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Examining Hippocampal Volume as a Mediator in the Relationships of Self-Reported Frequency  
of Moderate-Intensity Exercise With Depressive Symptoms and Episodic Memory in Middle-  
Aged Adults at Risk for Alzheimer's Disease

by

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Under the Direction of Vonetta M. Dotson, Ph.D.

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## ABSTRACT

This project examined whether frequency of moderate-intensity exercise was associated with episodic memory and depressive symptoms in middle-aged adults at risk for Alzheimer's disease (AD), and whether hippocampal volume mediated these relationships. Data were drawn from adults aged 45–60 in the Wisconsin Registry for Alzheimer's Prevention (WRAP) and included MRI, depressive symptoms, and verbal and visual memory scores. Mediation analyses tested both direct and indirect effects of exercise frequency on the outcomes, accounting for hippocampal volume. It was hypothesized that greater hippocampal volume would be associated with more frequent exercise, fewer depressive symptoms, and better memory, and that hippocampal volume would mediate these associations. Results partially supported hypotheses: more frequent exercise was associated with fewer depressive symptoms but was not linked to memory performance. Hippocampal volume did not mediate any relationships. However, right hippocampal volume predicted visual memory, suggesting a lateralized effect. Additional research is needed to explore alternative neurobiological mechanisms.

**INDEX WORDS:** Exercise, Depression, Visuospatial memory, Verbal memory, Episodic memory, Hippocampal volume, Alzheimer's Disease, Risk factors

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## **DEDICATION**

This work is dedicated to my family, whose unwavering support and encouragement have been essential in supporting me to achieve my goals. Much of the work I pursue is inspired by each of you and the values you have instilled in me. I am deeply grateful and recognize that none of this would be possible without your sacrifices.

## ACKNOWLEDGMENTS

I am deeply grateful to my committee chair and mentor, Dr. Vonetta Dotson, for her committed support and encouragement throughout this project. Her guidance has been invaluable, and she exemplifies what it means to be a researcher centering the diverse communities we serve, a value I aspire to carry forward in my own work. I would also like to thank my committee members, Dr. Rebecca Ellis, Dr. Ashley Ware, and Dr. Ozioma Okonkwo, as well as the Aging Well for Everyone lab, whose thoughtful feedback and support have helped me grow as a researcher committed to creating clinically translatable work.

## 1 INTRODUCTION

### 1.1 Overview

Dementia affects around 50 million people worldwide, an estimation expected to triple by 2050 (World Health Organization, 2023a). With no cure currently available for Alzheimer's disease (AD), the most common cause of dementia, identifying effective prevention strategies is imperative, particularly for individuals at risk for AD. Physical activity, including structured exercise, has garnered increasing attention as a potential prevention strategy for dementia. The World Health Organization (2024) defines physical activity as bodily movement produced by skeletal muscles that require energy, including everyday tasks such as light walking and gardening. Physical exercise, a subclassification of physical activity, refers to planned, structured, or repetitive movements aimed at improving or maintaining physical fitness (World Health Organization, 2023a). Exercise training includes parameters such as type, frequency, intensity, and session duration (Boa Sorte Silva et al., 2024). Moreover, exercise can be classified as aerobic or anaerobic based on the intensity, interval, and category of muscle fibers involved (Boa Sorte Silva et al., 2024; Patel et al., 2017). Aerobic exercise—the focus of the current study—targets changes in cardiorespiratory fitness, such as walking, running, or cycling (Boa Sorte Silva et al., 2024; Patel et al., 2017).

Both exercise and structured physical activity are associated with improved brain health and a reduced risk of developing AD and other types of dementia (Yan et al., 2023). Among the cognitive benefits, research suggests that regular physical activity, whether structured exercise or general movement, assists with preserving and improving memory function, which tends to decline in mid-to-late life and in individuals with dementia (Voss et al., 2019; Contreras-Osorio et al., 2022; Sewell et al., 2021; Ponce & Loprinzi et al., 2018; Yan et al., 2023). Physical

activity also has a known benefit on mood, with studies showing its impact on reducing depressive symptoms, a significant risk factor for dementia (Hakim et al., 2022; Khodadad et al., 2023). Hippocampal changes could underlie the benefits of physical activity for memory and mood. Physical activity has been associated with increased volume in the hippocampus, a brain region critical for memory function (Aghjayan et al., 2022; Augusto-Oliveira et al., 2023; Dougherty et al., 2017; Erickson et al., 2011; Raichlen et al., 2019) and implicated in the neurobiology of depression (Dotson et al., 2021; Souza et al., 2023).

Regarding dementia prevention, research remains mixed on exercise's impact in people at risk for dementia. A systematic review concluded that exercise may protect against memory and cognitive decline in APOE  $\epsilon$ 4 carriers, who have a heightened risk for AD and often show signs of memory decline decades before diagnosis (Tokgöz et al., 2021). However, it is unclear whether this is also true for the benefits of exercise for depression: One study showed that APOE genotype did not moderate the effect of exercise on depressive symptoms (Dotson et al., 2016), while another study showed that exercise was more strongly associated with reduced depressive symptoms in non-carriers of APOE  $\epsilon$ 4 (Ku et al., 2017). Also unclear is whether hippocampal volumes mediate the effects of exercise on episodic memory and depressive symptoms in middle-aged adults at risk for AD. The current study aimed to address these gaps in the literature.

## **1.2 Exercise and Memory**

Memory is known to decline with age, particularly in individuals at risk for AD (El Haj et al., 2016). In aging and AD, episodic memory, a type of long-term memory that involves forming and retrieving conscious memories of specific past events, may be especially vulnerable. Despite the existing vulnerabilities, research has shown that exercise can protect against episodic memory loss and reduce risk factors for developing AD (Ren & Xiao, 2023). Furthermore, a

meta-analysis found that physical activity improves brain health, including memory, in APOE  $\epsilon$ 4 carriers (De Frutos-Lucas et al., 2020).

Current literature suggests that exercise improves verbal episodic memory. For instance, a randomized control trial (RCT) found that twice-weekly resistance training improved verbal memory compared to balance-and-toning training in older women aged 65 to 75 (Best et al., 2015). Similarly, another RCT demonstrated that 12 weeks of high-load, long-resistance training improved performance on a delayed verbal memory test compared to moderate-load, short-resistance training in middle-aged adults (Marston et al., 2019). Another recent study showed that moderate-to-vigorous physical activity measured by accelerometer was associated with better verbal memory in midlife (Mitchell et al., 2023). These findings are supported by recent meta-analyses showing that aerobic exercise improves verbal memory among older adults without dementia (Aghjayan et al. 2022) and that anaerobic exercise improves memory function in older adults with mild cognitive impairment (Huang et al., 2022). Consistent with these meta-analyses, memory consolidation was associated with moderate-intensity physical activity in older adults in a recent study (G., M., Berisha, 2024). Taken together, these results suggest that exercise of different modalities improves verbal episodic memory in middle-aged and older adults.

Relative to verbal memory, literature examining the effects of exercise on visual episodic memory is limited; however, findings are generally positive. For instance, a seminal study in adults aged 55 to 80 found that improvements in fitness after 12 months of moderate-intensity cardiovascular exercise training was associated with improved visuospatial memory (Erickson et al., 2011). A six-month RCT found that a dancing program improved performance on a visuospatial memory task in older adults aged 63 to 80 compared to strength-endurance training

(Rehfeld et al., 2018). Further supporting these results, another RCT examined sedentary older adults who participated in six months of stretching, aerobic, or resistance training, revealing that the aerobic intervention group demonstrated improved visual memory compared to the other exercise groups (Jonasson et al., 2016). Overall, the literature suggests exercise improves performance on tasks involving visual episodic memory, in addition to verbal episodic memory.

### **1.3 Exercise and Depression**

Depression is a leading cause of disability globally, disproportionately impacting older adults (Hu et al., 2022). Annually, more than 280 million people worldwide suffer from depression (World Health Organization, 2023b), emphasizing the urgent need to address this issue. Depression across the lifespan manifests as affective, somatic, and interpersonal symptoms (Chen et al., 2023; Dehn & Belbo, 2019), and often impairs memory, as shown by a recent meta-analysis (James et al., 2021); however, depression-related memory deficits can be magnified in later life (James et al., 2021; Kuo et al., 2021). Given the impact of depression on disability and on cognitive functioning in older adults, effective treatments are essential to a healthy aging population.

Prior studies noted physical activity as an essential treatment for depression (Imboden et al., 2020; Hidalgo & Sotos, 2021). Numerous studies consistently demonstrated that individuals who engage in more physical exercise experience fewer depressive symptoms and have a lower risk for developing depression, a finding observed across countries and cultures (D., Elliott et al., 2022; Koo et al., 2020; Lewis et al., 2021; Schuch et al., 2019). In an umbrella review, Bigarella et al. (2022) conducted 12 meta-analyses of 97 RCTs, ascertaining that exercise significantly improved depression and depressive symptoms in older adults. Another recent meta-analysis revealed that resistance training decreased depressive symptoms in older adults (Khodadad Kashi

et al., 2022). Exercise may differentially impact particular components of depression in older adults, as one study found that a walking intervention mitigated somatic symptoms of depression but not anhedonia or negative mood (Dotson et al., 2016). In middle-aged samples, while one study found that cardiovascular risk factors may limit the effectiveness of exercise for mood and cognitive functioning among diverse older adults aged 45 and older (Minto et al., 2023), another study in otherwise healthy adults aged 50 years or older found that both moderate walking exercise (150 minutes/week) and vigorous walking (75 minutes/week) for 12 weeks reduced depressive symptoms compared to a stretching control group (Chin et al., 2022). These results underscore how frequency of exercise may confer psychological benefits from consistent behavioral engagement. In addition to the benefits on mood, exercise may be a viable alternative or adjunctive treatment to address cognitive impairment in late-life depression (Dotson et al., 2021). These results underscore the broad effects of the frequency of exercise in reducing depressive symptoms.

#### **1.4 Exercise and the Hippocampus**

The benefits of exercise for memory and depression may stem from its impact on the hippocampus, a region critical in facilitating various neural networks that support the encoding, consolidation, and retrieval of episodic memory (Bonnici & Maguire, 2018; McCormick et al., 2018; Rolls, 2022). The hippocampus tends to atrophy more rapidly than other brain regions in populations at higher risk for neurodegeneration, such as those with a genetic risk for AD (Gorbach et al., 2020). Despite this vulnerability, research has shown that modifiable lifestyle factors, such as exercise and cognitive engagement, are associated with increased hippocampal volumes in older adults carrying APOE- $\epsilon$ 4, a genetic risk factor for AD (Fraser et al., 2022; Heneghan et al., 2023).

Exercise has been shown to counteract age-related changes in brain structure and function in healthy aging adults and adults at risk for dementia (Agusto-Oliveira et al., 2023; Firth et al., 2018; Schoenfeld & Swanson, 2021). Exercise-induced increases in grey matter volume are particularly evident in the hippocampus, entorhinal cortex, and prefrontal cortex (Jonasson et al., 2016; Zhao et al., 2020). In a meta-analysis of RCTs across the lifespan, aerobic exercise had a significant effect on left hippocampal volumes compared to control conditions, with post hoc analyses suggesting benefits were due to exercise preventing volume decreases over time (Firth et al., 2018). However, physical exercise also appears to stimulate hippocampal growth. Demonstrating this, an RCT conducted by Frodl et al. (2019) showed that aerobic exercise significantly increased left hippocampal volumes in healthy adults aged 18 to 65 compared to a non-exercise control group. Furthermore, a separate RCT ascertained that a combination of anaerobic and aerobic exercise significantly increased hippocampal volume compared to balance and tone training in older women aged 70 to 80 years with probable mild cognitive impairment (ten Brinke et al., 2015). These findings are further supported by a meta-analysis of 22 studies, suggesting that combining aerobic and anaerobic exercise may assist in preserving hippocampal volumes or reversing age-related hippocampal atrophy in older adults (Wilckens et al., 2021).

Taken together, the literature reviewed highlights the interrelationships between memory, depression, hippocampal volumes, and exercise in middle-aged to older adults, suggesting that hippocampal volumes may mediate the effects of exercise on memory and depression. Specifically, exercise has been shown to increase hippocampal volume in middle-aged to older adults, with some evidence linking these changes to memory improvement and reduction of depressive symptoms. Less clear is whether hippocampal volumes mediate the relationships of

exercise frequency with memory and depression, or whether individuals at risk for AD experience these benefits. Thus, the current project aimed to address these gaps in knowledge.

### **1.5 The Present Study**

The current project investigated the potential role of hippocampal volumes in mediating the relationships of exercise frequency with memory and depressive symptoms in middle-aged adults at risk for AD. The focus on individuals at risk for AD is important because there is currently no cure for AD, thus prevention efforts in at-risk populations are critical. A growing body of research suggests modifiable lifestyle activities not only reduce the risk of dementia in the general population, but also promote better cognitive function in individuals at risk for AD based on APOE genotype or family history (Dotson et al., 2021; Passeri et al., 2022). For example, a recent study found middle-aged adults with a family history of AD who were more physically, socially, and intellectually active had better verbal and visual memory at baseline and at two-year follow-up compared to their less active peers (Heneghan et al., 2023).

While existing literature suggests that exercise increases hippocampal volume, and that in general larger volumes are associated with better memory and lower depressive symptoms, there are gaps in the literature on 1) associations of exercise with hippocampal volumes, memory, and depressive symptoms in middle-aged adults, particularly in those at risk for AD; and 2) the potential mediating role of hippocampal volumes in the relationships of exercise with memory and depression. Moreover, investigating moderate-intensity exercise frequency may be particularly salient, as it associated with behavioral activation, an evidence based-treatment for depression. The current study addressed these gaps. Identifying neurobiological mechanisms of lifestyle interventions that attenuate depressive symptoms and support memory function in

individuals at risk for AD may have significant implications for reducing healthcare burden, assisting families, and promoting healthier aging in at-risk populations.

### **1.6 Aims of the Proposed Study**

**Specific Aim 1.** The first goal of the present study was to assess associations of moderate-intensity exercise frequency with episodic memory, depressive symptoms, and hippocampal volumes in middle-aged adults at familial or genetic risk for AD.

**Hypothesis 1.** Consistent with previous research, I anticipated that greater frequency of moderate-intensity exercise would be associated with (1a) higher verbal and visual episodic memory, (1b) lower depressive symptoms, and (1c) larger hippocampal volumes.

**Specific Aim 2.** The second goal of the study was to examine if total hippocampal volume mediated the relationships of moderate-intensity exercise frequency with episodic memory and depressive symptoms described in Aim 1.

**Hypothesis 2.** I hypothesized that total hippocampal volume would partially mediate the associations of frequency of moderate-intensity exercise with (2a) episodic memory and (2b) depressive symptoms, reflected in both direct and indirect effects in mediation models. Specifically, I hypothesized that greater frequency of moderate-intensity exercise would still significantly predict higher episodic memory and lower depressive symptoms after controlling for total hippocampal volume (path  $c'$  in the mediation models). I also expected a significant indirect effect (path  $ab$ ), reflecting the extent to which the relationship between frequency of moderate-intensity exercise and the outcome variables are accounted for by differences in total hippocampal volume.

## 2 METHODS

A secondary data analysis was performed on data from the Wisconsin Registry for Alzheimer's Prevention (WRAP), a longitudinal study at the University of Wisconsin-Madison designed to identify midlife factors associated with the development of AD.

### 2.1 Participants

The WRAP is an ongoing longitudinal study that currently includes over 1,700 healthy adults aged 40 to 65 who were recruited from the University of Wisconsin-Madison and the surrounding community from memory clinics attended by individuals with a parent diagnosed with AD, radio and newspaper advertisements, and referrals. Inclusion criteria for WRAP included being a fluent English speaker, possessing intact visual and auditory acuity, being right-handed, having nine or more years of education, and having good mental and physical health with no diseases, including cardiovascular diseases, expected to interfere with study participation over time. To be included, participants were also required to either have at least one parent with AD or carry an APOE  $\epsilon$ 4 allele. Exclusion criteria included prior diagnosis of dementia or evidence of dementia at baseline testing. All participants provided written and verbal consent to participation in the study consistent with the University of Wisconsin-Madison's IRB guidelines.

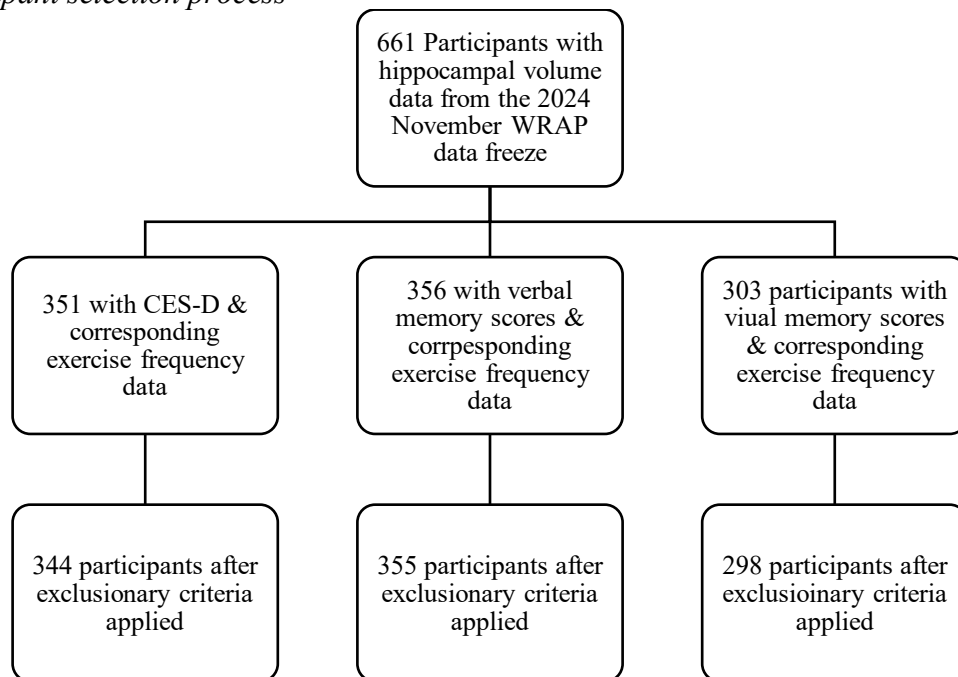
Data for the current analyses came from the November 2024 WRAP data freeze. The data we received included hippocampal volumes for 661 participants. In the WRAP dataset, CES-D, moderate-intensity exercise frequency, and memory data were obtained from participants on different dates than their MRI scans. In the interest of using questionnaire and cognitive data that were relevant to the MRI data, the scores were only included if they were obtained near the time of the MRI scan. The age at study visit was rounded to the nearest whole number, and MRI visits were matched with questionnaire and cognitive data at the same rounded age for each

participant. This resulted in the following sample sizes for each outcome variable: CES-D = 351, verbal learning tests = 356, and visual memory tests = 303. The present analyses excluded participants who reported confounding medical conditions (e.g., neurological disease), documented vascular disease (coronary artery disease, cerebrovascular disease, peripheral arterial disease, or congestive heart failure), uncontrolled type I or II diabetes mellitus, or severe untreated hypertension ( $> 200/100$  mmHg). A flowchart summarizing this process is presented in Figure 1.

Participants ranged in age from 55 to 70 years (mean age  $62.70 \pm 7.52$ ), were 95% white and 71% female, and had  $16.6 \pm 2.8$  years of education. Demographic characteristics are summarized for each analysis in Table 1.

### Figure 1

#### *Participant selection process*



**Table 1**  
*Sample characteristics*

	<b>Total Sample (N = 661)</b>	<b>Mediation Analysis with Depression (N = 344)</b>	<b>Mediation Analysis with Visual Memory (N = 298)</b>	<b>Mediation Analysis with Verbal Memory (N = 355)</b>
Age	62.7 ± 7.5	62.7 ± 7.5	62.7 ± 7.5	62.6 ± 7.5
Sex (% female)	80 (70.8 %)	244 (70.9 %)	79 (70.4 %)	79 (71.3 %)
Race (% white)	97 (95.3 %)	327 (95.2 %)	286 (95.7 %)	344 (95 %)
Vascular burden	1.4 ± 1.2	1.4 ± 1.2	1.4 ± 1.2	1.4 ± 1.2
Education (years)	16.6 ± 2.8	16.6 ± 2.8	16.5 ± 2.8	16.5 ± 2.8
Moderate-intensity exercise (days per week)	2.6 ± 1.5	2.6 ± 1.6	2.6 ± 1.6	2.6 ± 1.6
CES-D Total Score	6 ± 6.8	6 ± 6.8	-	-
Verbal memory composite	<.0	-	-	<.0
RAVLT delayed	10.8 ± 3.0	-	-	-
RAVLT total	52.5 ± 8.8	-	-	-
Visual memory composite	0.30	-	0.30	-
BVMT-R delayed	10.0 ± 5.3	-	-	-
BVMT-R total	25.8 ± 5.2	-	-	-
Total hippocampal volume	7696.1 ± 962.9	7679.4 ± 962.4	7732.2 ± 963.9	7676.8 ± 962.4
Left hippocampal volume	3762.1 ± 493.3	-	-	3762.1 ± 493.3
Right hippocampal volume	3954.4 ± 501.6	-	3954.5 ± 501.6	-

*Note.* RAVLT = Rey Auditory Verbal Learning Test. BVMT-R = Brief Visuospatial Memory Test-Revised. The individual mediation analysis samples are all subsets of the total sample due to missing data.

## 2.2 Measures

### 2.2.1 Episodic Memory

To measure episodic memory, participants completed the Rey Auditory Verbal Learning Test (RAVLT) and the Brief Visuospatial Memory Test, Revised (BVMT-R). The RAVLT is a commonly used measure of a person's ability to store, encode, and retrieve verbal information (Moradi et al., 2017). Participants are given a list of 15 unrelated words repeated over five

different trials and are asked to repeat them after each trial. Following presentation and recall of a distractor list of 15 unrelated words, the participant must recall the original list of 15 words immediately and again after 30 minutes. During a recognition trial, the 15 original words are presented in addition to 15 new words, and the participants identify whether words were on the original list. The current study used the WRAP's verbal learning & memory factor score composite, consisting of the of the RAVLT Learning Trials 3-5 and the RAVLT delayed recall trial (Zuelsdorff et al., 2020). Factor scores have been standardized into z-scores, using means and standard deviations obtained from the WRAP Wave 1 baseline data.

The BVMT-R is a commonly used assessment tool to measure visuospatial memory. There are three learning trials in which an array of six geometric figures is viewed and then immediately reproduced from memory. The array is then reproduced after a 25-minute delay, followed by a recognition trial during which participants identify which of 12 figures were included in the original display. The visual learning & memory factor score composed of the BVMT-R immediate total and delayed recall scores that were also standardized into z scores, using means and standard deviations obtained from the whole baseline sample.

### 2.2.2 *Depressive Symptoms*

Participants completed the Center for Epidemiologic Studies-Depression Scale (CES-D) (Radloff, 1977), a commonly used 20-item self-report measure of depressive symptoms with high internal consistency among the general population (Cronbach's  $\alpha = 0.85$ ). Each item includes statements such as "I had crying spells" or "My sleep was restless," and participants rate how often they felt that way over the previous week, on a 0 to 3 scale. Each item is summed to achieve a total score (four items are reverse scored), with higher scores indicating more depressive symptoms. The CES-D total score was used as an outcome variable.

### 2.2.3 Exercise

Participants completed the Women’s Health Initiative (WHI) Personal Habit Update questionnaire, which includes self-report of physical activity. The current study used responses to the question about **weekly** frequency of moderate-intensity exercise (e.g., calisthenics, easy swimming), with responses ranging from none to  $\geq 5$  days/week (see Table 2). Responses served as a predictor variable in the primary analyses. Duration of moderate-intensity exercise was also investigated in follow-up analyses.

**Table 2**

<i>Moderate-intensity exercise question from the WHI Personal Habits Update Questionnaire</i>	
Not including walking outside the home, how often each week (7 days) do you usually do the exercises below?	
MODERATE EXERCISE (Not exhausting). For example, biking outdoors, using an exercise machine (like a stationary bike or treadmill), calisthenics, easy swimming, popular or folk dancing.	1 day per week
	2 days per week
	3 days per week
	4 days per week
	5 or more days per week
How long do you usually exercise like this at one time?	Less than 20 minutes
	20-39 minutes
	40-59 minutes
	1 hour or more

### 2.2.4 Covariates

Age, sex, race, years of education, vascular burden, and total gray matter volume were included as covariates. Variables from the WRAP dataset assessing participants’ self-reported history of vascular conditions were summed to create a cumulative vascular burden score. The items included a history of heart disease, heart attack, congestive heart failure, recurrent chest pain with exercise, irregular heartbeat, coronary bypass surgery, and other heart problems. Additionally, vascular risk factors of hypertension, diabetes, and high cholesterol were also included in the cumulative score. This resulted in a vascular burden variable with a possible range of 0 to 10, which was used as a continuous covariate.

### 2.3 Imaging Procedure

Participants underwent T1-weighted 3-T MRI (GE Signa 750) with an 8- or 32-channel phased array head coil at the University of Wisconsin-Madison Waisman Brain Imaging Lab. Three-dimensional T1-weighted inversion recovery-prepared spoiled gradient echo scans were collected (inversion time (TI)/echo time (TE)/repetition time (TR) = 450 ms/3.2 ms/8.2 ms, flip angle = 12°, slice thickness = 1 mm no gap, field of view (FOV) = 256, matrix size = 256×256 yielding a voxel resolution of 1 mm×1 mm×1 mm).

Volumetric estimates were derived from the T1-weighted images. T1-weighted MRI was tissue-class segmented using the unified segmentation in SPM12 (Langhough Koscik et al., 2021). T1-weighted MRIs were bias-corrected, tissue class segmented into gray matter, white matter, and cerebral spinal fluid, and spatially normalized to Montreal Neurological Institute standard space (SPM12; [www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)). Intracranial volume was the sum of estimated gray matter, white matter, and cerebral spinal fluid volumes. Hippocampal volume was estimated using the automated FSL FIRST version 6 software (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST>). FSL FIRST is a segmentation tool that identifies subcortical brain regions given the observed intensity gradients (e.g., gray/white matter, CSF borders) on the T1-weighted image (Patenaude et al., 2011). The FSL FIRST segmentation methods are widely used and have been validated against other automated segmentation tools and gold-standard manual segmentation methods image (Patenaude et al., 2011). All images were visually inspected to ensure they were accurately reconstructed and without topological defects. Total hippocampal volume was used as the mediator for the analyses.

### 2.4 Data Analysis

To address both aims, three mediation analyses were performed using SPSS Version 28.0 (IBM Corp., 2023) with the SPSS PROCESS macro by Andrew Hayes (Hayes, 2017), output 4. Following the Baron and Kenny (1986) approach to establish partial mediation with a significant direct and indirect effect, analyses of the three mediation outputs (Table 3) involved the following steps:

1. Interpret the total effect of X on Y (path  $c$ ).
2. Interpret the relationship between X and M (path  $a$ ).
3. Interpret the relationship between M and Y (path  $b$ ).
4. Assess the direct effect of X on Y after controlling for M (path  $c'$ ), and determine the indirect effect by assessing how the relationship between X and the Y is mediated by M (path  $ab$ ).

**Figure 2.** Baron and Kenny's (1986) mediation model.

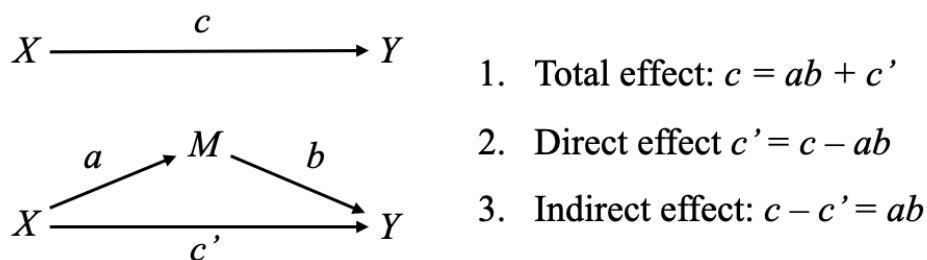
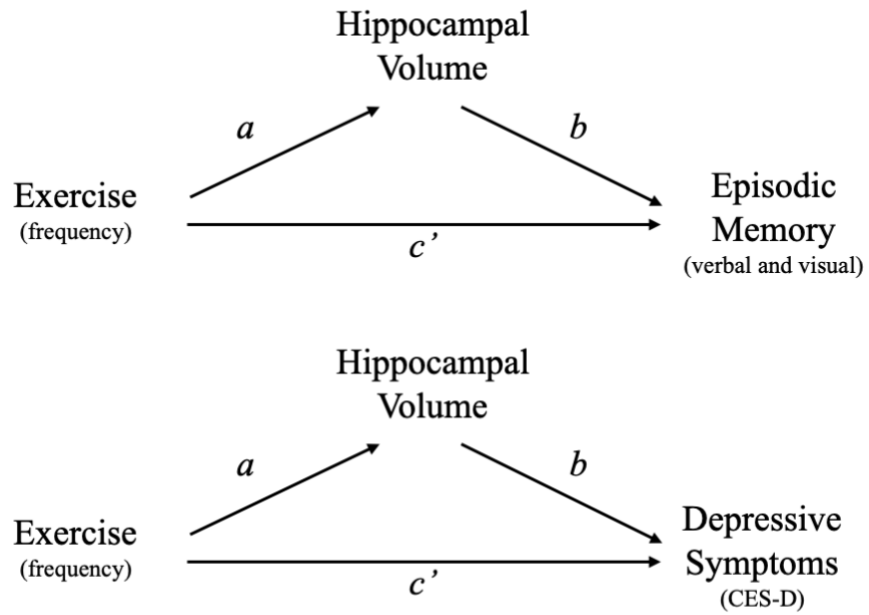


Figure 2 illustrates the mediation model structure with paths  $c$  (total effect),  $c'$  (direct effect),  $a$ , and  $b$ , while Figure 3 depicts the hypothesized mediation pathways for each analysis. Sex, race, age, education, total gray matter volume and vascular burden (sum of vascular risk factors and conditions) were included as covariates in all analyses. An  $\alpha \leq 0.05$  was considered significant for all analyses. Correction for multiple comparisons were not conducted because each outcome was analyzed independently (García-Pérez, 2023). Bootstrapping with

5,000 samples was conducted due to its high statistical power for detecting mediation effects and greater robustness to outliers.

For Aim 1, the total effect (path c) for frequency of moderate-intensity exercise (X) on the outcome variables—verbal memory composite, visual memory composite, and CES-D total scores (Y)—were analyzed without controlling for total hippocampal volume (M). Additionally, the relationship between exercise frequency (X) and total hippocampal volume (M) (path a) and the relationship between total hippocampal volume (M) and the outcome variables (Y) (path b) were analyzed. To address aim 2, the direct effect (path c') of exercise frequency on the outcome variables, accounting for hippocampal volume (M), was examined, as shown in Figure 3. Indirect effects (path ab) were analyzed to examine whether hippocampal volume (M) mediated the relationships between exercise frequency (X) and the outcome variables (Y).

**Figure 3.** Hypothesized mediation models for Aim 2.

### 3 RESULTS

#### 3.1 Mediation models: Total, direct, & indirect effects

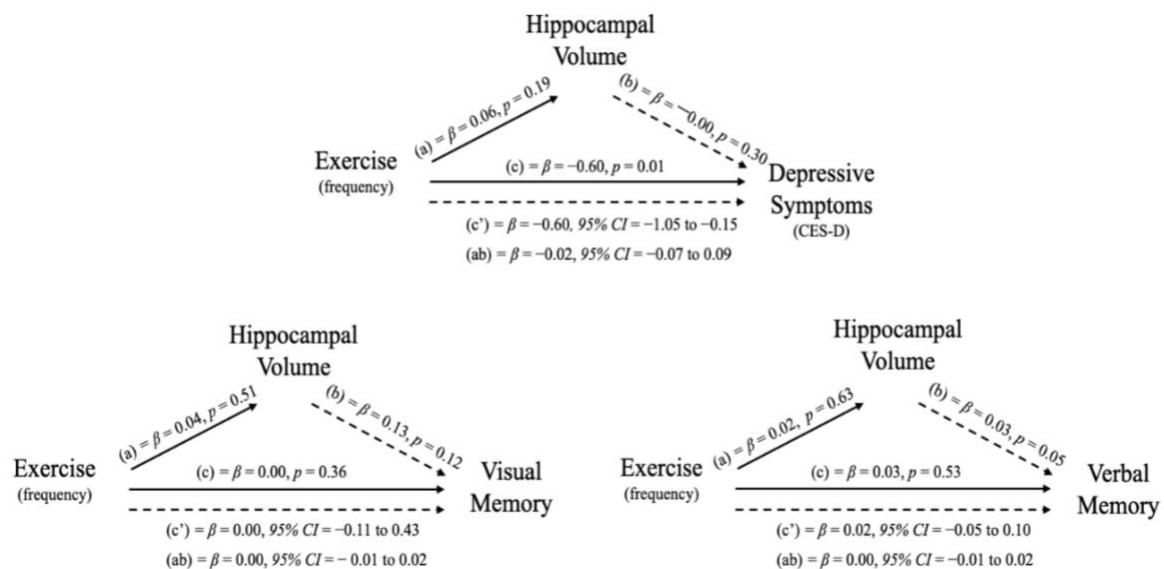
Figure 4 depicts results of the mediation models, with detailed results summarized in Tables 3-5. Aim 1 examined the associations of moderate-intensity exercise frequency with depressive symptoms, episodic memory, and total hippocampal volume. The results partially supported hypotheses for Aim 1, as exercise frequency was negatively associated with depressive symptoms (path c:  $\beta = -0.60$ ,  $SE = 0.23$ ,  $t = -2.62$ ,  $p = 0.01$ ), reflecting lower depressive symptoms as a function of greater frequency of moderate-intensity exercise. However, Aim 1 was not supported for episodic memory. Exercise frequency did not predict visual memory (path c:  $\beta = -0.06$ ,  $SE = 1.46$ ,  $t = -0.92$ ,  $p = 0.36$ ), nor was it associated with verbal memory (path c:  $\beta = .04$ ,  $SE = 0.04$ ,  $t = 0.62$ ,  $p = 0.53$ ). Lastly, exercise frequency did not predict total hippocampal volume in any of the analyses (path a,  $p \geq 0.19$ ).

Aim 2 assessed whether hippocampal volume mediated the relationships between frequency of moderate-intensity exercise and the outcome variables. Aim 2 was not supported for depressive symptoms. Although the direct effect of exercise frequency on depressive symptoms remained significant after controlling for total hippocampal volume (path c':  $\beta = -0.60$ ,  $SE = 0.23$ ,  $95\% CI = -1.05$  to  $-0.15$ ,  $p = 0.01$ ), the indirect effect via hippocampal was not significant (path ab:  $\beta = -0.02$ ,  $SE = .02$ ,  $95\% CI = -0.07$  to  $0.09$ ), indicating no evidence of full or partial mediation.

Similarly, Aim 2 was not supported for episodic memory outcomes. Frequency of moderate-intensity exercise did not have a direct effect with visual memory (path c':  $\beta = 0.00$ ,  $SE = 0.04$ ,  $95\% CI = -1.11$  to  $0.43$ ,  $p = 0.51$ ), and the indirect effect via hippocampal volume was not significant (path ab:  $\beta = 0.00$ ,  $SE = -0.01$ ,  $95\% CI = 0.02$ ). Similarly, the direct

effect of moderate-intensity exercise frequency on verbal memory was not significant after controlling for total hippocampal volume (path  $c'$ :  $\beta = 0.02$ ,  $SE = 0.04$ ,  $95\% CI = -0.05$  to  $0.10$ ,  $p = 0.51$ ), nor was the indirect effect via hippocampal volume significant (path  $ab$ :  $\beta = 0.00$ ,  $SE = 0.01$ ,  $95\% CI = -0.01$  to  $0.02$ ). Thus, analyses indicated no evidence of full or partial mediation for Aim 2. It should be noted that larger hippocampal volumes predicted better verbal memory (path  $b$ :  $\beta = 0.03$ ,  $SE = 0.00$ ,  $t = 2.00$ ,  $p = 0.05$ ) but not visual memory (path  $b$ :  $\beta = 0.13$ ,  $SE = 0.00$ ,  $t = 1.57$ ,  $p = 0.12$ ).

**Figure 4.** Results of mediation analyses.



**Table 3**  
Results of the mediation analysis with depressive symptoms as the outcome

DV	IV	$\beta$	SE	<i>t</i>	<i>p</i>	LLCI	ULCI	<i>F</i>	<i>R</i> <sup>2</sup>
<b>Hipp. Volume</b>	<b>Constant</b>	0.57	954.62	6.42	0.00	4248.22	8003.80	22.83	0.33
	<b>Exercise</b>	0.06	26.87	1.30	0.19	-17.82	87.93		
	<b>Age</b>	-0.22	6.96	-4.29	< 0.00***	-43.57	-16.19		
	<b>Sex</b>	-0.14	105.23	-2.86	< 0.00***	-508.53	-94.52		
	<b>Race</b>	-0.01	64.33	-0.11	0.91	-133.77	119.31		
	<b>Education</b>	0.02	15.60	0.43	0.6654	-23.93	37.42		
	<b>Vascular Burden</b>	0.10	36.27	2.16	.0314	7.06	149.73		
<b>CES-D</b>	<b>Constant</b>	20.75	8.60	2.41	<0.01*	3.83	37.66	1.97	0.12
	<b>Exercise</b>	-0.60	0.23	-2.62	<0.01*	-1.05	-0.15		
	<b>Hippocampal volume</b>	-0.14	0.00	-1.03	0.30	-0.00	0.00		
	<b>Age</b>	-0.11	0.06	-1.86	0.06	0.23	0.01		
	<b>Sex</b>	0.57	0.90	0.95	0.40	-1.60	-0.55		
	<b>Race</b>	-0.52	0.55	-0.96	0.34	-1.60	0.55		
	<b>Education</b>	0.03	0.13	0.54	0.59	-1.60	0.55		
	<b>Vascular Burden</b>	-0.3	0.31	-0.63	0.53	-0.81	0.41		
	<b>Total Gray Matter Volume</b>	-0.00	1.22	-0.03	0.97	-2.45	2.38		
	<b>Direct effect</b>		-0.60	0.23	-2.62	0.01	-1.05	-0.15	
<b>Indirect effect</b>		-0.02	0.02			-0.07	0.09		

\**p* < .05, \*\**p* < .01, \*\*\**p* < .001. CES-D = Center for Epidemiologic Studies Depression Scale, DV = Dependent variable, IV = Independent variable,  $\beta$  = Unstandardized estimates, SE = Standard error, LLCI = Lower limit confidence interval, ULCI = Upper limit confidence interval

**Table 4**

Results of the mediation analysis with the visual memory composite as the outcome

DV	IV	$\beta$	SE	$t$	$p$	LLCI	ULCI	$F$	$R^2$
<b>Hipp. Volume</b>	<b>Constant</b>	0.59	1188.60	4.93	0.00	3522.10	8207.34	17.01	0.35
	<b>Exercise</b>	0.04	35.16	0.65	0.51	-46.13	92.48		
	<b>Age</b>	-0.21	8.74	-3.34	0.00	-46.46	-11.99		
	<b>Sex</b>	-0.13	131.73	-2.17	< 0.03*	-545.94	-26.69		
	<b>Race</b>	-2.97	66.17	-0.04	< 0.96	-133.40	127.45		
	<b>Education</b>	-0.01	19.03	-0.17	0.86	-40.80	34.24		
	<b>Vascular Burden</b>	0.10	44.23	1.72	0.09	-10.92	163.44		
	<b>Constant</b>	0.32	1.46	-0.34	0.73	-3.34	2.36	1.33	0.08
<b>Visual Memory</b>	<b>Exercise</b>	-0.06	0.04	-0.92	0.36	-0.12	0.42		
	<b>Hippocampal Volume</b>	0.13	0.00	1.57	0.12	0.00	0.00		
	<b>Age</b>	-0.13	0.01	-1.72	0.87	-0.03	0.00		
	<b>Sex</b>	0.05	0.15	0.77	0.44	-0.18	0.42		
	<b>Race</b>	-0.13	0.08	-1.70	0.09	-0.28	0.02		
	<b>Education</b>	0.19	0.02	3.02	0.00	0.02	0.10		
	<b>Vascular Burden</b>	-0.01	0.05	-1.24	0.22	-0.16	0.04		
	<b>Total Gray Matter Volume</b>	-0.01	1.25	-.07	0.94	-2.56	2.39		
	<b>Direct effect</b>	0.00	0.04	-0.96	0.36	-0.11	0.43		
	<b>Indirect effect</b>	0.00	0.01			-0.01	0.02		

\* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ . DV = Dependent variable, IV = Independent variable,  $\beta$  = Unstandardized estimates, SE = Standard error, LLCI = Lower limit confidence interval, ULCI = Upper limit confidence interval

**Table 5**

Results of the mediation analysis with the verbal memory composite as the outcome

DV	IV	$\beta$	SE	<i>t</i>	<i>p</i>	LLCI	ULCI	<i>F</i>	<i>R</i> <sup>2</sup>
<b>Hipp. Volume</b>	<b>Constant</b>	0.59	1078.99	5.84	0.00	4181.80	4181.80	5.66	0.24
	<b>Exercise</b>	0.02	31.92	0.49	0.63	-47.27	78.46		
	<b>Age</b>	-0.25	7.66	-4.29	< 0.00***	-47.90	-17.73		
	<b>Sex</b>	-0.13	122.86	-2.22	<0.03*	-514.58	-30.73		
	<b>Race</b>	0.00	66.20	-2.22	0.27	-130.18	130.54		
	<b>Education</b>	-0.03	18.25	-0.58	0.56	-46.44	25.43		
	<b>Vascular Burden</b>	0.10	41.48	1.98	<0.05*	0.39	163.75		
<b>Verbal Memory</b>	<b>Constant</b>	0.43	1.42	-1.06	0.29	-4.29	1.29	5.50	0.27
	<b>Exercise</b>	0.04	0.04	0.62	0.53	-0.05	0.10		
	<b>Hippocampal Volume</b>	0.03	0.00	2.00	<0.05*	0.00	0.00		
	<b>Age</b>	-0.21	0.01	-0.02	<0.02	-0.05	-0.01		
	<b>Sex</b>	0.75	0.15	4.88	< 0.00***	0.45	1.05		
	<b>Race</b>	-0.00	0.08	-0.10	0.91	-0.17	0.15		
	<b>Education</b>	0.60	0.02	2.67	0.01	0.02	0.10		
	<b>Vascular Burden</b>	0.20	0.01	-3.12	<0.02*	-0.08	0.12		
	<b>Total Gray Matter Volume</b>	0.45	921.13	6.56	<.000***	4220.37	7856.91		
	<b>Direct effect</b>		0.02	0.04	0.62	0.53	-0.05	0.10	
<b>Indirect effect</b>		0.00	0.01			-0.01	0.02		

\**p* < .05, \*\**p* < .01, \*\*\**p* < .001. DV = Dependent variable, IV = Independent variable,  $\beta$  = Unstandardized estimates, SE = Standard error, LLCI = Lower limit confidence interval, ULCI = Upper limit confidence interval

### 3.2 Post-hoc power analyses

Post-hoc power analyses were conducted using MedPower (Kenny, 2020) based on an alpha of .05, the effect sizes (beta) of each path, and the sample size for each of the three mediation models. Power was low for the ab path in each of the models (Table 6). Power was sufficiently high for the c, b, and c' paths in the CES-D model and for the b path in the visual memory model, but otherwise power was low. These findings suggest the lack of significance in the mediation

results may be attributed to small effect sizes, which could potentially be addressed in larger samples.

**Table 6**  
Results of Power Analysis

Effect	Power		
	CES-D Model	Verbal Memory Model	Visual Memory Model
<b>c (total)</b>	virtually 1	.067	.051
<b>a</b>	.198	.066	.105
<b>b</b>	.909	.087	.611
<b>c' (direct)</b>	virtually 1	.066	.050
<b>ab (indirect)</b>	.180	.006	.064

### 3.3 Post-hoc analyses

Post-hoc mediation analyses explored potential lateralized effects of hippocampal volume, given the established functional associations between the left hippocampus and verbal memory and the right hippocampus and visual memory (Hardcastle et al., 2020). Both the left ( $\beta = .12$ ,  $SE = 0.00$ ,  $t = 2.11$ ,  $p = .04$ ) and right hippocampus ( $\beta = .12$ ,  $SE = 0.00$ ,  $t = 2.01$ ,  $p = .05$ ) significantly predicted the verbal memory composite, suggesting a bilateral relationship rather than hemispheric specialization in this sample. In contrast, the left hippocampus was not significantly associated with the visual memory composite ( $\beta = .00$ ,  $SE = 0.00$ ,  $t = 0.95$ ,  $p = .34$ ), whereas the right hippocampus showed a small but significant effect ( $\beta = .17$ ,  $SE = 0.00$ ,  $t = 2.56$ ,  $p = .01$ ). However, neither left nor right hippocampal volume significantly mediated the relationship between frequency of moderate-intensity exercise and any outcome variables (all  $ps \geq .47$ ).

Another set of analyses examined age as a potential moderator of the primary mediation models. Age significantly moderated the pathway between moderate-intensity exercise frequency and total hippocampal volume in the model with the verbal memory composite as the outcome ( $\beta = .01$ ,  $SE = 0.00$ ,  $t = 2.56$ ,  $p < .01$ ). The moderation reflected a stronger relationship

between moderate-intensity exercise frequency and hippocampal volume at younger ages than at older ages. The remaining results did not differ from the primary analyses.

Exploratory analyses also 1) examined exercise duration (categorized as < 20 min, 20–39 min, 40–59 min, and  $\geq$  60 min) in relation to memory and mood outcomes, 2) examined verbal and visual memory raw scores (verbal and visual immediate and delayed memory) rather than the composites, and 3) separately examined participants who were APOE  $\epsilon$ 4 positive and participants who had a family history of Alzheimer’s disease. Results did not differ from the primary analyses.

## 5 DISCUSSION

The present study investigated whether frequency of moderate-intensity exercise was associated with depression, visual memory, and verbal memory and whether total hippocampal volume mediated these relationships in predominantly middle-aged adults with a family history of AD or at least one APOE  $\epsilon$ 4 allele. The results partially supported the first hypothesis, indicating that greater frequency of moderate-intensity exercise was associated with lower depressive symptoms. However, self-reported frequency of moderate-intensity exercise was not associated with better visual or verbal episodic memory. Hypotheses for the second aim were also not supported, because there was no evidence that total hippocampal volume mediated the relationships between exercise frequency and the outcome variables.

### **5.1 Effects of Moderate-Intensity Exercise Frequency on Depression, Visual Memory, and Verbal Memory**

Consistent with previous research, our findings corroborate the association between frequency of moderate-intensity exercise and depressive symptoms (Chin et al., 2022; Maruta et al., 2024; Shannon et al., 2023). This aligns with the abundant evidence that more frequent exercise is associated with lower depressive symptoms across various populations (Koo et al., 2020; Lewis et al., 2021; Schuch et al., 2019). Notably, this study adds to the existing literature by showing this association in a middle-aged to older group at increased risk for AD. Clinically, these results highlight the particular importance of regular exercise habits in middle-aged adults at risk for AD, as regular exercise is associated with reduced depressive symptoms. Because depression is a risk factor for developing AD, exercise could mitigate the risk for AD by improving mood.

Contrary to our hypotheses, frequency of moderate-intensity exercise did not predict visual or verbal episodic memory. This finding contrasts from the literature, which generally shows that higher exercise frequency is linked to better visual and verbal memory (Best et al., 2015; Jonasson et al., 2016; Mitchell et al., 2023) and that people at risk for AD benefit even more. Indeed, a systematic review concluded that exercise is a non-pharmacological treatment option with several benefits for APOE  $\epsilon$ 4 carriers, including protecting against cognitive decline (Tokgöz et al., 2021). There is also evidence that among AD patients, APOE  $\epsilon$ 4 carriers experience more memory benefits from exercise than non-carriers (Jensen et al., 2019), though it should be noted that some studies have not found greater cognitive benefits of exercise in  $\epsilon$ 4 carriers (Podewils et al., 2005; Rodriguez et al., 2018). These mixed findings may suggest individual differences that may influence the extent to which exercise impacts episodic memory.

In this context, gender-related factors may contextualize these null findings. The sample was predominantly composed of women at risk for AD, and prior research has shown that women tend to report lower levels of physical activity, often due to domestic and caregiving responsibilities (Althoff et al., 2017). These demands may partly account for the relatively low frequency of moderate-intensity exercise observed in the sample ( $2.6 \pm 1.5$ ). Moreover, exercise frequency may have been further reduced by the COVID-19 pandemic due to lockdowns, depending on the timing of the participants' visits and their self-reported exercise within the past seven days (Zimmerman et al., 2023). Taken together, these factors may have contributed to lower exercise frequency and lack of significant relationships with depressive symptoms and episodic memory.

Another potential explanation for the null results in the current analyses is the method used to assess exercise frequency. Relying on self-reported weekly exercise frequency may have

limited accuracy, whereas more precise measures, such as accelerometer-based tracking or a composite variable that accounts for intensity and duration to estimate metabolic equivalents (METs), may better capture the relationship between exercise and episodic memory. For example, some studies calculated MET hours per week by assigning MET values based on intensity levels and multiplying them by the hours exercised (Boots et al., 2015; Mueller et al., 2020). Operationalizing exercise in this manner could provide greater range and variability, potentially offering a more nuanced understanding of the relationship between exercise and episodic memory. Similarly, measures of physical fitness such as peak oxygen consumption might have stronger relationships with cognitive functioning. In an analysis of longitudinal WRAP data, higher cardiorespiratory fitness as assessed by  $VO_{2peak}$ , a measure of peak oxygen consumption, was associated with slower memory decline over a median 12 years of follow-up (Vesperman et al., 2022). In that study, effects were stronger in non-carriers of the APOE  $\epsilon 4$  allele. This highlights several factors that could contribute to the lack of relationship between exercise frequency and memory in the current study, including the cross-sectional design and the focus on  $\epsilon 4$  carriers.

Limited studies investigated the impact of frequency of moderate-intensity exercise on episodic memory in middle-aged adults, rather than older adults, at risk for AD. More research is needed to understand whether the benefits of exercise for memory differs in this group compared to at-risk older adults or middle-aged adults without heightened risk for AD. Additionally, a review illustrated how various environmental factors, such as higher education and vascular burden may also interact with APOE  $\epsilon 4$  status, influencing the possibility of developing AD. Further research is needed to explore moderating and mediating lifestyle factors in middle-aged

adults at risk for AD that may affect the relationship between exercise frequency and episodic memory.

## **5.2 Mediating Effect of Hippocampal Volume**

Contrary to hypotheses, hippocampal volume did not mediate the relationship between exercise frequency and depressive symptoms, or between exercise frequency and memory. While characteristics of the sample may have obscured the ability to detect effects, as previously noted, the results also suggest other variables may mediate the relationships of exercise frequency with memory and depressive symptoms, rather than hippocampal volumes. For example, neuroinflammation is associated with depression, memory decline, and hippocampal volume decline, and there is evidence that APOE- $\epsilon$ 4 status exacerbates neuroinflammation (Hassamal et al., 2023). Exercise has an anti-inflammatory, thus neuroinflammation might be a more salient mediator of the relationships of exercise with memory and depressive symptoms. In support of an interrelationship between inflammation, exercise, and depressive symptoms, low physical activity has been shown to partially mediate the relationship between inflammatory biomarkers and depressive symptoms in middle-aged to older adults (Frank et al., 2019). Yet, this relationship is not as explored in middle-aged adults at risk for AD. Provided the role of neuroinflammation in the pathophysiology of depression and memory decline, exploring inflammatory biomarkers as a potential moderator could help clarify the biological underpinnings through which exercise affects mood and hippocampal volume in this at-risk population (Han et al., 2021).

Similarly, brain-derived neurotrophic factor (BDNF) is potentially a relevant mediator. BDNF levels are associated with episodic memory and mood, as are variants in the BDNF gene. For example, one observational study found that BDNF variant was associated with long-term

visual memory (Avgan et al., 2017), while another study found that higher circulating BDNF levels in women at risk for AD partially mediated verbal memory (Edmunds et al., 2022).

BDNF is also considered a biomarker of depression (Cavaleri et al., 2023). By increasing blood flow, exercise has been shown to upregulate BDNF, which is crucial for hippocampal function, synaptic functioning, and learning (Mrówczyński, 2019; Tokgöz & Claassen, 2021).

Additionally, an RCT examining animal models found that exercise frequency significantly increased BDNF and improved memory performance (Loprinzi et al., 2019). These findings suggest that BDNF may serve as a more effective biomarker for synaptic plasticity and memory formation than hippocampal volume; however, future research is needed to explore the potential mediating role of BDNF in exercise effects in middle-aged adults at risk for AD.

### **5.3 Limitations**

There are several limitations of the study. The sample was predominantly white, female, and highly educated, with low levels of depressive symptoms ( $6 \pm 6.8$ ) and vascular burden ( $1.4 \pm 1.2$ ), which limits the generalizability of the findings to diverse or less healthy populations.

The study's relatively small sample size and missing data may also have impacted the robustness of the results, limiting statistical power. In addition, the study relies on self-reported measures to assess mood and exercise. These measures are vulnerable to response biases, including social desirability, and may not accurately capture participants' actual experiences or activity levels.

Furthermore, the average level of moderate-intensity exercise was low ( $2.6 \pm 1.5$ ), and the survey capped responses at "five or more days per week," reducing the accuracy of reports for participants who may have exercised six or seven days weekly. The study also focused on recent exercise and did not account for lifetime patterns of physical activity, which may have cumulative effects on brain structure and cognitive functioning. Moreover, operationalizing

exercise via frequency rather than caloric expenditure or METs may not fully depict the range in physical activity levels. Future research would benefit from incorporating more objective measures, such as digital activity trackers, to obtain more accurate estimates of exercise and mood. Longitudinal studies that incorporate caloric expenditure and its associations with depression, episodic memory, and hippocampal volume may also provide more insight into these relationships. Lastly, examining hippocampal volume as a mediator in exercise intervention studies may also elucidate how exercise may impact cognitive and emotional outcomes.

## 6 CONCLUSION

This study adds to the existing literature by improving our understanding of how greater exercise frequency is associated with reduced depressive symptoms in middle-aged adults at risk for AD. While exercise frequency did not significantly predict visual or verbal episodic memory in this sample, findings suggest that frequency of moderate-intensity exercise may be a valuable intervention for alleviating depression, a known risk factor for cognitive decline and AD. Clinically, these findings suggest recommending more frequent participation in moderate-intensity exercise as part of a treatment plan may offer benefits to improve mental health in middle-aged adults at risk for AD. Future research should examine potential mediators beyond hippocampal volume that contribute to the impact of exercise on episodic memory and mood.

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