated with BMI, body fat percent, lean mass, blood pressure, and total cholesterol in AD and nondemented subjects.

### DISCUSSION

This assessment of community-dwelling, ambulatory participants demonstrates individuals in the early stages of AD have comparable levels of cardiorespiratory fitness compared with nondemented individuals assessed in this study and those reported in the literature.<sup>35,48</sup> These results demonstrate that maximal exercise testing is feasible in the early AD population. Additionally, the results suggest that the well-known associations between

fitness and important health markers such as glucoregulatory profile and body composition appear to extend to individuals with AD. Individuals with early AD, however, demonstrated reduced levels of habitual physical activity compared with nondemented individuals, perhaps related to behavioral and functional changes associated with AD. These observations underscore the need to further define the role of increasing physical activity through exercise as a potential therapeutic intervention in the early stages of AD.

Physiologic adaptations to exercise are attenuated with age although increases in  $VO_2^{\text{peak}}$  of up to 15% have been demonstrated in healthy, nondemented 77 to 87-year-old individuals through a supervised endurance exercise program.<sup>47</sup> Whether similar increases in cardiorespiratory fitness can be attained with exercise in AD has not been clearly demonstrated and it remains possible that AD may attenuate beneficial physiologic changes associated with exercise. Our cross-sectional observation of a relationship between physical activity level and cardiorespiratory fitness (Table 4) suggests that exercise interventions to increase physical activity may lead to modifications of cardiorespiratory fitness in individuals with early AD. Our data also demonstrate that increased levels of fitness were associated with a beneficial glucoregulatory profile, reduced body fat, and a trend to increased lean mass in both nondemented and early AD. Physical activity is a well-known modifier of metabolic risk factors, several of which have been linked to increased risk for AD, including mid-life or late-life hypertension,<sup>48</sup> obesity,<sup>49</sup> reduced glucose tolerance,<sup>50–52</sup> and inflammation.<sup>53</sup> Despite these observations relating fitness and health markers in AD, whether exercise in AD is associated with physiologic adaptations and in turn if these physiologic adaptations would provide disease-modifying benefits has not been definitively established. Large exercise-intervention trials are necessary to more precisely define the role of exercise in AD.

Our data did not demonstrate an observable relationship between fitness measures and cognitive performance. We interpret this negative finding with caution given the study's small sample size and its limited power to resolve an association between cognition and fitness. Additionally, the findings in the literature have been mixed. Multiple individual studies have failed to uncover an association between exercise and cognition,<sup>54–57</sup> whereas across 30 studies and 2020 subjects a meta-analysis suggests exercise training has benefits on fitness, physical function, cognitive function, and behavior in dementia.<sup>14</sup> In addition to cardiorespiratory fitness, we also assessed the relationship between physical activity level and cognition. In AD subjects, physical activity level was associated with performance on verbal fluency ( $P = 0.015$ ) and a trend to better global cognitive performance on the MMSE ( $P = 0.06$ ). The study's cross-sectional design, however, limits our ability to infer causality and, as with findings from other large association studies, it remains possible that measures of physical activity are proxy measures reflecting better general

health that is alone associated with better cognitive health.

The relationship between fitness and reduced body fat raises additional theoretical concerns that exercise in AD could be associated with negative consequences. It is well known that exercise programs can lead to reduced body weight and fat mass.<sup>9</sup> Weight loss is present in the preclinical phases of dementia and after dementia onset<sup>58–61</sup> despite apparently adequate energy intake<sup>62,63</sup> and has negative prognostic implications given its association with disease severity and faster clinical progression.<sup>60</sup> Additionally, several studies in nondemented older adults have suggested that increasing BMI and fat mass are associated with increased cognitive performance and lower rates of cognitive decline.<sup>64,65</sup> Although the causal mechanisms relating weight loss with cognitive impairment and AD remain unclear, it remains plausible that exercise could potentially exacerbate AD-related alterations in body composition and thereby negatively influence disease progression. Further randomized controlled studies are necessary to examine the safety of exercise in AD.

The study is limited by its cross-sectional design and thus it is difficult to infer the causal nature of observed relationships. The study results are also limited by a relatively small sample size and the possibility that some of the results may be related to type I error, especially because of the large number of comparisons conducted in these analyses. The study's generalizability is limited by the inclusion of relatively healthy nondemented and early AD participants. Additionally, the physical activity data do not allow an assessment of the timing of any changes in physical activity; thus, we do not know if the reduced habitual activity is a chronic trait or a recent development related to the AD process. It also remains possible that alterations in physical activity are recent and have not yet affected cardiorespiratory fitness. Although there were no appreciable differences in cardiorespiratory fitness between the 2 groups, it remains possible that a larger sample size may allow the resolution of significant differences between the 2 groups.

The current study suggests that physically healthy individuals in the early stages of AD have similar levels of cardiorespiratory fitness as nondemented individuals and that fitness is associated with a beneficial glucoregulatory and body composition profile. These findings combined with the observed reduction in habitual physical activity levels present in early AD underscore the importance of further investigating the role of exercise as a therapeutic intervention in the early stages of AD.

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