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# Cardiorespiratory Fitness and Brain Atrophy in Early Alzheimer's Disease

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## Abstract

**Objective—**Examine the correlation of cardiorespiratory fitness with brain atrophy and cognition in early-stage Alzheimer's disease (AD).

**Background—**In normal aging physical fitness appears to mitigate functional and structural age-related brain changes. Whether this is observed in AD is not known.

**Methods—**Nondemented (n=64) and early-stage AD subjects (n=57) had MRI and standard clinical and psychometric evaluations. Peak oxygen consumption ($VO_2^{peak}$), the standard measure of cardiorespiratory fitness, was assessed during a graded treadmill test. Normalized whole brain volume, a brain atrophy estimate, was determined by MRI. Pearson's correlation and linear regression were used to assess fitness in relation to brain volume and cognitive performance.

**Results—**Cardiorespiratory fitness ($VO_2^{peak}$) was modestly reduced in AD (34.7(5.0)ml/kg/min) vs. nondemented subjects (38.1(6.3)ml/kg/min, p=0.002). In early AD, $VO_2^{peak}$ was associated with whole brain volume (beta=0.35, p=0.02) and white matter volume (beta=0.35, p=0.04) after controlling for age. Controlling for additional covariates of sex, dementia severity, physical activity, and physical frailty did not attenuate the relationships. $VO_2^{peak}$ was associated with performance on delayed memory and digit symbol in early AD but not after controlling for age. In nondemented participants, there was no relationship between fitness and brain atrophy. Fitness in nondemented participants was associated with better global cognitive performance (r=0.30, p=0.02) and performance on Trailmaking A and B, Stroop, and delayed logical memory but not after controlling for age.

**Conclusions—**Increased cardiorespiratory fitness is associated with reduced brain atrophy in AD. Cardiorespiratory fitness may moderate AD-related brain atrophy or a common underlying AD-related process may impact both brain atrophy and cardiorespiratory fitness.

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Statistical analyses were conducted by Dr. Burns and Benjamin Cronk.

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### Keywords

Alzheimer's disease; cardiorespiratory fitness; atrophy

## Introduction

Studies in cognitively normal older adults suggest that maintaining physical fitness may oppose functional and structural changes of the brain that occur with normal aging.[1, 2] Less is known about the role of exercise and fitness in pathological brain states, such as Alzheimer's disease (AD). A recent meta-analysis of studies utilizing various exercise techniques found evidence that exercise provides some benefits to individuals with dementia[3] although studies assessing exercise in AD have produced mixed results.[4-8] Animal study data suggest that physical activity can decrease the neuropathological burden in a mouse model of AD.[9] Whether exercise and fitness modify the disease process underlying AD in humans remains unknown.

Studies on physical activity and exercise often rely on self-reported activity measures and are thus limited by a lack of standard and objective definitions of physical activity.[10] Maximal treadmill testing to determine peak oxygen consumption ($VO_2^{peak}$) is the standard measure of cardiorespiratory fitness. Cardiorespiratory fitness is closely related to physical activity level[11] and is stronger than self-reported physical activity as a predictor of many health outcomes.[12] At least one study has demonstrated that healthy older adults with higher cardiorespiratory fitness have lower rates of cognitive decline over 6 years than individuals with lower cardiorespiratory fitness.[13] There is little data on cardiorespiratory fitness in AD, particularly in the early stages of the disease. Thus, we performed a cross-sectional study examining cardiorespiratory fitness in relation to brain structure and cognition in individuals in the earliest clinical stages of AD and nondemented controls. We hypothesized that increased cardiorespiratory fitness would be associated with less brain atrophy and higher cognitive performance in early AD.

## Methods

### Sample and Recruitment

Nondemented (Clinical Dementia Rating (CDR) 0, n = 64) and early-stage AD subjects (CDR 0.5 and 1, n = 57) aged 60 and over were enrolled in the University of Kansas Brain Aging Project. The CDR 0.5 (n = 45) and CDR 1 (n = 12) 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 anti-diabetic agent), history of ischemic heart disease (acute coronary artery event, angina), schizophrenia, clinically significant depressive symptoms, abnormalities in B12, RPR, or thyroid function, use of antipsychotic and investigational medications, and significant visual or auditory impairment, systemic illness, or orthopedic issues that could impair completion of the study.

### Clinical Assessment

The clinical assessment included a semi-structured 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.[14] The presence or absence of dementia, and its severity if present, was determined using the CDR.[15] These methods have a diagnostic accuracy for AD of 93%,[16] are sensitive to detecting the earliest stages of AD by focusing on intraindividual change rather than comparison with group norms[17] and are accurate in identifying the subset of individuals

meeting criteria for MCI who have early stage AD.[18] Only CDR 0, 0.5, and 1 subjects were enrolled into this study. The CDR sum of boxes was used as a measure of dementia severity.

Medications, past medical history, education, and demographic information were collected from the collateral source by the nurse clinician. A standard physical and neurological examination was performed to assess abnormalities in visual fields, cranial nerves, motor strength, sensation, reflexes, plantar responses, coordination, praxis, and gait.

## Neuropsychological Assessment

A trained psychometrician administered a psychometric battery including standard measures of memory (WMS-R Logical Memory I and II[19], Free and Cued Selective Reminding Task[20]), language (Boston Naming Test - 15 item[21]), working memory (WMS III Digit Span Forwards and Backwards[19], WAIS Letter-number sequencing[22]), executive function (Trailmaking A and B,[23] Verbal Fluency (animals, fruits and vegetables), and Stroop Color-Word Test[24]), and visuospatial ability (WAIS Block Design[22]). The mini-mental status examinantion (MMSE)[25] 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

$VO_2^{peak}$, the standard measure of cardiorespiratory fitness, was measured during a symptom-limited graded treadmill test, as previously described.[26] Subjects were attached to a 12-lead electrocardiograph to monitor cardiac stability and wore a non-rebreathing facemask. Subjects began walking at a pace of 1.7 miles per hour at 0% grade. Every two minutes the speed or grade was increased according to a protocol designed for a geriatric population.[27] Blood pressure and the participant's self-assessment of exertion using the 15-point Borg Rating of Perceived Exertion scale[28] 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.

$VO_2^{peak}$ was considered the highest observed value during the test.[29] Participant effort during the treadmill test was assessed with measures of the respiratory exchange ratio (value ≥1.0 considered near-maximal effort[30]) and 17 individuals were excluded for not attaining an RER≥1.0 (six nondemented vs. 11 early AD subjects, p=0.17). Subjects excluded for an RER<1.0 were predominantly women (14 women and three men) and tended to be older than those achieving an RER≥1.0 (77.5 (7.1) vs. 73.5 (6.5) years, p=0.04). There was no difference in global cognition, MMSE, and dementia severity in those excluded vs. those achieving an RER≥1.0.

The primary fitness measure was $VO_2^{peak}$ normalized by lean mass determined by DEXA scanning (Lunar Corporation). This measure was chosen as our primary fitness measure for several reasons. Normalizing $VO_2^{peak}$ for lean mass is more physiologic than indexing for body weight[29] given that 95% of oxygen consumption during exercise occurs in exercising muscles (i.e., lean mass). Additionally, $VO_2^{peak}$ normalized by lean mass minimizes gender differences in $VO_2^{peak}$. For instance, gender differences were not evident in our overall cohort (n=121) for $VO_2^{peak}$ normalized by lean mass (37.1 (6.8) in men vs. 36.1 (5.1) ml/kg/min in women, p=0.37) while robust gender differences are present when normalizing $VO_2^{peak}$ for total body weight (24.4 (5.2) in men vs. 19.9 (3.6) ml/kg/min in women, p<0.0001).

### Physical Activity and Frailty Assessments

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.[31] The PASE assesses an individual's level of physical activity within the last seven 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 serving as a composite measure of physical performance and used to assess physical frailty. The modified Physical Performance Test[32] 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, 5) turning 360 degrees and 7) walking 50 feet, 8) chair rises and 9) a progressive Romberg test.

### Neuroimaging

Structural MRI was obtained using a Siemens 3.0 Tesla Allegra MRI scanner at the Hoglund Brain Imaging Center. High-resolution T1 weighted anatomic images were acquired to provide detailed gross anatomy with high gray-white matter contrast (MP-RAGE; 1x1x1mm voxels; TR=2500, TE=4.38, TI=1100, FOV 256X256 with 18% oversample, 1mm slice thickness, flip angle=8 degrees). Normalized Whole Brain Volume was computed for each image session using a validated set of imaging tools from FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl). The images were pre-processed and skull-stripped using Brain Extraction Tool (BET). The skull stripped images were then segmented into white matter, gray matter, and cerebrospinal fluid using FMRIB's Automated Segmentation Tool (FAST) by registering them to a Montreal Neuroimaging Institute avg152 template. Image processing was conducted utilizing the Laboratory of Neuroimaging Pipeline (University of California Los Angeles, www.pipeline.loni.ucla.edu). Normalized volumes for white matter, gray matter, and whole brain (sum of white and gray matter) were calculated by dividing each by the total intracranial volume (the sum of white, gray, and cerebrospinal fluid volumes) and expressed as the percent of total intracranial volume. Normalized brain volumes minimize gender differences and produce an estimate of brain atrophy. As expected, normalized whole brain volumes were not related to gender (77.1% (3.3) in women vs. 76.9% (3.4) in men, p=0.76), lending validity to the normalization procedure.

### Statistical Analyses

Analyses were conducted using SPSS 15.0. Continuous variables were summarized by means and standard deviations while categorical variables were summarized by frequency and percent. Student's T-test was used to compare continuous demographic and imaging variables in early AD and nondemented groups. A chi square test was used to compare categorical variables. Pearson's correlation coefficients were calculated to assess simple relationships between variables. Linear regression was used to assess the relationships between variables while controlling for covariates. A univariate general linear model was used to examine for the presence of group × $VO_2^{peak}$ in predicting brain volume. To account for the apparent differential relationship between fitness and brain volume across groups (group × $VO_2^{peak}$ interaction, see results), we conducted all analyses within diagnostic groups (early AD and nondemented subjects separately) as opposed to the entire cohort combined. To minimize the confounding influence of age-related changes in brain volume we controlled all analyses for age.

# Results

## Descriptives

Table 1 summarizes the characteristics of the nondemented and AD groups. The mean age of the cohort (n = 121) was 73.5 (6.5) years with no difference between nondemented and early-stage AD groups. Individuals in the early AD group had mild global cognitive dysfunction with a mean MMSE score of 26.2. Whole brain atrophy was apparent in the early AD group, with whole brain differences primarily related to group differences in gray matter volume, consistent with studies suggesting gray matter is more vulnerable to AD than white matter.[33, 34] Whole brain volume was associated with global cognitive performance (r=0.53, p<0.001) and MMSE performance (r=0.33, p<0.001).

## Cardiorespiratory Fitness

Modest group differences in cardiorespiratory fitness were observed between AD (34.7 (5.0) ml/kg/min) and nondemented groups (38.1 (6.3) ml/kg/min, p=0.002). Group means of peak heart rate and RER were consistent with maximal effort (i.e., 90% of predicted maximum heart rate (220 - age) and RER≥1.1 for both groups). The duration of exercise testing to achieve $VO_2^{peak}$ was lower in the early AD group than nondemented participants.

The role of dementia severity on treadmill testing was examined by assessing the correlation between dementia severity (CDR box score) and measures of effort and $VO_2^{peak}$ in the early AD group. Dementia severity was not related to $VO_2^{peak}$ (r=-0.09, p=0.49), RER (r=-0.01, p=0.94), peak heart rate (r=0.14, p=0.30), exercise duration (r=-0.16, p=0.25), and rating of perceived exertion (r=-0.12, p=0.37).

## Fitness and Brain Structure

Simple correlations were first examined between $VO_2^{peak}$, brain atrophy, and cognition (table 2). Given the presence of a group × $VO_2^{peak}$ interaction in predicting whole brain volume (p=0.004), all analyses were performed within diagnostic groups (i.e., nondemented and early AD) rather than the overall group combined. $VO_2^{peak}$ was associated with whole brain volume in early AD (r=0.54, p<0.001; figure 1) but not nondemented controls (r=0.18, p=0.17, figure 2). In early AD, fitness was associated with both white matter volume (r=0.39, p = 0.003) and gray matter volume (r=0.36, p=0.007) with higher fitness levels associated with increased brain volume.

Next, these relationships were assessed when controlling for the effect of age (table 1) and other covariates. In early AD, controlling for age did not attenuate the relationship of fitness with whole brain volume (beta=0.35, p=0.02) and white matter volume (beta=0.35, p=0.04). Additionally, controlling for age and individual covariates of gender, dementia severity (CDR sum of boxes), physical activity level, and a measure of physical frailty (physical performance test) did not alter the relationship of fitness with whole brain volume and white matter volume. An overall model including all covariates did not alter the relationship between fitness and whole brain volume (beta=0.30, p=0.03) and partially attenuated the relationship of fitness and white matter volume (beta=0.27, p=0.096). After controlling for age, there was no relationship between fitness and gray matter volume in the early AD participants. In nondemented participants, there was no relationship between fitness and whole brain, white matter and gray matter volumes after controlling for age.

## Cognitive Performance

Simple correlations between $VO_2^{peak}$ and overall cognitive performance were assessed first. In early AD, $VO_2^{peak}$ was not associated with global cognitive performance or performance on the MMSE. On specific cognitive tasks, $VO_2^{peak}$ was associated with performance on

delayed memory (logical memory II, r=0.30, p=0.02) and digit symbol (r=0.37, p=0.05) in early AD although these associations were not present when controlling for age. In nondemented controls, $VO_2^{peak}$ was associated with global cognitive performance (r=0.30, p=0.02) with increasing fitness associated with higher global cognitive performance. On specific cognitive tasks, $VO_2^{peak}$ in nondemented participants was most strongly associated with timed tasks of Trailmaking A (r=-0.32, p=0.01) and Trailmaking B (r=-0.25, p=0.005). Additionally, fitness was associated with performance on the Stroop interference task (r=0.30, p=0.02), a measure reflecting executive function, and performance on delayed memory (logical memory II; r=0.26, p=0.04). These associations, however, were primarily driven by age and were not present when controlling for the effect of age.

## Discussion

These results demonstrate a relationship between cardiorespiratory fitness and brain atrophy in the earliest clinical stages of AD. Higher fitness levels in early AD participants were associated with preserved brain volume (less brain atrophy) independent of age and dementia severity. To our knowledge this is the first study to demonstrate a direct relationship between cardiorespiratory fitness and measures of whole brain atrophy in AD. Previous structural neuroimaging studies assessed nondemented controls, rather than AD, using less direct methods (i.e., voxel-based morphometry) to demonstrate regional brain structure (as opposed to whole brain) relationships with fitness. Importantly, the causal nature of these associations cannot be determined due to the cross-sectional design. As a result at least three explanations for these findings exist: 1) cardiorespiratory fitness moderates AD-related brain atrophy, 2) the AD process itself modifies cardiorespiratory fitness, or 3) a common underlying factor modifies both AD-related brain atrophy and cardiorespiratory fitness.

First, the possibility that enhanced cardiorespiratory fitness may moderate AD-related brain changes is biologically-plausible and supported by animal studies. Higher fitness through increased physical activity has been associated with enhanced neuronal survival to brain insults,[35, 36] increased vascularization,[37] and elevations of growth factors in areas important for memory.[38, 39] Physical activity increases neurogenesis in the hippocampus and enhances learning in mice.[40] Additionally, evidence suggests that increased physical activity may modify the AD process. Increased physical activity in an AD mouse model was associated with decreased neuropathological burden in both cortical and hippocampal regions, suggesting that exercise may mediate the amyloid cascade in favor of reduced production of beta-amyloid.[9] Our data is consistent with, but does not establish, cardiorespiratory fitness as a moderating factor in neurodegeneration.

A second explanation of the current results is that the AD process itself may modify an individual's fitness level resulting in fitness declines co-occuring with AD-related brain atrophy. Behavioral changes associated with the disease include reductions in physical activity[26] which in turn may result in reduced fitness levels. Individuals with AD may also potentially have reduced effort or increased frailty limiting their ability to perform a maximal treadmill test although we found little influence of these factors on the association between fitness and brain atrophy in AD. For instance, controlling for physical activity level (PASE) and physical frailty (physical performance test) did not alter the relationship between fitness and brain atrophy. Additionally, severity of dementia (CDR box score) was not associated with cardiorespiratory fitness or physiologic measures of effort (RER and peak heart rate). All participants met criteria for peak effort (RER≥1.0) while peak heart rate and RER were consistent with maximal effort for both groups. Lastly, the 11 AD subjects excluded for not meeting peak effort criteria were not more severely demented or cognitively impaired than those meeting performance criteria suggesting that reduced effort was not related to dementia severity or cognitive impairment. These observations suggest the relationship between fitness

and brain atrophy was not driven by the most severely demented of these early-stage AD subjects.

Third, it is possible that a common underlying AD-related process may impact both brain atrophy and cardiorespiratory fitness. Additionally, accumulating evidence suggests that AD may not only impact the brain but may have widespread systemic manifestations. For instance, mitochondrial dysfunction is evident in the CNS and periphery in AD[43] and abnormalities in metabolic and biochemical processes described in AD brains are reported in peripheral cells such as skin fibroblasts derived from AD patients.[44, 45] $VO_2^{peak}$ represents the peak rate of metabolic activity (oxygen utilization) in exercising muscle (ml of oxygen consumed per minute per kg of muscle mass) and as such our findings of 1) reduced $VO_2^{peak}$ in AD and 2) the correlation of $VO_2^{peak}$ with brain atrophy in AD suggests the possibility of metabolic dysfunction co-occurring in brain and muscle. Another possibility is that fitness may modify vascular-related damage (such as white matter lesions and subclinical infarcts) known to influence both brain atrophy[41] and cognitive symptoms of AD.[42] Further study of the relationship between fitness and vascular-related damage is needed to assess this possibility.

The cross-sectional study design limits the interpretation of the results. Further longitudinal and interventional studies will be necessary to define the role of fitness in modifying the brain aging and AD process. Validated clinical methods were used for diagnosing AD although these methods are imperfect in predicting AD pathology. Additionally, although cardiorespiratory fitness is influenced by physical activity and exercise, this study only assessed the standard measure of cardiorespiratory fitness $VO_2^{peak}$ at one point in time and therefore the data should be cautiously interpreted with respect to the role of exercise in early AD.

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## References

1. Colcombe SJ, Erickson KI, Raz N, et al. Aerobic Fitness Reduces Brain Tissue Loss in Aging Humans. Journals of Gerontology Series A: Biological Sciences and Medical Sciences 2003;58(2):M176–M180.
2. Colcombe SJ, Kramer AF, Erickson KI, et al. Cardiovascular fitness, cortical plasticity, and aging. Proceedings of the National Academy of Sciences 2004;101(9):3316–3321.
3. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis. Archives of Physical Medicine and Rehabilitation 2004;85 (10):1694–1704. [PubMed: 15468033]
4. Broe GA, Creasey H, Jorm AF, et al. Health habits and risk of cognitive impairment and dementia in old age: a prospective study on the effects of exercise, smoking and alcohol consumption. Aust.N Z.J Public Health 1998;22(5):621–623. [PubMed: 9744220]
5. Fraser GE, Singh PN, Bennett H. Variables associated with cognitive function in elderly California Seventh-day Adventists. Am J Epidemiol 1996;143(12):1181–1190. [PubMed: 8651216]
6. Joe V, Richard BL, Mindy JK, Charles BH. Leisure activities and the risk of dementia in the elderly. The New England Journal of Medicine 2003;348(25):2508. [PubMed: 12815136]

7. Yoshitake T, Kiyohara Y, Kato I, et al. Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study. Neurology 1995;45(6):1161–1168. [PubMed: 7783883]
8. Li G, Shen YC, Chen CH, Zhau YW, Li SR, Lu M. A three-year follow-up study of age-related dementia in an urban area of Beijing. Acta Psychiatr.Scand 1991;83(2):99–104. [PubMed: 2017918]
9. Adlard PA, Perreau VM, Pop V, Cotman CW. Voluntary Exercise Decreases Amyloid Load in a Transgenic Model of Alzheimer's Disease. Journal of Neuroscience 2005;25(17):4217–4221. [PubMed: 15858047]
10. Blair SN, Church TS. The Fitness, Obesity, and Health Equation: Is Physical Activity the Common Denominator? JAMA: The Journal of the American Medical Association 2004;292(10):1232–1234. [PubMed: 15353537]
11. American College of Sports M. Guidelines for exercise testing and prescription. Williams & Wilkins; Baltimore: 2000.
12. Blair SN, Cheng Y, Holder JS. Is physical activity or physical fitness more important in defining health benefits? Medicine And Science In Sports And Exercise 2001;33(6):S379–S399. [PubMed: 11427763]
13. Barnes DE, Yaffe K, Satariano WA, Tager IB. A Longitudinal Study of Cardiorespiratory Fitness and Cognitive Function in Healthy Older Adults. Journal of the American Geriatrics Society 2003;51(4):459–465. [PubMed: 12657064]
14. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939–944. [PubMed: 6610841]
15. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology November 1;1993 43(11):2412b–2414. [PubMed: 8232972]1993
16. Berg L, McKeel DW Jr. Miller JP, et al. Clinicopathologic Studies in Cognitively Healthy Aging and Alzheimer Disease: Relation of Histologic Markers to Dementia Severity, Age, Sex, and Apolipoprotein E Genotype. Archives of Neurology 1998;55(3):326–335. [PubMed: 9520006]
17. Storandt M, Grant EA, Miller JP, Morris JC. Longitudinal course and neuropathologic outcomes in original vs revised MCI and in pre-MCI. Neurology August 8;2006 67(3):467–473. [PubMed: 16894109]2006
18. Morris JC, Storandt M, Miller JP, et al. Mild Cognitive Impairment Represents Early-Stage Alzheimer Disease. Archives of Neurology 2001;58(3):397–405. [PubMed: 11255443]
19. Wechsler, D.; Stone, CP. Manual: Wechsler Memory Scale. Psychological Corporation; New York: 1973.
20. Grober E, Buschke H, Crystal H, Bang S, Dresner R. Screening for dementia by memory testing. Neurology 1988;38:900–903. [PubMed: 3368071]
21. Goodglass, H.; Kaplan, E. Boston Naming Test scoring booklet. Lea & Febiger; Philadelphia: 1983.
22. Wechsler, D. Manual: Wechsler Adult Intelligence Scale. Psychological Corporation; New York: 1955.
23. Armitage SG. An analysis of certain psychological tests used in the evaluation of brain injury. Psychological Monographs 1946;60:1–48.
24. Stroop J. Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643–662.
25. Folstein MF, Folstein SE, McHugh PR. Mini-mental State: A practical method for grading the cognitive state of patients for the clinicians. J.Psychiatr.Res 1975;12:189–198. [PubMed: 1202204]
26. Burns JM, Mayo MS, Anderson HS, Smith H, Donnelly JE. Cardiorespiratory Fitness in Early-Stage Alzheimer's Disease. Alzheimer Dis Assoc Disord. In Press
27. Hollenberg M, Ngo LH, Turner D, Tager IB. Treadmill Exercise Testing in an Epidepiologic Study of Elderly Subjects. Journal of Gerontology: Biological Sciences 1998;53A(4):259–267.
28. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377–381. [PubMed: 7154893]
29. Fleg JL, Morrell CH, Bos AG, et al. Accelerated Longitudinal Decline of Aerobic Capacity in Healthy Older Adults. Circulation 2005;112(5):674–682. [PubMed: 16043637]

30. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA Guidelines for Exercise Testing: Executive Summary: A Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Circulation July 1;1997 96(1):345–354. [PubMed: 9236456]1997
31. Washburn RA, McAuley E, Katula J, Mihalko SL, Boileau RA. The physical activity scale for the elderly (PASE): evidence for validity. J Clin Epidemiol 1999;52(7):643–651. [PubMed: 10391658]
32. Shah KR, Carr D, Roe CM, Miller JP, Coats M, Morris JC. Impaired Physical Performance and the Assessment of Dementia of the Alzheimer Type. Alzheimer Disease and Associated Disorders 2004;18(3):112–118. [PubMed: 15494615]
33. Thompson PM, Hayashi KM, de Zubicaray G, et al. Dynamics of Gray Matter Loss in Alzheimer's Disease 2003;23:994–1005.
34. Fotenos AF, Snyder AZ, Girton LE, Morris JC, Buckner RL. Normative estimates of cross-sectional and longitudinal brain volume decline in aging and AD. Neurology. 2005
35. Stummer W, Weber K, Tranmer B, Baethmann A, Kempski O. Reduced mortality and brain damage after locomotor activity in gerbil forebrain ischemia. Stroke; a Journal Of Cerebral Circulation 1994;25(9):1862–1869. [PubMed: 8073470]
36. Carro E, Trejo JL, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. The Journal Of Neuroscience: The Official Journal Of The Society For Neuroscience 2001;21(15):5678–5684. [PubMed: 11466439]
37. Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. Proceedings of the National Academy of Sciences of the United States of America 1990;87(14):5568–5572. [PubMed: 1695380]
38. Neeper SA, Gomezpinilla F, Choi J, Cotman C. Exercise and Brain Neurotrophins. Nature 1995;373 (6510):109–109. [PubMed: 7816089]
39. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends in Neurosciences 2002;25(6):295–301. [PubMed: 12086747]
40. van Praag H, Shubert T, Zhao C, Gage FH. Exercise Enhances Learning and Hippocampal Neurogenesis in Aged Mice. Journal of Neuroscience 2005;25(38):8680–8685. [PubMed: 16177036]
41. Hugenschmidt, CE.; Peiffer, AM.; Kraft, RA., et al. Relating Imaging Indices of White Matter Integrity and Volume in Healthy Older Adults. 2007. bhm080
42. Burns JM, Church JA, Johnson DK, et al. White Matter Lesions Are Prevalent but Differentially Related With Cognition in Aging and Early Alzheimer Disease. Arch Neurol December 1;2005 62 (12):1870–1876. [PubMed: 16344345]2005
43. Swerdlow RHK. SJ Mitochondria in Alzheimer's Disease. Int Rev Neurobiol 2002;53:341–385. [PubMed: 12512346]
44. Etcheberrigaray R, Ibarreta D. Ionic channels and second messenger alterations in Alzheimer's disease. Relevance of studies in nonneuronal cells. Rev Neurol Oct 16-31;2001 33(8):740–749. [PubMed: 11784972]
45. Bruel A, Cherqui G, Columelli S, et al. Reduced protein kinase C activity in sporadic Alzheimer's disease fibroblasts. Neurosci Lett Nov 25;1991 133(1):89–92. [PubMed: 1792001]

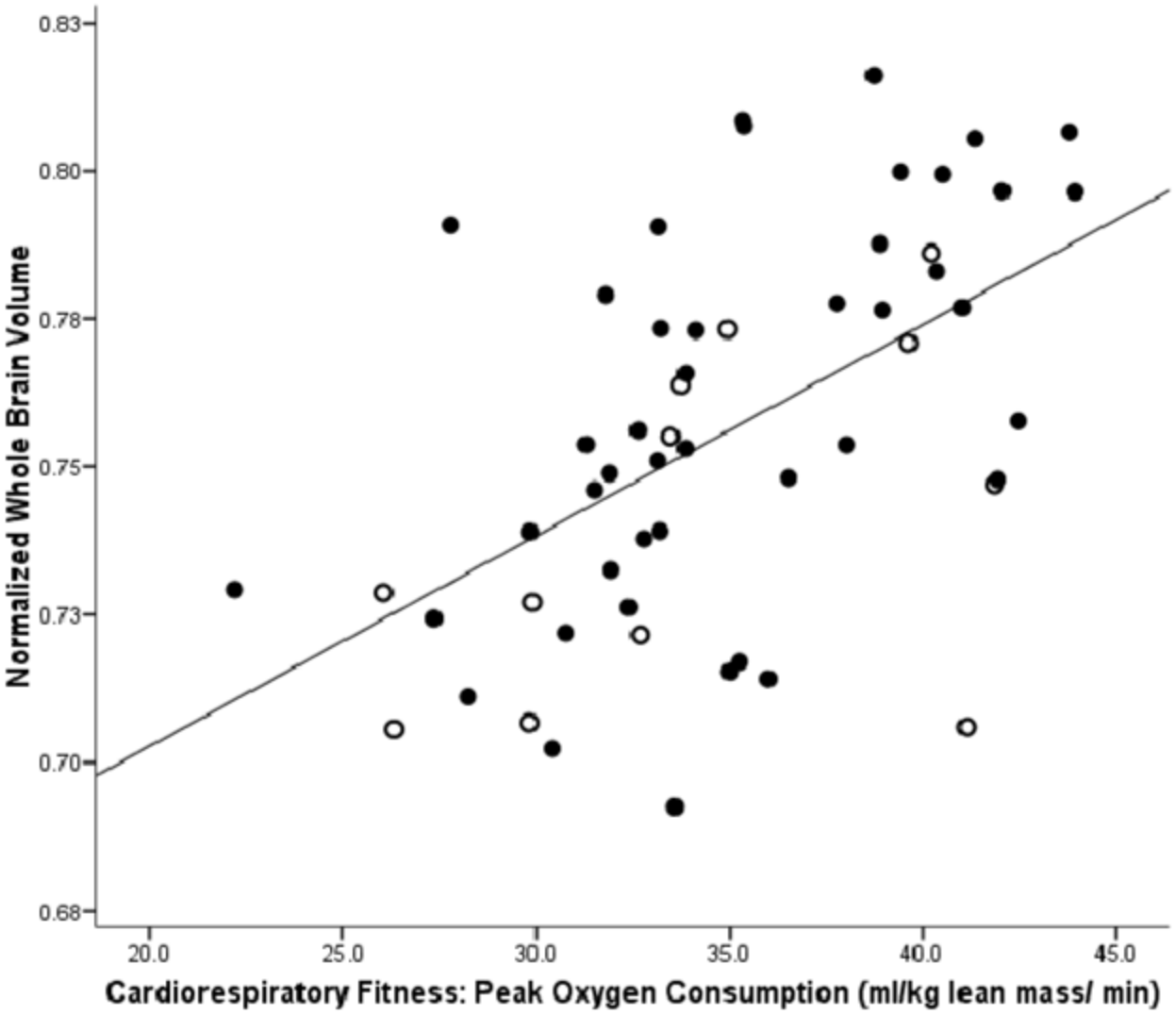


**Figure 1.**

The relationship between whole brain volume and cardiorespiratory fitness in early Alzheimer disease.

The relationship between whole brain volume (expressed as percent of total intracranial volume) and cardiorespiratory fitness (peak oxygen consumption during maximal treadmill testing normalized by lean mass) in early Alzheimer disease participants. Increased fitness levels are associated with increased normalized whole brain volume (less brain atrophy). Filled circles indicate participants with very mild dementia (CDR 0.5) and open circles indicated participants with mild dementia (CDR 1).

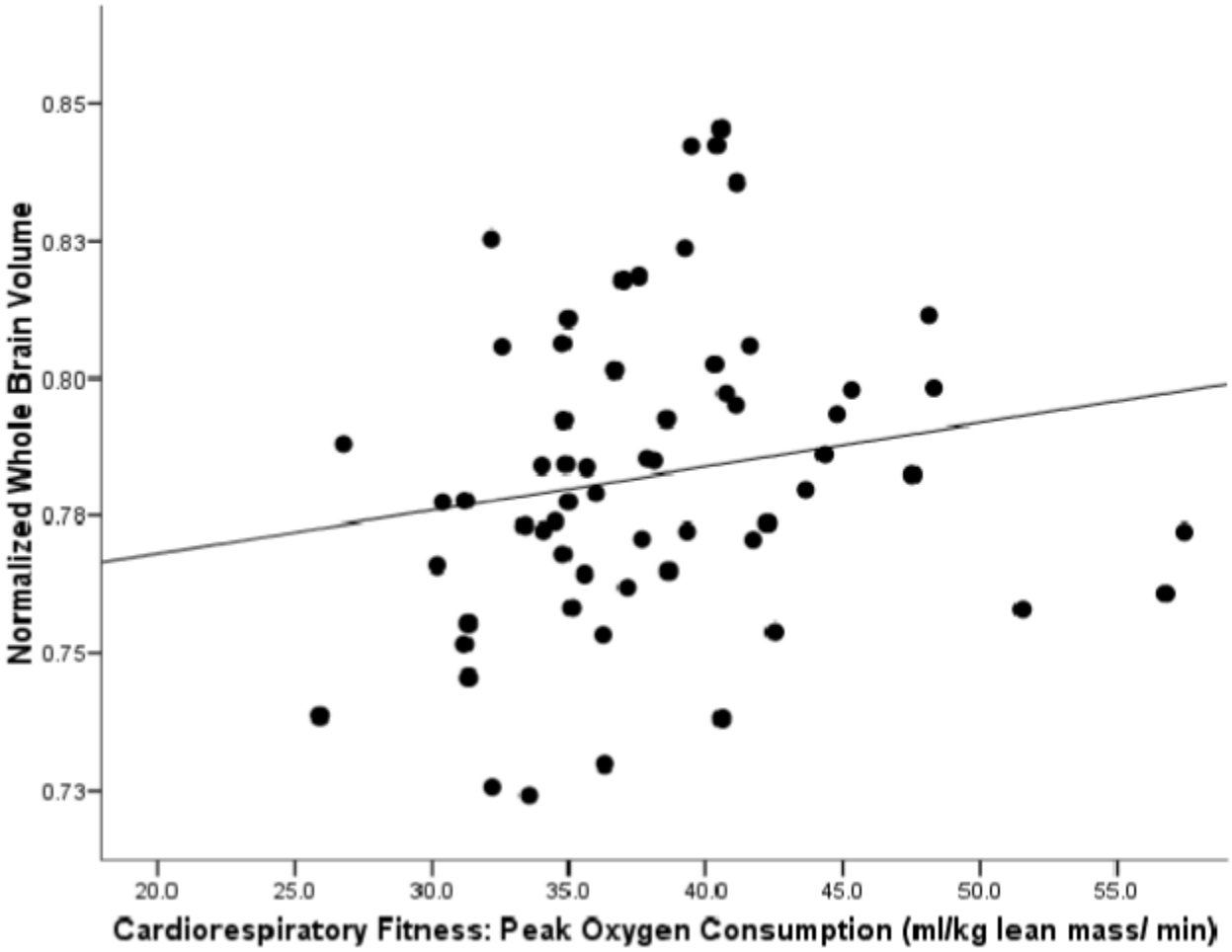


**Figure 2.**

The relationship between whole brain volume and cardiorespiratory fitness in nondemented aging

The relationship between whole brain volume (expressed as percent of total intracranial volume) and cardiorespiratory fitness (peak oxygen consumption during maximal treadmill testing normalized by lean mass) in nondemented participants.

## Table 1

### Sample Characteristics

| | Nondemented (n = 64) | Early AD (n = 57) | p value |
|---|---|---|---|
| Age, years | 72.7 (6.3) | 74.3 (6.7) | 0.17 |
| Education | 16.6 (2.7) | 15.5 (3.6) | 0.07 |
| Female % (n) | 52.3 (34) | 47.7 (31) | 0.52 |
| MMSE | 29.4 (0.8) | 26.2 (3.5) | <0.001 |
| Global Cognitive Performance | 0.005(0.5) | -1.60 (1.1) | <0.001 |
| Body Composition | | | |
| Body Mass Index | 26.3 (3.9) | 26.0 (5.5) | 0.76 |
| Lean Mass (kg) | 45.4 (10.4) | 42.7 (9.5) | 0.15 |
| Fat Mass (kg) | 25.7 (8.5) | 23.8 (9.0) | 0.23 |
| Neuroimaging Measures | | | |
| Whole Brain Volume (%ICV) | 78.2 (2.8) | 75.6 (3.3) | <0.001 |
| Gray Matter Volume (%ICV) | 43.1 (2.4) | 40.5 (2.4) | <0.001 |
| White Matter Volume (%ICV) | 35.2 (1.9) | 35.0 (2.4) | 0.72 |
| Fitness Measures | | | |
| $VO_2^{peak}$: Total (L/min) | 1.7 (0.6) | 1.5 (0.4) | 0.005 |
| $VO_2^{peak}$ by lean mass (m l/kg/min) | 38.1 (6.3) | 34.7 (5.0) | 0.002 |
| Respiratory Exchange Ratio | 1.12 (0.1) | 1.10 (0.1) | 0.07 |
| Rating of Perceived Exertion (6 - 20) | 17.0 (1.6) | 17.4 (2.0) | 0.27 |
| Maximum Heart Rate (beats per minute) | 150.4 (15.3) | 140.0 (20.7) | 0.002 |
| Exercise Duration (seconds) | 691.1 (196.9) | 583.4 (158.7) | 0.001 |

All data represent means (SD), unless otherwise noted. %ICV represents percent of intracranial volume.

**Table 2**

Relationship of Brain Structure and Cognition with Fitness and Physical Activity

| | Nondemented (n=64) | | Early AD (n = 57) | |
|---|---|---|---|---|
| **Dependent Variable** | **Simple Correlation (r)** | **Age-Controlled (β)** | **Simple Correlation (r)** | **Age-Controlled (β)** |
| Brain Structure | | | | |
| Whole Brain Volume | 0.18 | -0.20 | 0.54** | 0.35* |
| White Matter Volume | 0.15 | 0.04 | 0.39** | 0.35* |
| Gray Matter Volume | 0.08 | -0.27 (p=0.06) | 0.36** | 0.13 |
| Cognitive Performance | | | | |
| Global Cognition | 0.30* | 0.09 | 0.22 | 0.16 |
| MMSE | 0.17 | 0.14 | -0.05 | 0.11 |
| Logical Memory I | 0.24 | 0.07 | 0.22 | 0.17 |
| Logical Memory II | 0.26 | 0.12 | 0.30* | 0.24 |
| Verbal Fluency | 0.16 | 0.17 | 0.23 | 0.17 |
| Trails A | -0.32** | -0.21 | -0.20 | -0.10 |
| Trails B | -0.35** | -0.27 (p=0.07) | -0.29* | -0.28 (p=0.10) |
| Stroop Interference | 0.30* | 0.01 | 0.08 | 0.11 |
| Block Design | 0.17 | -0.01 | 0.23 | 0.17 |
| Boston Naming | 0.20 | 0.17 | 0.17 | 0.05 |
| Selective Reminding Task | 0.14 | -0.07 | 0.02 | 0.05 |
| Letter Number Sequencing | 0.19 | -0.04 | 0.03 | 0.11 |
| Digit Symbol | 0.18 | 0.01 | 0.37* | 0.20 |
| Digit Span Forward | -0.16 | -0.19 | -0.21 | -0.05 |
| Digit Span Backwards | -0.13 | -0.11 | 0.13 | 0.01 |

Pearson's r values represent the simple correlation between cardiorespiratory fitness and the dependent variables. Standardized betas represent the correlation between fitness and each dependent variable after controlling for age.

* $p < 0.05$;

** $p < 0.01$