Effects of Cognitively Stimulating Sedentary Activities on Cognition in Middle Aged Adults with Increased Genetic Risk for Alzheimer's Disease

E. Ruth Sharpe

Department of Kinesiology, University of North Carolina at Greensboro

Undergraduate Research and Creativity Awards

Faculty Mentor: Dr. Jenifer Etnier

Graduate Student Mentor: Chad Wessinger

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Dementia is a worldwide health epidemic, affecting approximately 50 million individuals in 2020, with this number expected to reach 152 million by 2050 (Alzheimer's Disease International, 2018). From 1990 to 2019, dementia cases increased by 160.84%, reflecting the rapidly growing burden of this neurodegenerative disease on individuals, families, and healthcare facilities. In response to these rising trends, The Lancet Commission has identified 12 modifiable risk factors (MRF) linked to developing dementia, wherein if all were eliminated, dementia cases would decrease by 40% globally. Of the 12 modifiable risk factors of dementia, nine are directly linked to physical inactivity, implicating it as a key MRF for dementia development in both men and women (Livingston et al., 2020). Sedentary behavior (SB), defined as waking activities involving less than or equal to 1.5 METs while sitting or reclining (SBRN, 2017) has increased in recent years (Yang et al., 2019) and is linked to cognitive decline (Yan et al., 2020). Increasing physical activity may help offset these effects by reducing overall sedentary time. However, some research has shown cognitively stimulating sedentary behavior (CSSB) such as reading, writing, or computer use may also benefit cognitive function (Verghese et al., 2003; Kurita et al., 2019). However, how PA and CSSB interact, particularly in midlife (ages 40-65) when MRF have the highest preventative potential, remains unclear. Additionally, the heightened susceptibility of APOE ε4 carrier status makes examining both behavioral and genetic risk factors together even more important for clarifying whether CSSB has an impact on delaying Alzheimer's disease (AD) in midlife. Therefore, this study aims to investigate the joint effects of CSSB and PA on cognitive outcomes in midlife adults with genetic risk.

In addition to behavioral factors such as PA and SB, genetic risk also plays a substantial role in AD development. Carrying the apolipoprotein E ε4 allele (APOE ε4) is a major non-modifiable genetic risk factor that increases the likelihood of developing late-onset Alzheimer's

disease at an earlier age, accounting for more than half of all cases (Corder et al., 1993; Duara et al., 1996). While APOE plays major roles in lipid transport, injury repair of the brain, and amyloid-β clearance, the ε4 variant significantly impairs these processes and can increase the risk of cerebral amyloid angiopathy and cognitive decline during aging (Liu et al., 2013). Possessing one copy of the ε4 allele doubles AD risk, while possessing two copies increases an individual's risk 8 to 12-fold (Corder et al., 1993). Because age and genetics heighten susceptibility to cognitive decline, lifestyle factors become increasingly important prevention targets in mid to late life. PA is one of the most significant MRFs, while prolonged SB has also been shown to elevate the risk of developing AD (Yan et al., 2020). In contrast, higher levels of PA are positively associated with white matter tract preservation in older adults with APOE ε4 carrier status, suggesting that PA may buffer genetic and age-related vulnerability (Raffin et al., 2021). It has been shown that midlife risk factors can trigger neuropathological developments like AD in adults aged 45-65 years (Livingston et al., 2020). Collectively, these findings underscore the importance of understanding how PA and SB interact with genetics and age risk to tackle MRF that may prevent or delay AD progression.

SB is linked to adverse brain outcomes, even in the context of moderate to vigorous PA. Gogniat et al. found in a study of adults aged 62-79 years that increased sedentary behavior led to decreased executive functioning skills, naming ability, and slower processing speed even after adjusting for moderate to vigorous PA. These findings illustrate that SB negatively impacts brain health in those older than 60 years, independently from volume or intensity of exercise (2025). Results from this study also indicate that greater time spent in SB was significantly linked to a more pronounced Alzheimer's-related pattern of hippocampal atrophy, despite moderate to vigorous PA, resulting in declines in executive functioning skills, naming ability, and processing

speed. Longitudinal analyses after a mean follow up of 7 years demonstrated that APOE ε4 carriers experienced greater reductions in gray matter and cortical volume compared to non-carriers; although, reduced hippocampal volume was associated with increased time spent in SB despite carrier status (Gogniat et al., 2025). Together, these cognitive and structural findings underscore the independent and cumulative impact of SB on brain health in older adults.

In contrast to the risks associated with SB, other evidence suggests that even light intensity PA may help preserve brain structure in older adults. Raffin et al. (2021) reported that in adults with a mean age of 75 years over a 3 year longitudinal study that significant findings among high time spent in light physical activity and APOE ε4 carriers occurred primarily in white-matter pathways shared across both axial and mean diffusivity metrics, including the bilateral superior longitudinal fasciculus, right sagittal stratum, right anterior limb of the internal capsule (ALIC), and bilateral anterior corona radiata. Axial diffusivity additionally showed effects in the left ALIC and right posterior corona radiata, whereas mean diffusivity uniquely involved the bilateral cingulum bundle. Similarly, Varma et al. (2016) shared results that higher overall light-intensity daily walking in women aged 60-90 was strongly associated with better hippocampal integrity over 2 years than engagement in moderate to vigorous PA. Together, these findings indicate that even unstructured, light intensity movement accumulated through the day can support brain health in older adults. Rosano et al. (2017) showed that structured, moderate intensity PA increased hippocampal volume in older and frailer adults at risk of mobility disability. After one year, participants in the exercise group exhibited significant increases in hippocampal volume compared with those in the control group. Rosano et al. and Varma et al.'s findings jointly indicate that both spontaneous, light movement and structured, moderate exercise benefit brain structure, but planned exercise may yield larger effects. Rosano et al. also

found that individuals with higher baseline hippocampal volume experienced larger gains than those with lower baseline volume status. These findings suggest hippocampal volume may serve as a biomarker for personal PA recommendations in dementia prevention (Rosano et al., 2017). Collectively, these studies indicate that while SB contributes to cognition across populations, the neuroprotective effects of light-intensity PA may be noteworthy in APOE ε4 carriers, suggesting that even minimal increases in activity could help mitigate genetic vulnerability.

Physical inactivity is associated with a 30% increased risk of dementia (Yan et al., 2020), whereas sustained PA in mid and late life appears protective against AD by enhancing memory function (Etnier et al., 2018). With trends in sedentary behavior on the rise (Li et al., 2022), it may prove to be useful to determine a synergistic effect between CSSB and PA. Prolonged SB is associated with elevated risk of mild cognitive impairment (MCI) in adults aged 60 and older (Duan et al., 2024) and greater long-term impact among adults under 60 years of age (Sun et al., 2022). Sun et al. studied a cohort of 484,169 individuals (mean age of 56.5 years) and established that individuals who spent 8 hours per day in SB had a 25% increased risk of developing dementia compared with those spending below 5 hours per day in SB. Each additional 2.33 hours per day spent in SB was linked to a 6% higher incidence of developing dementia. Replacing 30 minutes of SB with PA was linked to a 6% lower chance of developing dementia and APOE ε4 carriers exhibited greater risk reduction when replacing SB with PA compared to non-carriers in this study (2022). Complementing these results, Duan et al. (2024) examined SB and PA in relation to MCI risk among APOE ε4 carriers and noncarriers. Their analyses determined that high levels of PA reduced MCI incidence across all groups, whereas prolonged SB increased MCI risk. Duan et al. also found a significant interaction between SB and APOE ε4 status, indicating that the combined presence of high SB and genetic risk further

increased the likelihood of developing MCI. Cut off times were also determined for daily sedentary time. Interestingly, non-carriers of the allele showed a cut off predictive of MCI of 3.03 hours per day, whereas carriers of the APOE ε4 allele showed less tolerance of SB before MCI with a cutoff of 2.09 hours per day (Duan et al., 2024).

However, some evidence suggests that certain cognitively stimulating sedentary activities (CSSB) may also reduce dementia risk in older adults. While some studies suggest that PA is most effective in combatting cognitive decline and that sedentary lifestyles increase dementia risk, others have reported that certain CSSB may also have a protective effect against MCI and dementia risk. Verghese et al. (2003) found in adults aged 75-85 years a 7% reduced risk of developing dementia when engaging in CSSB each day such as: reading, writing, completing crossword puzzles, playing board games, playing instruments, and attending educational classes. Engaging in more than 11 distinct CSSB per week displayed a 63% lower risk of developing dementia, highlighting the potential importance of both frequency and variety of cognitive engagement. To further support these findings, Kurita et al. (2018) examined 5,300 community dwelling adults in Japan (mean age = 75 years) and found that participation in 5 distinct CSSB was significantly associated with lower risk of cognitive impairment: reading, writing, completing cross word puzzles, playing board and card games, and using a computer. This study further indicates that engaging in a wider range of CSSB can be protective of cognitive decline and dementia. Both Kesse-Guyot et al. (2012) and Hamer and Stamatakis (2014) revealed in their studies that higher computer and internet use in those between 60 and 70 years of age correlated with better cognition, including executive function and verbal memory. Inversely, both studies revealed higher time spent watching television to be negatively correlated with cognition. Evidence of CSSB effect on cognition among adults in midlife (40-65 years of age) remains

sparse and there are definite gaps in the literature within this age group. Recent preliminary analyses using baseline data from the from PAAD-2 clinical trial (Park et al., 2020) contribute to this gap by revealing that among adults aged 40-65 years with positive APOE ε4 carrier status, greater time spent sedentary and reading was associated with lower cognition scores (Sharpe, et al., 2025), while CSSB like computer use were not associated with cognition. Given that midlife presents a crucial opportunity for dementia prevention, further research on CSSB in this age range is paramount. Understanding how different forms of sedentary activities influence cognition during this stage may help identify low cost and effective intervention targets than those initiated in later life.

Baseline data in PAAD2 identified some SB to be linked to poorer cognition, whereas results from the original PAAD trial (Etnier et al., 2018) demonstrated that adults aged 50-65 years who engaged in an 8-month structured exercise program exhibited significant improvements in memory. However, our results and prior work collectively suggest that the type, timing, and cognitive nature of sedentary activity may be key factors in driving these differences in cognition scores. For example, while television viewing has consistently been associated with poorer cognitive performance, other sedentary behaviors, such as computer use, often show null or positive effects based on age. Thus, while CSSB appears to offer protective benefits in older age, engagement in regular PA during midlife may be more effective in combatting Alzhemier's disease in those who are at a heightened genetic risk. The 2020 Lancet Commission on Dementia Prevention, Intervention, and Care posits that the period between 40 and 65 years of age is a critical window during which MRF, including PA, exert their greatest impact on cognitive health (Livingston et al., 2020). Building on this framework, our present study aims to extend prior work by examining how CSSB and PA interact within this midlife window, and whether APOE

ε4 carrier status further modifies these associations. Understanding these interrelationships will help clarify whether cognitively engaging sedentary activities can offset the risk of mild cognitive impairment due to inactivity, or if traditional physical activity remains the most potent protective behavior for long term brain health.

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