

# Cardiorespiratory fitness is associated with atrophy in Alzheimer's and aging over 2 years

Eric D. Vidoni<sup>a</sup>, Robyn A. Honea<sup>a</sup>, Sandra A. Billinger<sup>b</sup>, Russell H. Swerdlow<sup>a</sup>,  
Jeffrey M. Burns<sup>a,\*</sup>

<sup>a</sup> KU Alzheimer and Memory Program, Department of Neurology, University of Kansas Medical Center, Kansas City, KS, USA

<sup>b</sup> Department of Physical Therapy and Rehabilitation Science, University of Kansas Medical Center, Kansas City, KS, USA

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## Abstract

We sought to describe change in cardiorespiratory (CR) fitness over 2 years in those with early-stage Alzheimer's disease (AD) and nondemented aging and assess the relationship of CR fitness with cognitive decline, brain atrophy, and dementia progression. Individuals with early-stage AD ( $n = 37$ ) and without dementia ( $n = 53$ ) attended clinical evaluations, cognitive and exercise tests, and magnetic resonance imaging (MRI) at baseline and 2 years later. CR fitness was lower in those with AD over the study period. Lower baseline CR fitness was associated with progression of dementia severity in AD. Declining CR fitness over 2 years was associated with brain atrophy in AD, especially in the parahippocampus. In nondemented participants, there was a trend for lower baseline fitness to be related to cognitive decline. Both lower baseline CR fitness and declining CR fitness over 2 years were associated with regional brain atrophy. We conclude that CR fitness is chronically reduced in those with AD. Further, in those with AD, CR fitness is associated with progression of dementia severity and brain atrophy in AD, suggesting a link between progression of dementia severity and cardiorespiratory health.

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## 1. Introduction

The benefits of physical activity for brain health are receiving increased attention (Kramer et al., 2005). In animals, exercise increases neuronal survival and resistance to brain insults (Carro et al., 2001; Stummer et al., 1994), promotes vascularization (Black et al., 1990; Isaacs et al., 1992), stimulates neurogenesis (van Praag et al., 1999), and mobilizes gene expression profiles predicted to benefit brain plasticity (Cotman and Berchtold, 2002). Additionally, running increases brain-derived neurotrophic factor levels in the hippocampus and dentate gyrus and influences long term potentiation (Neeper et al., 1995; van Praag et al., 1999). In

humans, several randomized controlled trials have examined the cognitive effects of increasing activity in healthy, older adults and found a beneficial impact on cognitive performance (Dustman et al., 1984; Hassmen and Koivula, 1997; Hill et al., 1993; Kramer et al., 1999; Williams and Lord, 1997). Several longitudinal studies report a positive relationship between self-reported physical activity and cognitive function (Laurin et al., 2001; Pignatti et al., 2002; Weuve et al., 2004; Yaffe et al., 2001).

There is an increasing interest in assessing the therapeutic role of exercise and physical activity in individuals with Alzheimer's disease (AD). Recently, greater physical activity and exercise in adults without dementia was associated with lower levels of AD biomarkers such as Pittsburgh Compound B binding (Liang et al., 2010). Additionally, a recent report showed that increased physical activity in those with dementia was associated with lower mortality risk (Scarmeas et al., 2010). Epidemiological studies sug-

\* Corresponding author at: Department of Neurology, KU Alzheimer and Memory Program, University of Kansas Medical Center, MS 1063, 3901 Rainbow Boulevard, Kansas City, KS 66160, USA. Tel.: +1 913 588 0555; fax: +1 913 945 5035.

E-mail address: jburns2@kumc.edu (J.M. Burns).

gest regular physical activity may prevent cognitive decline and dementia, and in midlife is associated with a reduced risk of developing mild cognitive impairment and AD (Friedland et al., 2001; Geda et al., 2010). One such study found that dancing, an aerobic activity, was associated with lower risk for developing dementia (Verghese et al., 2003). Others have demonstrated in randomized controlled trials that aerobic fitness training improves cognitive performance in mild cognitive impairment (Baker et al., 2010; Scherder et al., 2005).

Limitations to previous studies include a reliance on reported activity levels and a lack of standard objective measures of physical activity. Physical activity and exercise influence cardiorespiratory (CR) fitness, an objective measure of an individual's peak level of oxygen consumption during a graded exercise test. CR fitness is associated with lower rates of cognitive decline in nondemented older adults (Colcombe and Kramer, 2003) but there is a paucity of data on individuals with AD regarding the relationship of CR fitness with dementia progression and structural brain change (Rolland et al., 2008). We previously reported cross-sectional data suggesting that CR fitness relates to whole brain (Burns et al., 2008) and medial temporal lobe volume (Honea et al., 2009) in individuals with AD. Additionally, we reported that CR fitness levels were lower in those with AD compared with nondemented peers (Burns et al., 2008). We now extend these findings by reporting the results of a 2-year observational study of individuals with early-stage AD and nondemented controls. We hypothesized that individuals with AD would have greater CR fitness decline compared with nondemented control subjects and that CR fitness would be associated with progression of dementia severity and brain atrophy.

## 2. Methods

### 2.1. Sample

Participants were enrolled in the University of Kansas Brain Aging Project for baseline and follow-up evaluations (mean follow-up time 2.1 [SD 0.2] years). Data used in these analyses were from nondemented individuals (Clinical Dementia Rating [CDR] 0,  $n = 53$ ) and individuals with early-stage AD (CDR 0.5 and 1,  $n = 37$ ) aged 60 years and older. Study exclusions at baseline included neurologic disease other than AD with the potential to impair cognition (e.g., Parkinson disease), current or past history of diabetes mellitus (defined as a clinical diagnosis, use of an anti-diabetic agent, or 2-hour postload serum glucose  $>199$ ), recent history of cardiovascular disease (e.g., diagnosis of congestive heart failure, acute coronary artery event, or angina in the 2 years previous to the baseline evaluation), clinically significant depressive symptoms, use of investigational medications, significant visual or auditory impairment, systemic illness that may have impaired completion of the study, current or past history of alcoholism, and

magnetic resonance imaging (MRI) exclusions (e.g., pacemakers). Baseline measures of these individuals have been reported previously as part of a larger cohort (Burns et al., 2008; Honea et al., 2009). Informed consent was obtained from all participants or their legal representative as appropriate before enrollment into the study.

### 2.2. Clinical assessment

The clinical assessment included a semistructured interview with the participant and a collateral source knowledgeable about the participant. Medications, past medical history, education, demographic information, and family history were collected from the collateral source. Dementia status of the participant was based on clinical evaluation (Morris et al., 2001). Diagnostic criteria for AD require the gradual onset and progression of impairment in memory and at least 1 other cognitive and functional domain (McKhann et al., 1984). The CDR (Morris, 1993) assesses function in multiple domains and was used to assess dementia severity. The ratings in each of the 6 domains can be summed ("CDR Sum of Boxes") to expand the CDR scale. The range of Sum of Boxes extends from 0 (no impairment) to 18 (maximum impairment). A Global CDR score is derived from individual ratings in each domain such that CDR 0 indicates no dementia, CDR 0.5 indicates very mild, CDR 1 indicates mild, CDR 2 indicates moderate, and CDR 3 indicates severe dementia. Nondemented status was defined as having a Global CDR 0 at both timepoints. Individuals with AD met criteria for very mild or mild dementia and had persistent impairment at follow up (Global CDR 0.5 or greater). These methods have a diagnostic accuracy for AD of 93% and have been shown to be accurate in discriminating those with mild cognitive impairment who have early-stage AD (Berg et al., 1998; Morris et al., 2001).

### 2.3. Cognitive assessment

A trained psychometrician administered a psychometric battery including standard measures of memory, language, working memory, executive function, and visuospatial ability as described previously (Burns et al., 2008). All cognitive performance scores were standardized (Z-score) to a larger set ( $n = 82$ ) of nondemented subjects (positive scores represent better performance). The mean of each participant's Z-scores was calculated to create an index of global cognition, a composite measure of performance on the battery. The Mini Mental State Examination (MMSE) (Folstein et al., 1975) was also administered to facilitate comparison across the literature.

### 2.4. Cardiorespiratory fitness assessment

CR fitness was assessed as peak oxygen consumption ( $\text{VO}_2$  peak; mL/kg/minute) during a symptom-limited, graded treadmill test using a modified Bruce protocol (Burns et al., 2008; Hollenberg et al., 1998) and metabolic cart (Parvomedics, Sandy, UT, USA) to measure the con-

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