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Moderate intensity physical activity associates with CSF biomarkers in a cohort at risk for Alzheimer's disease

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Abstract

Introduction: Alzheimer's disease (AD) is characterized by the presence of amyloid β (Aβ) plaques, neurofibrillary tangles, and neurodegeneration, evidence of which may be detected in vivo via cerebrospinal fluid (CSF) sampling. Physical activity (PA) has emerged as a possible modifier of these AD-related pathological changes. Consequently, the aim of this study was to cross-sectionally examine the relationship between objectively measured PA and CSF levels of Aβ42 and tau in asymptomatic late-middle-aged adults at risk for AD.

Methods: Eighty-five cognitively healthy late-middle-aged adults (age = 64.31 years, 61.2% female) from the Wisconsin Registry for Alzheimer's Prevention participated in this study. They wore an accelerometer (ActiGraph GT3X+) for one week to record free-living PA, yielding measures of sedentariness and various intensities of PA (i.e., light, moderate, and vigorous). They also underwent lumbar puncture to collect CSF, from which Aβ42, total tau, and phosphorylated tau were immunoassayed. Regression analyses were used to examine the association between accelerometer measures and CSF biomarkers, adjusting for age, sex, and other relevant covariates.

Results: Engagement in moderate PA was associated with higher Aβ42 ($P = .008$), lower total tau/Aβ42 ($P = .006$), and lower phosphorylated tau/Aβ42 ($P = .030$). In contrast, neither light nor vigorous PA was associated with any of the biomarkers. Increased sedentariness was associated with reduced Aβ42 ($P = .014$).

Discussions: In this cohort, moderate PA, but not light or vigorous, was associated with a favorable AD biomarker profile, while sedentariness was associated with greater Aβ burden. These findings suggest that a physically active lifestyle may play a protective role against the development of AD.

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1. Introduction

The preclinical stage of Alzheimer's disease (AD) is characterized by the emergence of pathognomonic brain changes in the absence of cognitive decline [1]. These brain alterations include amyloid β (Aβ) plaques, neurodegeneration, and neurofibrillary tangles [1]. Although these lesions are only definitively ascertained via histologic assessments at autopsy, it is now accepted that it is possible to probe their occurrence ante mortem by measuring specific cerebrospinal fluid (CSF) biomarkers intended to reflect these pathologies. These biomarkers include Aβ42, total tau (t-tau), and phosphorylated tau (p-tau), respectively [2]. Because persons in the preclinical stage of AD are yet asymptomatic, they collectively represent a unique target population for therapeutics aimed at slowing the progression of AD pathology and ultimately preventing the manifestation of clinical symptoms [3].

A vast body of work has shown that physical activity (PA) ameliorates cognitive dysfunction and the risk of dementia in the elderly [4–6], with a recent evidence review reporting that PA is the modifiable risk factor with the highest potential for arresting the increasing national prevalence of AD [7]. Spurred by encouraging data from animal models of AD, a growing number of human studies have sought to determine the extent to which PA might modulate core pathogenic markers of AD. The evolving evidence suggests that higher levels of PA associate with reduced Aβ and tau burden [8–10]. Furthermore, we found that, in a middle-aged group at increased risk for AD, those who were physically active exhibited fewer age-related alterations in Aβ deposition, glucose metabolism, hippocampal volume, and episodic memory relative to their less active peers [11]. In addition, PA may also have the potential to attenuate the adverse effects of genetic risk [12,13] and poor diet [14] on Aβ deposition.

Although less studied, a growing body of evidence suggests that high levels of sedentary behavior (SB) may also serve as an independent risk factor for negative outcomes [15,16]. Studies indicate that most older adults engage in high amounts of SB, up to 8.5 hours a day [17], and those at risk for AD due to family history exhibit higher levels of SB than those without a family history [18]. As such, it is especially important to examine these behaviors among those at risk for AD. Previous studies have examined SB among older adults in relation to cognitive performance [19], cerebral blood flow [20], and risk of AD [21]. However, to our knowledge, no study has yet examined the relationship between SB and CSF biomarkers in older adults at risk for AD.

Furthermore, although the foregoing studies are important for providing initial evidence for potentially disease-modifying effects of PA and SB in the AD cascade, many are limited by the use of self-report questionnaires for ascertaining such levels. These assessment approaches are vulnerable to measurement error stemming from faulty recall, social desirability, and other biases that might mask or inflate associations between PA, SB, and relevant outcomes [22,23]. Recent evidence indicates accelerometer-based measures may be more sensitive to distinctions between PA intensities and SB than self-report and more valuable when examining AD outcomes [24]. Second, to our knowledge, no studies have assessed the association between objectively measured PA, SB, and CSF biomarkers in an asymptomatic, middle-aged cohort at risk for AD. Accordingly, the objective of this study was to investigate the relationship between accelerometer-measured PA, SB, and CSF biomarkers of AD among at-risk, late-middle-aged adults. We specifically seek to ascertain the intensity of PA most conducive to a favorable AD biomarker profile and examine whether SB confers an additional risk beyond that of low levels of PA.

2. Methods

2.1. Participants

Eighty-five cognitively normal adults from the Wisconsin Registry for Alzheimer's Prevention (WRAP) participated in this study. WRAP is a longitudinal cohort consisting of approximately 1500 late-middle-aged adults who were cognitively healthy and between the ages of 40 and 65 years at study entry [25]. The cohort is enriched with persons who have a parental history of AD and/or carry ≥1 apolipoprotein ε4 (*APOE* ε4) alleles. Cognitive normalcy was determined based on intact performance on a comprehensive battery of neuropsychological tests, absence of functional impairment, and absence of neurologic/psychiatric conditions that might impair cognition [11,25]. In addition, all participants were living and functioning independently. The 85 participants for the present study were selected based on their participation in two WRAP substudies that included a 7-day PA assessment using an accelerometer and collection of CSF via lumbar puncture. Similar to the larger WRAP cohort, these individuals overrepresented persons who had a parental family history of AD (81.2%) and were *APOE* ε4–positive (42.4%). Table 1 details participants' additional background characteristics. All study procedures were approved by the University of Wisconsin Institutional Review Board and each participant provided informed consent before participation.