THE DOSE-RESPONSE EFFECT OF SHORT-TERM EXERCISE ON COGNITIVE FUNCTION

by

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ABSTRACT

Physical activity (PA) is increasingly recognized as an effective approach for improving cognitive function. However, it is unclear how short-term PA or physical inactivity might influence cognition, and whether this effect is associated with other health outcomes such as vascular function. A series of three studies were conducted to address this knowledge gap. The first study systematically reviewed and meta-analyzed 90 effects from 16 randomized controlled trials to examine the effect of acute exercise on cognitive function in healthy older adults aged 60 years or above. The results revealed that acute exercise elicited a small but significant improvement in cognitive function compared to the non-exercise control condition (standardized mean difference [SMD] = 0.17, $p = 0.003$), and greater improvements were found in time- than accuracy-related cognitive outcomes (SMD = 0.24 versus 0.11, $p < 0.05$). The second study investigated the effects of a single bout of moderate-intensity walking on cognitive and vascular function in physically inactive older adults aged 60 years or above. Compared to the control (sitting) condition, acute exercise (30-min walking at 100 steps/min) significantly improved performance in executive function, whereas reduced carotid to femoral pulse wave velocity (p-values < 0.05). Changes in processing speed and aortic augmentation index were similar between conditions ($p > 0.05$), whereas central mean arterial blood pressure was increased after sitting (p

< 0.05) but remained unaltered after acute exercise ($p > 0.05$). The third study focused on the impact of short-term physical inactivity (i.e., walking below 5000 steps/day for one week) on cognitive performance and vascular function among physically active individuals aged 50 years or above. Results from the Bayesian analysis demonstrated minimal changes in all variables before versus after step reduction, indicating that one week of reduction in PA did not yield detrimental effects on cognitive performance and vascular function. Collectively, this body of work supports a small but positive effect of acute exercise on cognition among generally healthy older adults without cognitive impairment. In addition, significant associations were found between changes in cognitive performance with arterial stiffness and central blood pressure in response to acute exercise or short-term PA reduction.

DEDICATION

This dissertation is dedicated to my parents, Hongying Du and Liyuan Zheng, thank you for your unconditional support in all my endeavors. I would not have made it to this point in my academic career and my life in general without your love and support.

LIST OF ABBREVIATIONS AND SYMBOLS

%Δ	Percent change
β	Beta coefficient
AIx	Aortic augmentation index
AIx75	Aortic augmentation index standardized to a heart rate of 75 beats per minute
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BP	Blood pressure, mmHg
cfPWV	Carotid to femoral pulse wave velocity, m/s
CI	Confidence interval
cMAP	Central blood pressure, mmHg
CONSORT	Consolidated Standards of Reporting Trials Statement
CRF	Cardiorespiratory fitness
d	Cohen's *d*
DCCS	Dimensional Change Card Sort Test
ES	Effect size
Flanker	Flanker Inhibitory Control and Attention Test

g	Hedges' *g*
hr	Hour
IPAQ	International Physical Activity Questionnaire
MD	Mean difference
min	Minute
mmHg	Millimeters of mercury
MMSE	Mini-Mental State Examination
MSQ	Methodological study quality
MVPA	Moderate-to-vigorous intensity physical activity
NIHTB-CB	NIH Toolbox Cognition Battery
PA	Physical activity
$P_{(diff=0)}$	Probability that the posterior distribution of the estimated difference includes zero
PAR-Q+	Physical Activity Readiness Questionnaire
PCPS	Pattern Comparison Processing Speed Test
PRISMA	Systematic Reviews and Meta-Analysis
r	Pearson correlation coefficient
RCT	Randomized controlled trial
RT	Resistance training
SD	Standard deviation
SE	Standard error

SMD	Standardized mean difference
$\dot{V}O_{2max}$	Maximal oxygen uptake

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CONTENTS

ABSTRACT ii

DEDICATION iv

LIST OF ABBREVIATIONS AND SYMBOLS v

ACKNOWLEDGMENTS viii

LIST OF TABLES xi

LIST OF FIGURES xii

CHAPTER 1 INTRODUCTION 1

REFERENCES 7

CHAPTER 2 THE EFFECTS OF ACUTE EXERCISE ON COGNITIVE FUNCTION IN HEALTHY OLDER ADULTS: A SYSTEMATIC REVIEW WITH META-ANALYSIS 12

ABSTRACT 12

INTRODUCTION 14

METHODS 17

RESULTS 21

DISCUSSION 26

CONCLUSIONS 33

REFERENCES 34

CHAPTER 3 COGNITIVE FUNCTION, ARTERIAL STIFFNESS, AND CENTRAL BLOOD PRESSURE FOLLOWING A SINGLE BOUT OF WALKING IN PHYSICALLY INACTIVE OLDER ADULTS 64

ABSTRACT 64

INTRODUCTION 66

METHODS 69

RESULTS 76

DISCUSSION 79

CONCLUSION 87

REFERENCES 89

CHAPTER 4 THE IMPACT OF ONE-WEEK STEP REDUCTION ON COGNITIVE PERFORMANCE AND VASCULAR FUNCTION AMONG PHYSICALLY ACTIVE INDIVIDUALS: A BAYESIAN ANALYSIS 102

ABSTRACT 102

INTRODUCTION 104

METHODS 107

RESULTS 117

DISSCUSSION 120

CONCLUSION 125

REFERENCES 126

CHAPTER 5 CONCLUSION 142

REFERENCES 145

APPENDIX 146

LIST OF TABLES

Table 2. 1 Characteristics of the studies included in the systematic review 40

Table 2. 2 Bivariate and subgroup moderator analysis results (k = 90) 45

Table 3. 1 Sample characteristics 96

Table 3. 2 Acute effects on cognitive and vascular function 97

Table 3. 3 Correlations between changes in cognitive and vascular function 98

Table 4. 1 Sample characteristics 133

Table 4. 2 Summary of descriptive statistics and Bayesian analysis results 134

Table 4. 3 Correlations between changes in cognitive and vascular function 135

LIST OF FIGURES

Figure 2. 1 PRISMA flow diagram of the selection process.....46

Figure 2. 2 Forest plot displaying acute effects of exercise versus control on cognition 47

Figure 2. 3 Funnel plot displaying the distribution of observed effect sizes (k = 90) 48

Figure 3. 1 Diagram of acute sessions 99

Figure 3. 2 Acute effects on cognitive and vascular function after sitting versus walking ...100

Figure 3. 3 Acute changes in cognitive and vascular function after sitting versus walking ..101

Figure 4. 1 Experimental design and order of procesures involving step reduction.....136

Figure 4. 2 Impact of one-week step reduction on cognitive and vascular function 137

Figure 4. 3 Estimated changes in cognitive and vascular outcomes after step reduction.....138

CHAPTER 1

INTRODUCTION

The benefits of physical activity (PA) for health and well-being have been well-documented since the last century (1-3). Regular PA confers benefits for improving physical fitness and overall quality of life, as well as reducing adiposity, risk of all-cause mortality, and the incidence of cardiovascular disease and type-2 diabetes (4, 5). The current U.S. PA guidelines recommend a target of at least 150-300 minutes of moderate-to-vigorous intensity PA (MVPA; i.e., over 3-6 metabolic equivalents [METs]; 1 MET = 3.5 mL O_2/kg/min) per week for adults of all ages to achieve substantial health benefits (5). In recent years, there is also a growing body of evidence that participating in PA may enhance cognitive function (e.g., perception, memory, attention, decision making, and language abilities) (6, 7). Such beneficial PA-related effects are particularly important in middle-aged and older adult populations, who are at risk of age-related deteriorations in both physical and cognitive function (8, 9). Given the increasing proportion of the aging population worldwide (10), effective strategies for building cognitive reserve, maintaining physical independence, and preventing common geriatric diseases (e.g., Alzheimer's disease) are crucial for successful aging.

Previous research has highlighted a positive relationship between habitual PA (i.e., all forms of PA in daily living) and cognitive performance, especially in older adults (5, 11, 12). A

moderate level of evidence from longitudinal studies and randomized controlled trials suggests that long-term MVPA (e.g., chronic, or more than a single episode) is associated with favorable effects on cognitive outcomes in adults aged 50 years and older (Hedges' g effect sizes range from 0.2 to 0.48), with greater effects found in the domains of executive function, global cognition, and attention (4, 5, 13). Notably, it has been acknowledged that a single brief session of PA (i.e., acute PA) also yields a transient improvement in cognition, with larger positive effects observed from PA bouts lasting 11 to 20 minutes (5). Although the underlying mechanisms are not yet fully elucidated, limited evidence suggests that exercise-induced changes in cognition might be associated with an increased release of catecholamines and endorphins, upregulation and expression of neurotrophic growth factors, and cerebral hemodynamic responses (12, 14-22). However, to date, little is known about the dose of PA (volume, duration, or intensity) needed to elicit the optimal benefits in various domains of cognitive function (5). Discrepancies exist in studies that involved various PA modalities (e.g., aerobic vs. resistance exercises) and cognitive assessments in specific population groups (5, 13). For instance, cognitive performance is likely to vary following acute exercise among individuals who have lower cardiorespiratory fitness or PA levels (23-25) due to potential interactive effects between cognitive and other physiological responses (e.g., cardiovascular outcomes) (26-29). There is a need for research to address these knowledge gaps and facilitate the understanding of the relationship between PA and cognitive function (5), as well as their health implications for successful aging.

In addition to the well-known positive relationship between PA and health, there is also an increasing interest regarding the impact of physical inactivity as a modifiable risk factor for numerous diseases (e.g., cardiovascular disease) (30). Despite widespread public health messaging for PA, there is still a large proportion of the population that remains physically inactive (31). For example, around 50% of U.S. adults (aged 18 or older) do not meet the minimum recommended PA target (32). To reduce the prevalence of physical inactivity and protect against chronic diseases, effective and feasible approaches are needed to encourage individuals to increase their PA participation and avoid excessive sedentary behavior.

Walking is an essential component of many activities of daily living and requires little skill and low cost, making it an ideal choice for most individuals to achieve PA guidelines (33). For example, it is appropriate for sedentary or inactive individuals to add as little as 5 to 10 minutes of walking to one's daily PA initially, and then increase the duration and intensity (e.g., speed) slowly over time to become more physically active (34, 35). Previous research has highlighted the feasibility of using pedometers and wearable devices to self-monitor and modulate step-based metrics (i.e., daily step count [steps/day] and cadence [steps/min]) associated with walking activity to achieve certain volumes and intensities of PA (36, 37). For example, a goal of 7500 steps/day has been suggested as a direct translation of the current PA guidelines (i.e., ≥150 min/week of MVPA), whereas a threshold of less than 5000 steps/day is used to classify a "sedentary" lifestyle (38). Furthermore, in an effort to quantify the cadence-intensity relationship, a cadence of 100 steps/min has been consistently found to be associated with

achievement of a moderate intensity (i.e., 3 METs) (39-43). Self-monitoring of step-based metrics may provide a feasible, intuitive and economical way to motivate those with environmental barriers to improve their PA engagement and adherence (44). Thus, exploring the practical application of step-based PA metrics (e.g., self-monitoring of step-count and/or cadence-controlled walking) has clear public health appeal.

To date, most PA-cognition intervention studies have implemented cycling or running within specific heart rate or oxygen uptake ranges to regulate exercise intensity (13, 21, 45). The use of these complex and technical expressions of intensity, which are generally reserved to laboratory settings, limits their generalizability and utility in real life. In contrast, PA recommendations expressed in terms of step-based metrics have the potential to improve public health messaging as they are more likely to be understood by a lay audience. Notably, manipulating walking activity with step-based metrics has not seen considerable attention in exercise-cognition research (46). Only one study investigated the acute effect on cognition following self-paced walking (7000-10000 steps in 80-120min) (47), while no studies to date have investigated the use of cadence as a proxy for intensity and associated effects on cognitive function. On the other hand, few studies have focused on the potential impact of reduced PA utilizing a model of step reduction (e.g., walking below 750 to 5000 steps/day) (48-50). Considering the potential dose-response relationship between PA and cognition (5), it is unknown whether short-term step reduction would impact cognitive performance and other related health outcomes (e.g., blood pressure). Given the aforementioned benefits of walking,

and the practicality and simplicity of step-based metrics, examining how the modulation of daily step count and cadence may affect cognitive outcomes may have practical meaning for the health promotion of middle-aged and older adults.

Working to address several aforementioned limitations in the extant literature on PA and cognition, the purpose of this dissertation is to examine the effects of short-term exercise on cognitive function among healthy middle-aged and older adults with differing habitual levels of PA (i.e., physically active or inactive). The specific aims of each study were as follows:

Study 1: To systematically review and meta-analyze randomized controlled trials investigating the effects of acute exercise on cognitive function in healthy older adults aged 60 years old or above. We hypothesized that acute exercise would improve cognitive outcomes compared to non-exercise control, and that characteristics of the sample (e.g., gender, fitness level, baseline cognition), exercise intervention (e.g., type, intensity, duration), and cognitive assessments (e.g., domain, component) would modulate these effects.

Study 2: To investigate the effects of an acute bout of walking at moderate intensity (100 steps/minute) on cognitive function (i.e., executive function, attention, and processing speed) among older adults (≥ 60 years old) who were considered to be physically inactive (i.e., did not meet the minimum PA recommendations). We hypothesized that 1) a single bout of moderate-intensity walking would improve cognitive function compared to a control (sitting) condition, and 2) changes in cognitive performance would be associated with the exercise-induced changes in vascular function.

Study 3: To examine the influence of short-term (one week) physical inactivity on cognitive function (executive function, attention, working memory, and processing speed) among individuals who were considered to be physically active (i.e., met or exceeded the minimum PA recommendations) using a step-reduction model (i.e., walking below 5000 steps/day on average for one week). We hypothesized that one week of step reduction would impact cognitive function, and there would be associations between changes in cognitive and vascular function following step reduction.

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CHAPTER 2

THE EFFECTS OF ACUTE EXERCISE ON COGNITIVE FUNCTION IN HEALTHY OLDER ADULTS: A SYSTEMATIC REVIEW WITH META-ANALYSIS

ABSTRACT

Purpose: The purpose of this study was to systematically review and meta-analyze randomized controlled trials (RCTs) to examine the effects of acute exercise on cognitive function in healthy older adults (≥ 60 years old). **Methods:** Electronic databases (PubMed, PsycINFO, Web of Science, CINAHL, and ProQuest) were searched to identify potentially relevant reports. Aggregate-level random-effects multivariate meta-analysis was used to generate an overall standardized mean difference (SMD) effect size, and moderator analyses were performed to identify potential study-level effect modifiers. **Results**: 16 original RCTs (cross-over or parallel design) met the inclusion criteria, with a combined total sample of 507 healthy older adults (mean age range: 62.6–71.7 years, 47.3% female), yielding 90 effects to be analyzed. Acute exercise (10-30 minutes of any intensity) elicited a small but significant improvement in cognitive function compared to the control condition (SMD [95% confidence interval] = 0.17 [0.06, 0.29], $p = 0.003$), and these effects lacked heterogeneity ($Q_{89} = 141.9$, $p < 0.001$, $I^2 = 0.8\%$). Study-level effect modifiers characterizing the sample and exercise intervention did not modulate changes in cognitive function, however, the type of cognitive assessment test did ($\beta =$

0.16, $p = 0.004$). Specifically, following acute exercise, greater improvements were found in time-related than accuracy-related cognitive outcomes (SMD = 0.24 [0.11, 0.37] vs. 0.11 [-0.04, 0.26]). **Conclusion:** Acute exercise improved cognitive function in generally healthy older adults without diagnosed cognitive impairment, and greater improvements were observed in the time-related cognitive outcomes (e.g., reaction time). The findings of this study have practical implications, supporting the prescription of a single bout of exercise for older adults to accumulate immediate benefits on cognitive performance.

INTRODUCTION

Maintaining brain health is essential to ensure quality of life and physical independence in older adults (1). The aging process leads to changes in brain structure (e.g., hippocampal atrophy) and interferes with an individual's cognitive capacity (2). Given the rapid increase in population aging worldwide (3), there is a need to identify effective approaches to delay or reduce cognitive decline in later life, and prevent age-related health conditions (e.g., dementia). Engaging in regular physical activity (PA) has been demonstrated to reduce the risk of dementia and age-related neurodegenerative diseases (4, 5). However, questions remain unresolved concerning the dose-response relationship and distinct effects of various PA modalities among specific population groups (4-6). Understanding how a single bout of exercise may impact cognitive performance is critical to prescribing daily PA for older adults to obtain immediate improvements and accumulate optimal health benefits.

Emerging evidence supports a small and positive influence of acute moderate-to-vigorous intensity PA (MVPA) on cognitive performance, including executive function, processing speed, attention, and memory (6). Nevertheless, results remain inconsistent across studies that involved various cognitive domains and population groups (7, 8). Ludyga et al. (9) meta-analyzed 40 experimental studies and found significant effects of aerobic exercise (10-40 min, cycling or running) on both time- and accuracy-related components of executive function tasks (effect size [ES] = 0.35 and 0.22, p-values < 0.001) across the lifespan (range of mean age: 4.1–69.3 years), but the effects were not significantly different between these two components (p = 0.15) when

not considering other study-level moderators. While the acute effects seemed to be similar across various levels of aerobic fitness, exercise duration, and components of executive function (i.e., inhibitory control, set shifting, and working memory) in their study, subgroup analysis demonstrated a greater effect in older (50+ years; 7 studies) compared to younger (18–35 years; 23 studies) adults (ES difference = 0.47, $p < 0.001$) (9). However, McMorris and Hale (10) observed a significantly greater effect of acute exercise on speed (or time) than accuracy-related outcomes (ES = 0.30 vs. 0.04, $p = 0.01$) in their samples of all ages (range of mean age: 9.6–66.3 years) based on 53 studies, and these differences also appeared to be influenced by exercise intensity. They found that 6 to 60 minutes of moderate-intensity exercise (40-79% maximum power output or equivalent) acutely increased processing speed (ES = 0.50, $p < 0.01$), but acute exercise of all intensities did not significantly change accuracy-related measures (ESs range from -0.14 to 0.09, $p > 0.05$) (10). On the other hand, Rathore and Lom (11) observed a negligible effect (ES = -0.15, $p = 0.53$) of acute PA on working memory in healthy participants of all ages (9–93 years) based on seven studies.

Collectively, previous reviews and meta-analyses conducted to date (7-12) have produced mixed findings regarding the acute effects of exercise on cognitive function. This lack of consensus may be partially explained by differences in the characteristics of the samples, dose of acute exercise, and the type and domain of cognitive assessments (7). For example, in addition to the age effect mentioned above, the moderating roles of cardiorespiratory fitness (CRF) and habitual PA level have also been highlighted in observational and experimental evidence (9, 13-

16). Indeed, two recent studies compared low- and high-fit groups (categized by maximal oxygen uptake) and found differences in cognitive performance in response to acute exercise, which might be led by the cognitive status and brain activation patterns between the two groups (13, 15). Previous research syntheses, however, have failed to comprehensively evaluate and quantitatively explore these important study-level effect modifiers, which is especially true for those focusing on healthy older adults without cognitive impairment (6). In addition, the six previous systematic reviews (7-12) included population samples of all ages, and only included small numbers of studies (less than ten) that involved older adults, which might lead to limited generalizability of their results. Moreover, three recent reviews (17-19) concerning healthy older adults only focused on one type of exercise (18) or cognitive domain (19), or did not conduct a meta-analysis that controlled for potential moderators such as fitness and exercise modalities (17). Considering the rapid growth in research on exercise and cognition over the last decade, there is a need for an updated review that summarizes the existing literature in a more comprehensive manner.

Therefore, the current study aimed to systematically review and meta-analyze available randomized controlled trials (RCTs) to examine the effects of acute exercise on cognitive function in healthy older adults ($\geq$ 60 years old). We hypothesized that acute exercise would improve cognitive outcomes (e.g., test scores) compared to non-exercise control, and that characteristics of the sample (e.g., gender, age, fitness level, baseline cognition), exercise

intervention (e.g., type, intensity, duration), and cognitive assessments (e.g., domain, component) would modulate these effects.

METHODS

This systematic review with meta-analysis was conducted in accordance with established guidelines from Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (20, 21). A completed PRISMA checklist is provided in supplemental table SDC 2.1.

Search Strategy

A systematic search was conducted in five electronic databases (PubMed, PsycINFO, Web of Science, CINAHL, and ProQuest) from inception up to December, 2021. The relevant studies were retrieved using a Boolean search strategy that combined specific MeSH terms (PubMed), Thesaurus (PsycINFO, ProQuest), and Subject Headings (CINAHL) and nonspecific terms. In addition, cross-referencing and hand searching were used to supplement the electronic search. The terms and strategies for electronic search are provided in the supplemental table SDC 2.2.

Inclusion and Exclusion Criteria

We included studies that: (1) were RCTs with parallel or repeated measures cross-over designs; (2) evaluated the effects of cognition following a single-bout of exercise (e.g., aerobic, resistance, or a combination) compared to a non-exercise or minimal activity control group/condition (e.g., seated control, sham session, or stretching activity); (3) included participants who were 60 years or older, generally healthy, and without a diagnosed cognitive or

mobility issue that might impact the potential cognitive outcomes or physical ability to participate in the exercise intervention; and (4) measured cognitive function acutely, starting within 15 minutes post-exercise (defined as “immediate” effect). Studies involving participants diagnosed with dementia and other health conditions (e.g., cognitive impairment, Parkinson’s disease, stroke, depression, diabetes), or that reported on the effects of exercise in combination with other interventions (e.g., dietary, pharmacological, cognitive therapy) were excluded.

Data Extraction and Study Quality

Two investigators (PZ and MC) independently performed the title/abstract and full-text screening based on the selection criteria. The following data were extracted separately by two independent coders (PZ and MZ) using a standardized assessment sheet following the PRISMA checklist: study information (e.g., publication year, study design), sample characteristics (e.g., sample size, body mass index [BMI], fitness level, baseline Mini-Mental State Examination [MMSE] score), intervention characteristics (exercise modality, duration, intensity; control session type and duration), cognitive measurements (e.g., tool or test used, timing of post-session assessment), and the effect estimate and variance data used to calculate effect sizes. Cognitive domains related to a specific test used in each study were further coded according to the compendium of neuropsychological tests (22). Methodological study quality (MSQ) was assessed using the Consolidated Standards of Reporting Trials Statement (CONSORT) and its extension for randomized cross-over trials (23), with individual items modified to reflect the intervention (both parallel and cross-over designs) and outcomes of interest (see supplemental

document SDC 2.3 for the amended guidelines and scoring criteria). The sum score of the instrument is based on the rating of 39 items assessing potential sources of bias. Disagreements during screening, data extraction and quality assessment were resolved by discussion until consensus was achieved.

Data Synthesis and Statistical Analysis

All ESs were calculated and reported as standardized mean differences (SMDs) and 95% confidence intervals (CIs) to compare the changes in cognitive performance following acute exercise versus control condition (or group) (24). Where available, the mean values with standard deviations (SDs) or standard errors (SEs) of pre- and post-assessments (or mean change, or post-session only as per study design) were retrieved from all exercise and control conditions; where these values were not available, results from the F test were used for ES calculation. Different ESs were used to generate the SMD based on the experimental design used (25). The SMD ES by Becker for comparison of two independent groups (26) was used for parallel-group (between-subject) experimental designs, while the SMD ES for a single-group repeated measure design by Gibbon et al. (27) was used for cross-over trials (within-subject design). To control for the correlation between repeated measures, a conservative value of 0.5 was assumed and included in the ES calculation if the correlation coefficient could not be extracted from publications or raw data. Before combining, scores were adjusted to ensure that a positive SMD indicated improved cognitive function in the exercise group compared to a non-exercise control (i.e., when a lower test score represented better performance (e.g., reaction time, error rate), the

SMD was multiplied by -1). The magnitude of the effect was interpreted as small (≤ 0.20), medium (0.50), and large (≥ 0.80) (28).

Several *a priori* study-level moderators were examined based on the evidence available to date (7-12, 17-19) or because of their influence with other health-related outcomes (6, 13-16). Percentage of female, age, BMI, maximal oxygen uptake ($\dot{V}O_{2max}$), and year of education were calculated based on extracted information and coded as continuous variables; while other moderators were coded as categorical variables, including study designs (parallel vs. cross-over, and pre-post vs. post-only measure), exercise type (cycling vs. walking vs. resistance training [RT] vs. other), exercise duration (≤ 20 min vs. > 20min), intensity (light vs. moderate vs. vigorous, according to American College of Sports Medicine's guidelines for older adults (29)), component of cognitive measures (time vs. accuracy), and cognitive domains (attention, general cognitive functioning, executive function, and working memory). Univariate meta-regression models and subgroup analyses were performed first, and if appropriate, multiple meta-regression models were used to explore how one or more combinations of moderators might influence the overall effects that contribute to the heterogeneity between studies (30, 31).

A multilevel random effects model was used to pool the SMD with 95% CI between exercise vs. control conditions. Since multiple comparisons and outcomes were extracted from an individual study, dependency of ES was taken into account by: 1) nesting the "study" terms as random factors to extend a conventional meta-analysis (one level) to a three-level model to further estimate within- (level 2; clusters) and the between-study (level 3; studies) variances

(32); and 2) employing robust variance estimation with this hierarchical model (33). Consistency across ESs were estimated by the Q statistic and transformed to the I^2 statistic with 95% CIs, where I^2 was interpreted as low (25%), moderate (50%), and high (75%) levels of heterogeneity (34, 35). The within- and between-study variances were represented by sigma square (σ^2).

Publication bias was examined by means of visual inspection of funnel plots for outliers and asymmetries in the ES distribution (30, 36). Statistical tests using Begg (37) and Egger (38) methods were conducted as a supplement to the funnel plot. If outliers were identified visually, sensitivity analysis was performed to determine the influence (if any) on the overall SMD ES. Briefly, potential outliers were removed and the overall SMD ES was re-calculated with the outlying study or effect removed.

All statistical analyses were conducted using R (version 4.0.2) and *metafor* package (39). Descriptive characteristics of the aggregate sample were presented as mean ± *SD* unless otherwise stated, and categorical variables were presented as numbers with percentages. SMD estimates and 95% CIs were reported for all included observations. Significance level was set at $p < 0.05$.

RESULTS

Characteristics of Included Studies

Our systematic search of 5 databases yielded 6,022 potentially relevant records for review. Systematic screening of the records ultimately resulted in 16 original studies (*n*), published

between 2009 to 2021, being identified for inclusion (7, 40-54). Extraction of multiple effects from studies with ≥ 2 comparisons yielded a total of 90 exercise vs. control comparisons/effects (*k*). A detailed description of the search, screening, and identification of relevant records is shown in Figure 2.1.

Of the 16 studies in our final sample (Table 2.1), seven studies with multiple comparison groups were treated as separate studies (clusters), including those comparing: the effects of different intensities (*n* = 2) (40, 41), participants with low versus high fitness (*n* = 2) (7, 44), different exercise modalities (*n* = 2) (52, 53), and post-session cognitive outcomes at multiple time points (*n* = 1) (42). Note, two studies (42, 51) investigated the immediate and delayed effects of exercise on cognition (15~60 minutes post-exercise), we only extracted and used data from the ≤ 15-minute post-exercise measurement consistent with our definition of "immediate" effects". Ten studies reported both time- and accuracy-related outcomes (40, 41, 43-45, 48, 51-54), five studies (7, 42, 46, 47, 49) reported time-related outcomes only, and one study (50) reported accuracy-related outcomes only. The sample sizes, types of tasks, and SMDs with 95% CIs for all studies are reported in Table 2.2 and Figure 2.2.

Table 2.1 presents a methodological summary of included studies and their sample characteristics. Briefly, the included studies collectively evaluated 507 healthy older adults (47.3% female) with mean ages ranging from 62.6 to 71.7 years old. Samples were cognitively healthy (*n* = 11 reported MMSE scores of 27.1-29.7 for their sample), in good physical condition (BMI: 24.2 ± 1.1 kg/m^2, *n* = 10; and $\dot{V}O_{2max}$: 26.5 ± 5.1 mL/min/kg, *n* = 9) and an average of

12.4 ± 3.1 years of education (n = 11). There were 10 studies that employed a cross-over design, and 6 parallel group RCTs. Over half of the included studies measured cognitive function pre- and post-sessions (n = 10), while the rest of the studies measured post-session only (n = 6). The exercise modality employed included cycling (n = 8), walking (n = 3), resistance training (n = 3), and other types (n = 3; yoga, multicomponent, and seated exercise). Exercise intensity was mostly moderate (n = 11), with fewer examining light (n = 3) or vigorous (n = 2) intensities. Cognitive function was assessed using various neuropsychological tests, with the most common being the Stroop tasks (n = 8). Of the 90 ESs (comparison groups*tests), time (n = 54) or accuracy-related (n = 36) components of cognitive tasks were commonly reported.

On average, the included articles achieved moderate quality (72.7%), with scores ranging from 62.1% to 92.2%. Over half of the studies did not describe the process of determination of sample size (56.3%), sequence generation (56.3%), and allocation concealment in sufficient detail (75%). The majority of studies were not identified as an RCT in the title (81.3%), or specified a cross-over/parallel design with adequate information reported in the abstract (75%). In addition, despite the description of "immediate effect" or "immediately after exercise", two studies (52, 54) did not clearly define the timing of cognitive measures (in minutes) post-exercise. Overall and itemized MSQ for each individual study are provided in supplemental document SDC 2.4.

Main Results and Moderator Analysis

The multilevel meta-analysis provides an overall (pooled) estimate (i.e., SMD) quantifying the acute effect of exercise vs. non-exercise control on cognitive function across the 16 studies (90 effects) without controlling for any study-level moderators. Figure 2.2. displays the forest plot of the overall (pooled) SMD with 95% CIs as well as the effect estimates for each study. Among the 90 effects, the majority of SMDs were positive (k = 69), meaning that more studies observed an improved cognitive performance (higher accuracy or faster reaction time/processing speed) following acute exercise vs. control condition. This was confirmed by the multilevel random-effect model, which revealed that acute exercise had a small but significant effect on improving cognitive performance compared to the control condition (SMD [95% CI] = 0.17 [0.06, 0.29], p = 0.003). The tests of homogeneity suggested heterogeneity was present (Q_{89} = 141.9, $p < 0.001$), however, I^2_{total} values (0.8%) and the between- and within-study variances were all minimal (σ^2 = 0.00 and 0.0008, respectively). The funnel plot (Figure 2.3) displays the symmetrical distribution of the observed SMDs, which was plotted against the standard errors of individual SMDs (a measure of precision). The results of Egger (Z = 0.28, p = 0.78) and Begg (τ = 0.08, p = 0.26) tests also support the absence of funnel plot asymmetry.

Despite the relatively homogenous effects, moderator analysis was still performed, and the results were summarized in Table 2.2. Study-level effect modifiers related to study design, exercise intensity, and cognitive assessment emerged as significant moderators (all p-values < 0.05). Acute exercise improved cognitive function to a greater extent than non-exercise control

among studies that: (1) used a cross-over design, (2) measured cognitive performance post-session only, (3) prescribed moderate-intensity exercise, or (4) exercise lasting longer than 20 minutes (all p-values < 0.05). The effectiveness of acute exercise compared to non-exercise control for improving cognitive performance was greater in executive function ($p = 0.007$). However, these results should be interpreted with caution, as the number of effects for each level of categorical moderator varied, and the level with the greatest number of effects was often the level that reached statistical significance. Further, *post hoc* analysis did not detect between-level differences in these effect modifiers ($p > 0.05$). As for continuous variables characterizing study samples, small and non-significant moderation effects were observed, which was likely a reflection of our homogenous sample and overall pooled SMD. In addition, we did not detect any significant interaction effect among the above modifiers when including two or more of them into multiple meta-regression models (all p-values > 0.05).

Notably, there was a significant group difference between time- and accuracy-related cognitive outcomes ($\beta = 0.16$, 95% CI: 0.05, 0.27), where univariate meta-regression model revealed a greater effect in time compared to accuracy component (the results of this subgroup analysis are presented in Figure 2.2). Briefly, the pooled SMD for time-related outcomes was small but significant (SMD = 0.24, $p = 0.0003$), and homogeneous across studies ($Q_{54} = 66.13$, $p = 0.12$), indicating an improved time-dependent performance (e.g., reaction time, processing speed) after exercise vs. control. In contrast, the pooled SMD for accuracy-related outcomes was small, non-significant (SMD = 0.11, $p = 0.14$), and lacked homogeneity ($Q_{34} = 63.34$, $p = 0.002$).

DISCUSSION

The current systematic review investigated the immediate effects of acute exercise on cognitive function in healthy adults aged 60 years old and above using outcome data from 16 studies. The key finding from this systematic review is that acute exercise-induced a small but positive improvement in cognitive function compared to the non-exercise control group/condition in generally healthy older adults (e.g., not diagnosed with cognitive impairment). Moderator analysis revealed a significant difference in the mean effect on time and accuracy components of cognitive performance, suggesting that the effect of acute exercise was greater in studies involving time-related measures. Although there were significant moderation effects of study designs, exercise type (cycling), intensity (moderate) and duration (> 20 min), and cognitive domain (executive function), no differential effect was found within levels of those moderators, which was likely the result of unequal numbers of effects across levels of those categorical variables. In addition, sample characteristics did not emerge as significant effect moderators, reflecting the homogeneity of the included sample and limited range in these important variables.

Our overall (pooled) SMD of 0.17 was similar to the results from McMorris and Hale (10) and Chang et al. (7) that were both obtained from samples inclusive of younger to older adults (ES = 0.14 and 0.11, respectively), but it was smaller than the meta-analysis by Wilke et al. (18) that involved only older adults (ES = 0.56) and from Ludyga et al.'s (9) subgroup analysis of older adults (ES = 0.67). One possible explanation is that the current meta-analysis used a more

robust analytical approach when computing ESs. This approach quantified the difference in cognitive responses between two conditions (acute exercise and control), obtained data from both cross-over or parallel (within- and between-subject) experimental study designs, and used a multilevel model that accounted for the correlated (nested) effects and robust variance estimation. Indeed, the exploratory follow-up analyses that did not control for correlated/nested effects yielded a slightly larger result (SMD = 0.22, $p < 0.001$), but still lesser in magnitude than reported by others (9, 17, 18). In addition, the current review had rigorous inclusion criteria that restricted the samples to generally healthy older adults (inclusion criteria for an age range or mean age ≥ 60 years) without cognitive disorders, as well as only including studies that examined immediate effects on cognitive function within 15 min post exercise. Given the variability across studies, we used a focused search strategy and strict inclusion criteria in an attempt to minimize a large proportion of between-study variability. Our overall (pooled) SMD ES was determined to be homogenous, indicating that the 16 studies included in the current meta-analysis were similar in effect.

Despite the homogenous overall SMD ESs, there was a significantly greater effect on time- than accuracy-related cognitive outcomes (SMD = 0.24 and 0.11, $p < 0.01$). Although similar differential effects have been reported previously (9, 10), our study is the first to identify this moderating effect among generally healthy older adults without diagnosed cognitive impairment. Based on the non-significant effect on accuracy-related cognitive outcomes from this subgroup analysis, it appears that time-related measures of cognition are more sensitive to exercise-

induced changes among this population (10, 55). Our findings were similar to those reported in McMorris and Hale's analysis (10), but were in contrast to the non-significant group difference between time vs. accuracy reported by Ludyga et al. (ES = 0.35 vs. 0.22, $p = 0.15$) (9). These contrasting results in time- and accuracy-related measures of cognition are poorly understood in the existing literature. It is hypothesized that the complexity of cognitive tasks would require different levels of arousal for optimal performance in time or accuracy, which are also associated with the release of brain-derived neurotrophic factor (BDNF) and activation of different brain areas (10, 56). Exploration of these underlying mechanisms is beyond the scope of this meta-analysis, and the findings of other subgroup analyses should be interpreted with caution as these results are correlational in nature rather than causal. Future RCTs on this topic are warranted to better understand such differential effects on components of cognitive assessment (e.g., task complexity) so that, perhaps, there may be recommendations regarding which type of assessment performs better to gauge exercise-induced improvements in cognition in healthy older adults.

The present review considered potential moderators based on the extant literature, which is more rigorous than several previous reviews that did not examine moderating effects due to insufficient sample size (17-19). In the current study, however, we did not find any moderating effect of sample characteristics, which might be attributable to the restricted selection of RCTs that only involved healthy older adults. The same results may not be observed among older adult samples with chronic age-related conditions (e.g., cardiovascular disease) and/or cognitive impairment. Presumably, these samples may achieve a different level of cerebral circulation and

arousal due to impaired vascular function (e.g., arterial stiffness) (57), resulting in different effects (or a lack of effect) in cognitive performance following acute exercise compared to their healthy counterparts (58). Collectively, given several moderating effects found in the acute exercise-cognition studies, future work should always incorporate other potential moderators to facilitate the understanding of potential mechanisms where available, especially when having diverse samples.

This systematic review with meta-analysis has several strengths. Unlike previous reviews that investigated the acute effect of either aerobic (18) or RT exercise (17), or included studies with participants across a wide age range (9, 10, 12), the present review focused exclusively on healthy older adults aged 60 years or above and obtained ESs from RCTs with well-defined exercise and control conditions. In addition to adhering to current methodological standards, the study provides SMDs between exercise and control conditions, and statistically evaluated potential moderators (MSQ, age, %female, BMI, $\dot{V}O_{2max}$; exercise type, intensity, duration; cognitive tasks, domains, and timing of post-measurement) where available. The dose of acute exercise employed in the included studies was generally in accordance with PA guidelines, with a short acute session (10~30min) and at a moderate intensity. Of the 16 studies (90 ESs) included in this review, only a 20-min yoga session in one study had decreased performance on working memory (SMDs = -0.02 and -0.3), others all presented positive effect (SMDs > 0) on at least one cognitive score following an acute exercise.

Despite the strengths of this meta-analysis, there are several limitations that should be acknowledged. First, since this meta-analysis used a strict and narrow research question to guide the systematic search and review process, our results are only applicable to generally healthy older adult samples without diagnosed cognitive impairment. Based on the 16 studies we analyzed, our results should be interpreted in lieu of the cognitive domains (e.g., executive function, attention, and working memory) and acute exercise modalities (e.g., 10-30 minutes, light to vigorous intensity) included in our final sample, which has limited generalizability to other populations and experimental study designs. Second, because we limited our sample, there was a risk that important study-level moderators would also be limited, preventing our ability to explore, and potentially identify, "who" may benefit the most in terms of cognition and "what" dose of exercise is best to induce optimal cognitive performance. Further, characteristics of sample and acute exercise were largely similar and lacked sufficient range to be fully explored during moderator analysis (a common problem in aggregate-level meta-analysis termed "ecological fallacy"). Third, in addition to study-level effect modifiers lacking sufficient range or variability, some other moderators were also poorly reported. For example, objective measures or estimates of cardiorespiratory fitness ($\dot{V}O_{2max}$) were not reported in 44% of our sample (7 studies) (42, 43, 45-47, 50, 52). Lack of reporting in primary-level studies may contribute to the mixed and inconsistent results of meta-analyses in this review and in others.

Future Recommendations

This study contributes to the body of evidence supporting the beneficial effects of acute exercise performed at light to vigorous intensity and for durations lasting 10-30 minutes on cognitive function in healthy older adults. Despite the more recent interest in exercise and cognition research and the rapid growth of the literature, there are notable gaps in our understanding of exercise-induced cognitive benefits that future studies should address. First, exploring the distinct effects on time- versus accuracy-related cognitive outcomes found in this study. It would be a worthwhile endeavor for future studies to investigate how acute exercise impacts cognitive performance in these components within various cognitive domains, and to identify potential neurobiological mechanisms underlying the differences documented via meta-analysis. Second, investigating the effects of other exercise modalities. All studies included in the current review prescribed exercise (e.g., cycling, treadmill walking) in a controlled environment (e.g., laboratory). So far, there is less evidence supporting the efficacy of other modalities, particularly PA forms under free-living conditions (e.g., self-modulated walking using step-based metrics (59)), which may have tremendous practicality for translating laboratory theories to real world application. Third, future studies should improve study quality by following the guidelines for RCTs (e.g., CONSORT), such as including a non-exercise control, adding sufficient baseline measures of sample characteristics (e.g., objectively measured or estimated cardiorespiratory fitness), as well as clarifying the definition of "immediate" or "acute" effect(s). For example, it is highly encouraged for future studies to report the average time across all participants for both

cognitive measurement(s) and the interval (in minutes) between the end of exercise and cognitive measurement(s); however, only one study in the current review provided both (53). This would enable investigation of the effect of time course and how it might interact with other moderators. Fourth, in addition to cognitive measures using neuropsychological tests, exploring other physiological biomarkers that could help elucidate the underlying mechanisms of exercise-induced changes in cognition. A handful of neurophysiological underpinnings have been proposed by researchers (e.g., lactate, BDNF, cortical activation, cerebral oxygenation) (54, 60-62); however, there is little replication across studies regarding other biomarkers (e.g., vascular endothelial growth factor) or health outcomes (e.g., brachial and central pressures, arterial stiffness) that might associate with specific cognitive domains or subcomponents (63, 64). Last, there is limited evidence linking the acute and chronic effects of exercise on cognition, with few studies reporting contradictory findings despite using exercise training programs among similar samples (18). As such, continued efforts should be made to examine the relationship between acute and chronic exercise with cognitive performance, the time course of these changes (i.e., the accumulation of acute effects and subsequent chronic adaptions), and how these factors vary by populations with different levels of cognitive impairments, health status, fitness levels, among others. Studies addressing these questions may yield important findings that can be used towards developing evidence-based exercise recommendations for older adults that will help build cognitive reserve for successful aging.

CONCLUSIONS

In summary, this meta-analysis observed a small yet significant improvement in cognitive function following a single bout of exercise compared to a non-exercise control group/condition in healthy older adults. We failed to identify significant group differences within study-level effect modifiers relating to characteristics of the sample, study design, exercise intervention, and domain of cognitive assessment based on the 16 RCTs in our sample. Interestingly, we found that acute exercise elicited a greater effect on cognitive performance when measured using time- than accuracy-related assessments, suggesting that the time-related component of cognitive measures (e.g., reaction time) might be more sensitive to the acute effect of exercise. Our findings have important practical implications, supporting the prescription of a single bout of exercise (10-30 min, light to vigorous intensity) for immediate benefits on cognitive function among healthy older adults. Future research in this area should consider including various exercise modalities while considering potential interactions between moderators. Additional well-designed RCTs with transparent reporting are needed to explore the underlying neurophysiological mechanisms regarding acute and chronic effects of exercise on cognition.

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Table 2. 1 Characteristics of the studies included in the systematic review

Study		Sample	Acute intervention characteristics		Cognitive assessment
Author and Year	Design	characteristics	Exercise	Control	and timing post-exercise
Córdova et al., 2009	Parallel; pre/post	48 healthy women. CG: n=12; Age: 62.2±4.4 yr, BMI: 24.0±2.4 kg±m^2, $\dot{V}O_{2max}$: 22.8±3.9 mL/min/kg, Education: 8.3±2.3 yr, MMSE: 26.9±1.4 60% AT: n=12; Age: 64.5±4.4 yr, BMI: 26.3±2.5 kg/m^2, $\dot{V}O_{2max}$: 20.6±6.2 mL/min/kg, Education: 8.8±1.6 yr, MMSE: 27.6±2.7 90% AT: n=12; Age: 63.5±4.9 yr, BMI: 24.2±3.2 kg/m^2, $\dot{V}O_{2max}$: 22.2±5.9 mL/min/kg, Education: 8.8±1.3 yr, MMSE: 27.1±1.1 110% AT: n=12; Age: 63.1±5.1 yr, BMI: 24.3±3.6 kg/m^2, $\dot{V}O_{2max}$: 23.2±4.5 mL/min/kg, Education: 8.7±2.4 yr, MMSE: 27.2±1.5	5 min WU, 20 min ergometer cycling at: 60% AT (~22% $\dot{V}O_{2max}$), 90% AT (~50% $\dot{V}O_{2max}$), 110% of AT (~60% $\dot{V}O_{2max}$)	25 min seated rest	Simple response time, verbal fluency test (count), Tower of Hanoi test (time, accuracy count), Trial Making test Part A&B (time). 8 min post
Kamijo et al., 2009	Cross-over; post only	12 men, Age: 65.5±1.5 yr, $\dot{V}O_{2max}$: 32.4±1.3 mL/min/kg, Education: 12.5±0.7 yr, MMSE: 29±0.3	20 min ergometer cycling at 50% $\dot{V}O_{2max}$	20 min seated rest	Modified Flanker test (time, %accuracy) Less than 2 min.
Barella et al., 2010	Parallel; pre/post	40 community-dwelling older adults (16 women). CG: Age: 68.47±8.28 yr EX: 70.05±8.53 yr	5 min WU, 20min treadmill walking at 60% HRR	25 min seated rest	Stroop tasks, including Color, Interference, and Inhibition (time +/- 10 ms based on accuracy). 0, 5, 10, 15 min post

Hyodo et al., 2012	Cross-over; pre/post	16 healthy older adults (3 women), Age: 69.3±3.5 yr, weight: 60.8±4.6 kg, height: 164.0±8.6 cm, MMSE: 28.8±1.6	10 min ergometer cycling at 50% $\dot{V}O_{2max}$	10 min resting	Stroop task, including neutral and incongruent (time, %error) 15 min post
Chang et al., 2015	Cross-over; post only	42 healthy men. Low-fit: n=21, Age: 63.43±3.34 yr, BMI: 23.37±2.72 kg/m^2, $\dot{V}O_{2max}$: 23.71±1.88 mL/min/kg, Education: 9.97±3.25 yr, MMSE: 28.29±1.3 High-fit: n=21, Age: 62.76±2.42 yr, BMI:22.45±2.97 kg/m^2, $\dot{V}O_{2max}$: 35.99±2.90 mL/min/kg, Education: 10.51±3.98 yr, MMSE: 28.81±1.48	5min WU, 20 min ergometer cycling at 65% HRR, 5 min CD	30 min reading	Stroop Color Word task, including congruent and incongruent (time). Within 5 min
Chu et al., 2015	Cross-over; post only	46 healthy older adults (22 women). Low-fit: n=24, Age: 64.9±4.0 yr, BMI: 24.3±0.95 kg/m^2, $\dot{V}O_{2max}$: 23.5±2.8 mL/min/kg, Education: 10.0/4.1 yr High-fit: n=22, Age: 63.8±2.3 yr, BMI: 24.2±2.5 kg/m^2, $\dot{V}O_{2max}$: 36.0±1.2 mL/min/kg, Education: 9.3±3.5 yr	5 min WU, 20 min ergometer cycling at 65–75% HRR, 5 min CD	30 min reading a book related to exercise and cognition	Stroop task, including congruent and incongruent (time, %accuracy). After 10 min
Hsieh et al., 2016 (a)	Cross-over; post only	17 healthy men, Age: 66.4±1.2 yr, BMI: 23.0±2.2 kg/m^2, Education: 16.2±1.5 yr; MMSE: 29.7±0.5	30 min resistance exercise at 70% 10-RM, 8 exercises with 2 × 10 repetitions	30 min reading information about physical activity and mental health	Go/No-Go Task (time, variability, %commission, %omission). After 10 min
Hsieh et al., 2016 (b)	Cross-over; pre/post	20 healthy active men, Age: 67.2±1.8 yr, BMI: 23.0±2.5 kg/m^2, Education: 16.3±1.5	30 min resistance exercise at 70%	30 min reading	Modified Sternberg paradigm, including in

		yr; MMSE: 29.5±0.7	10-RM, 8 exercises with 2 × 10 repetitions	information about physical activity and mental health	and out of set (time). After 10 min
Abe et al., 2018	Cross-over; pre/post	26 community-dwelling older adults (18 women), Age: 71.7±4.7 yr, Education: 14.4±2.2 yr; MMSE: 28.7±1.2	10 min seated stepping	10 min seated resting	Stroop tasks, including neutral, incongruent, and interference (time). After 5 min
Hsieh et al., 2018	Cross-over; post only	20 healthy men, Age: 70.0±3.3 yr, BMI: 23.6±2.1 kg/m^2, $\dot{V}O_{2max}$: 33.8±2.5 mL/min/kg, Education: 16.3±2.1 yr; MMSE: 28.2±1.6, IPAQ: 2397.6±1469.7 MET·min/week	5 min WU, 20 min moderate treadmill walking at 60-70% HRR, 5 min CD	30 min watching a video relating to sport science, seated	Stroop Color Word tasks, including congruent and incongruent (time, %accuracy). After 15min
Ji et al., 2019	Cross-over; pre/post	20 community-dwelling older adults (9 women), Age: 67.0±3.2 yr, BMI: 22.66±1.71 kg/m^2, $\dot{V}O_{2max}$: 26.0±2.09 mL/min/kg, Education: 11.25±1.48 yr; MMSE: 27.9±0.62, IPAQ: 2384.3±385.5 MET·min/week	5 min WU, 15 min walking at 65% HRR, 5 min CD	25 min reading materials related to exercise	Modified Stroop tasks, including naming and executive (time). Immediate when HR return to resting level
Nouchi et al., 2020	Parallel; pre/post	30 healthy women CG: n=15, Age: 70.07±5.38 yr, BMI: 23.16±2.16 kg/m^2, Education: 13.67±1.99 yr EX: n=15, Age: 69.73±5.32 yr, BMI: 23.90±2.21 kg/m^2, Education: 13.47±1.41 yr	24 min combined exercise (aerobic, strength, and stretching) at 60-80% HR_{max}, 6 min stretching	30 min seated rest	Digit Symbol Coding, Stroop task, reverse Stroop task, Verbal fluency task, Working memory updating task, Digit cancellation task (accuracy count). After 5 min

Stute et al., 2020	Parallel; pre/post	42 healthy older adults (20 women) CG: n=23, Age: 69.73±4.23 yr, BMI: 24.91±2.39 kg/m^2, $\dot{V}O_{2max}$: 24.52±6.29 mL/min/kg, HR_{max}: 135.4±16.94 beats/min, Education: 15.85±2.31 yr; MMSE: 29.09±1.16 EX: n=19, Age: 68.31±3.31 yr, BMI: 24.47±2.23 kg/m^2, $\dot{V}O_{2max}$: 25.48±5.98 mL/min/kg, HR_{max}: 138.55±18.27 beats/min, Education: 15.66±2.36 yr; MMSE: 29.28±0.11	15 min ergometer cycling at 50% $\dot{V}O_{2max}$, with cadence between 60-80 rpm	15 min listening to an audiobook	Letter n-back task (time, %accuracy, correct responses/sec). Only post 15 min included.
Boyle et al., 2021	Cross-over; pre/post	19 healthy active older adults (9 women), mean age: 65 yr	20 min yoga (14a) or multimodal proprioceptive exercise (14b)	20 min watching live sports, seated	Memory task (time, %accuracy). Immediate
McSween et al., 2021	Parallel; post only	60 healthy older adults (43 women). CG: n=20, Age: 67.9±4.4 yr, BMI: 25.6±4.2 kg/m^2, $\dot{V}O_{2max}$: 21.2±4.1 mL/min/kg, Education: 16.5±3.9 yr; MICE: n=20, Age: 65.5±4.9 yr, BMI: 25.2±3.0 kg/m^2, $\dot{V}O_{2max}$: 24.1±5.0 mL/min/kg, Education: 16.5±2.8 yr; HIIE: n=20, Age: 65.8±4.4 yr, BMI: 27.1±4.8 kg/m^2, $\dot{V}O_{2max}$: 23.2±7.6 mL/min/kg, Education: 15.1±2.8 yr	(15a) MICE: 5 min WU, 30 min cycling at 55-70% HR_{max}, 3 min CD. (15b) HIIE: 5 min WU, 25 min interval cycling for 4 × 4 min at 85–95% HR_{max}, 3×3 min at 50–65% HR_{max}, 3 min CD	38 min stretching	Novel word learning tasks, including recall and recognition (time, %accuracy). Immediate, on average 9.8 min post
Olivo et al., 2021	Parallel; pre/post	49 healthy older adults (22 women). CG: n=25, Age: 70.7±3.1 yr, $\dot{V}O_{2max}$:	30 min ergometer cycling at HR of	30 listening to relaxing	N-back task (time, %accuracy).

	32.3±5.6 mL/min/kg, MMSE: 28.4±1.0, IPAQ: 3268.2±2027 MET·min/week EX: n=24, Age: 69.6±2.8 yr, $\dot{V}O_{2max}$: 31.4±5.5 mL/min/kg, MMSE: 28.9±1.2, IPAQ: 2731±1442 MET·min/week	60% $\dot{V}O_{2max}$	music, recumbent	Immediate

Note: Data are summarized as mean ± standard deviation, where appropriate. *Abbreviations:* AT, aerobic threshold; BMI, body mass index; CD, cool-down; CG, control group; EX, exercise group; HIIE, high-intensity interval exercise; HR, heart rate; HR_{max}, maximal heart rate; HRR, heart rate reserve; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent; MICE, moderate-intensity continuous exercise; MMSE, Mini-Mental State Examination; PA, physical activity; RCT, randomized controlled trial; RM, repetition maximum; rpm, rotations per minute; $\dot{V}O_{2max}$, maximal oxygen uptake; WU, warm-up; yr, years.

Table 2.2. Bivariate and subgroup moderator analysis results (k = 90)

Moderator / Level		Summary effect			Test of moderation		
	k	SMD (95% CIs)	z	p	Q_M	p	I^2_{total}
Study design							
Trial type					8.82	**0.01**	1.06%
Cross-over	43	0.18 (0.04, 0.32)	2.56	**0.01**			
Parallel	47	0.16 (-0.05, 0.37)	1.51	0.13			
Measure					8.81	**0.01**	1.12%
Pre-post	56	0.16 (0.001, 0.33)	1.97	**0.05**			
Post-only	34	0.18 (0.02, 0.35)	2.22	**0.03**			
Sample Characteristic							
Age (yr)	90	-0.02 (-0.62, 0.02)	-0.93	0.35	0.87	0.35	0.32%
Sex (% W)	90	0.02 (-0.32, 0.37)	0.13	0.90	0.02	0.90	1.06%
BMI (kg/m^2)	69	-0.03 (-0.13, 0.08)	-0.49	0.62	0.24	0.62	~0.0%
$\dot{V}O_{2max}$ (mL/kg/min)	55	0.01 (-0.01, 0.02)	1.05	0.30	1.11	0.30	~0.0%
Education level (y)	68	-0.02 (-0.06. 0.03)	-0.69	0.49	0.48	0.49	~0.0%
Acute Exercise							
Type					9.03	0.06	1.82%
Cycling	53	0.19 (0.03, 0.36)	2.34	**0.02**			
Walking	18	0.19 (-0.07, 0.46)	1.48	0.14			
Resistance exercise	6	0.16 (-0.17, 0.49)	0.94	0.35			
Other [a]	13	0.10 (-0.19, 0.39)	0.69	0.49			
Intensity					9.16	**0.03**	1.24%
Light	16	0.12 (-0.07, 0.32)	1.24	0.22			
Moderate	63	0.18 (0.06, 0.30)	3.00	**0.003**			
Vigorous	9	0.18 (-0.06, 0.43)	1.45	0.15			
Duration					8.81	**0.01**	1.10%
≤20 minutes	30	0.16 (-0.06, 0.38)	1.44	0.15			
>20 minutes	60	0.18 (0.04, 0.32)	2.60	**0.001**			
Cognitive Assessment							
Component [b]					17.21	**<0.001**	1.41%
Accuracy	35	0.11 (-0.04, 0.26)	1.46	0.14			
Time	55	0.24 (0.11, 0.35)	3.77	**<0.001**			
Domains					10.20	**0.04**	1.39%
Attention	14	0.19 (-0.03, 0.42)	1.69	0.09			
Executive function	58	0.19 (0.05, 0.32)	2.70	**0.007**			
General cognitive function	7	-0.04 (-0.40, 0.33)	-0.20	0.84			
Working memory	11	0.18 (-0.07, 0.45)	1.46	0.14			

Note: Significant p values are in bold. [a] Includes yoga (k = 2), seated (k = 3) and multicomponent (k = 8) exercise. [b] *S*gnificant difference between groups. BMI, body mass index; CI, confidence interval; ES, effect size; RT, resistance training; SMD, standardized mean difference; $\dot{V}O_{2max}$, maximal oxygen uptake.

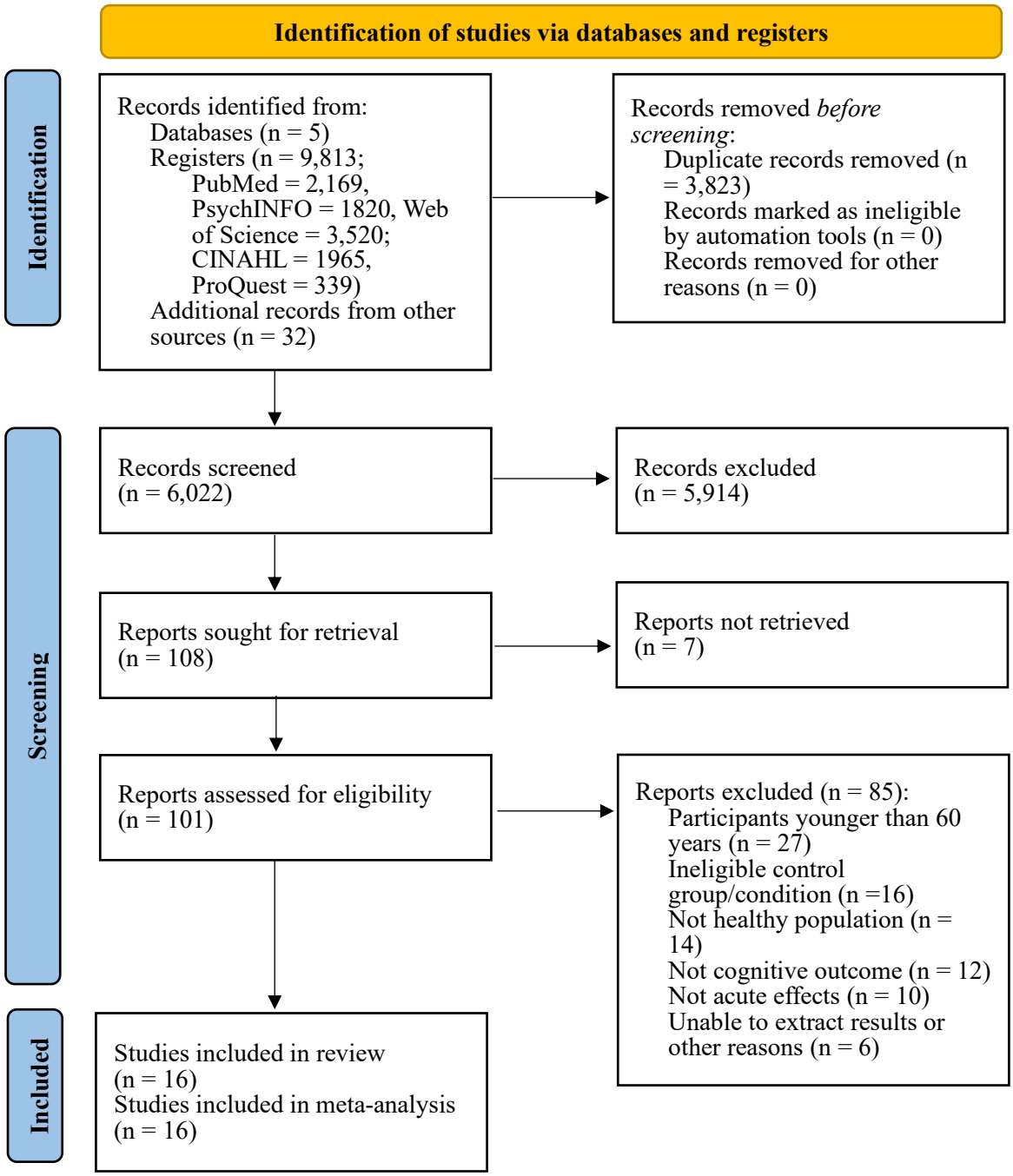

Figure 2. 1 PRISMA flow diagram of the selection process. PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

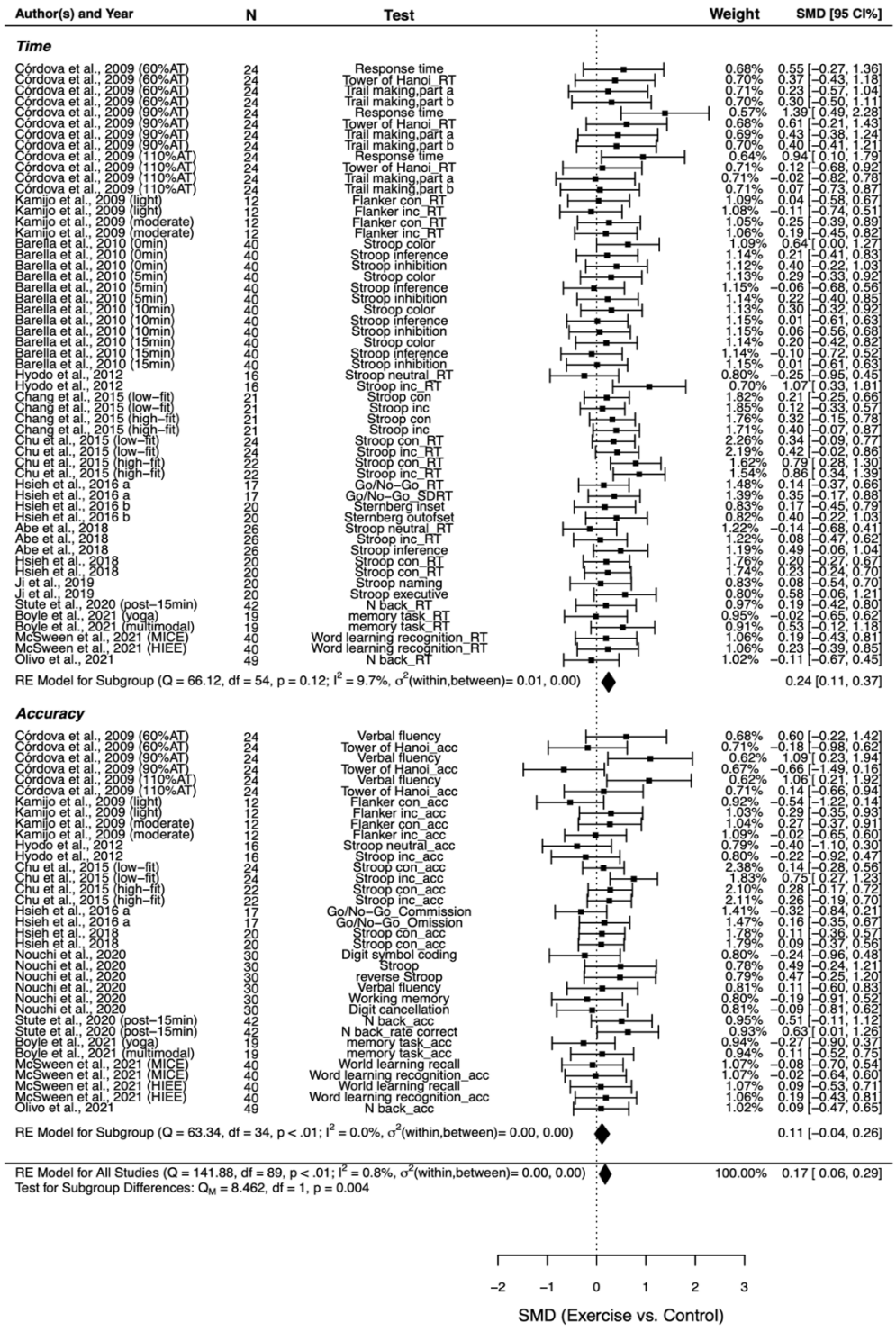

Figure 2. 2 Forest plot displaying acute effects of exercise versus control on cognition. Plot displays pooled standardized mean differences (SMDs) with 95% confidence intervals (CIs), weight, total sample sizes (N), and test names of individual study, separated by time- and accuracy-related outcomes. Results from the main meta-regression and subgroup analysis are also presented.

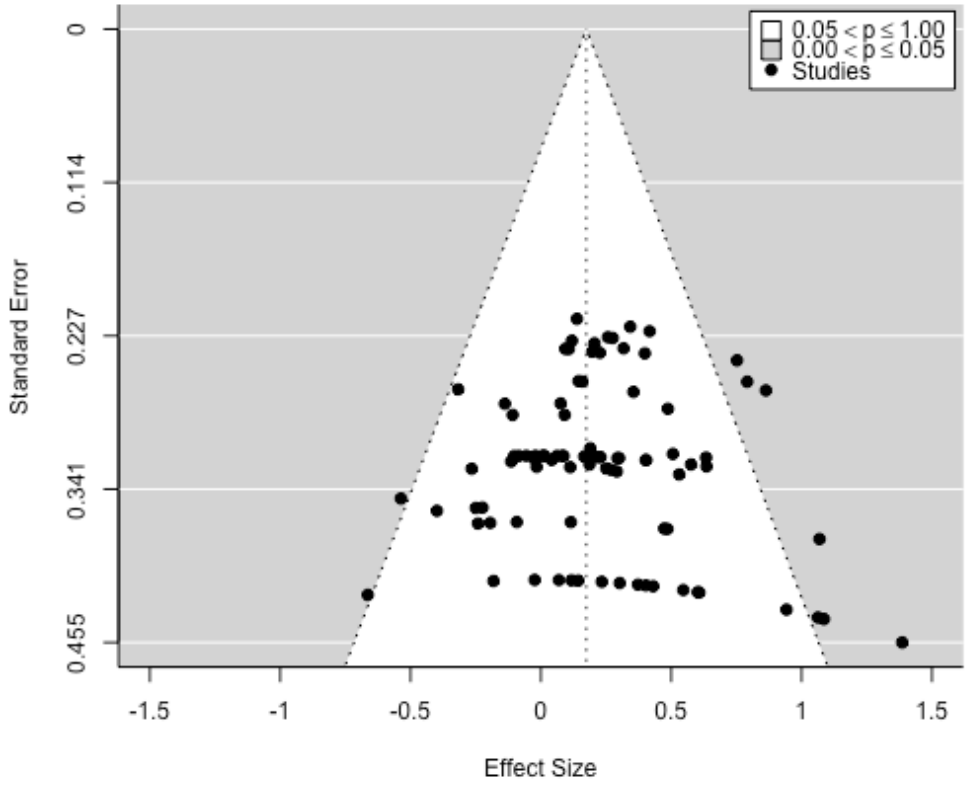

Figure 2. 3 Funnel plot displaying the distribution of observed effect sizes (k = 90). Non-independent effect sizes were plotted against a measure of precision (i.e., the standard error of the effect size). In the absence of publication bias and heterogeneity, the point estimates should be distributed symmetrically around the overall pooled effect estimate (vertical dashed line) forming a funnel shape, with the majority of points falling inside of the pseudo-confidence region (within the white triangle). Despite some asymmetry on the right-side of the funnel, the results of Egger and Begg tests support the absence of funnel plot asymmetry.

SDC 2.1. PRISMA network meta-analysis checklist

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	*11*
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	11-12
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	*13-15*
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	15
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria	*16-17*

		for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	16, 45
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	16, SDC 2.2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	16-17
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	17-18
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	17-19
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	*38-47*
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	19
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	17-20
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;*	17-20

		• *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	17-20
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	19
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	*18-20*
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	20, 45
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	*NA*
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	*NA*
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	20-22, 38-42
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	22-23
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and	*38-42, 46*

		confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	*22-23, 46*
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	*22-23*
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	22-23, 47
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	*23-24*
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	24-28
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	28
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	28-31
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	*NA*

Note: * Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement. † Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section. PICOS: population, intervention, comparators, outcomes, study design.

SDC 2.2 Terms and strategies for electronic search

"mental processes/physiology"[MeSH Major Topic] OR "mental processes"[Title/Abstract] OR "cognition"[Title/Abstract] OR "executive function"[Title/Abstract] OR "memory"[Title/Abstract] OR "attention/physiology"[MeSH Terms] OR "reaction time/physiology"[MeSH Terms] OR "set-shifting"[Title/Abstract] OR "nerve growth factors"[MeSH Terms] OR "Brain-Derived Neurotrophic Factor"[Title/Abstract] OR "BDNF"[Title/Abstract] OR "brain health"[Title/Abstract] OR "brain activity"[Title/Abstract] OR "brain activities"[Title/Abstract] OR "mental health"[MeSH Terms]

AND

"exercise"[MeSH Terms] OR "exercise"[Title/Abstract] OR "exercise"[MeSH Major Topic] OR "walking/physiology"[MeSH Terms] OR "walking"[Title/Abstract] OR "gait/physiology"[MeSH Terms] OR "gait"[Title/Abstract] OR "acute exercise"[Title/Abstract] OR "acute exercises"[Title/Abstract] OR "acute bout"[Title/Abstract] OR "acute bouts"[Title/Abstract] OR "acute effects"[Title/Abstract] OR "acute effect"[Title/Abstract] OR "acute responses"[Title/Abstract] OR "acute response"[Title/Abstract] OR "acute resistance"[Title/Abstract] OR "acute aerobic"[Title/Abstract] OR "acute physical"[Title/Abstract] OR "post exercise"[Title/Abstract] OR "postexercise"[Title/Abstract] OR "single bout"[Title/Abstract] OR "single bouts"[Title/Abstract] OR "cycling"[Title/Abstract] OR "running"[Title/Abstract] OR "acute strength"[Title/Abstract] OR "acute endurance"[Title/Abstract] OR "running"[MeSH Terms] OR "bicycling"[MeSH Terms] OR "Tai Ji"[MeSH Terms] OR "Yoga"[MeSH Terms]

AND

"aged"[MeSH Terms] OR "aged"[MeSH Major Topic] OR "older"[Title/Abstract] OR "elderly"[Title/Abstract] OR "elder"[Title/Abstract] OR "elders"[Title/Abstract] OR "seniors"[Title/Abstract] OR "senior"[Title/Abstract] OR "older adults"[Title/Abstract] OR "older population"[Title/Abstract] OR "older individuals"[Title/Abstract] OR "old people"[Title/Abstract] OR "old individuals"[Title/Abstract] OR "elderly people"[Title/Abstract] OR "geriatrics"[Title/Abstract] OR "retired"[Title/Abstract]

NOT

"adolescents"[Title/Abstract] OR "adolescent"[Title/Abstract] OR "children"[Title/Abstract] OR "child"[Title/Abstract] OR "minors"[Title/Abstract] OR "infants"[Title/Abstract] OR "infant"[Title/Abstract] OR "students"[Title/Abstract] OR "student"[Title/Abstract] OR "stroke"[Title] OR "cancer"[Title/Abstract] OR "cancers"[Title/Abstract] OR "Parkinson"[Title/Abstract] OR "heart failure"[Title/Abstract] OR "rehabilitation"[Title/Abstract] OR "rehabilitations"[Title/Abstract] OR "fracture"[Title] OR "fractures"[Title] OR "osteoporosis"[Title] OR "osteoarthritis"[Title/Abstract] OR "Alzheimer"[Title] OR "Alzheimer's"[Title] OR "dysfunction"[Title] OR "dietary"[Title] OR "diet"[Title] OR "patients"[Title] OR "patient"[Title] OR "rats"[Title/Abstract] OR "rat"[Title/Abstract] OR "mouse"[Title/Abstract] OR "mice"[Title/Abstract] OR "review"[Publication Type] OR "review"[Title] OR "meta-analysis"[Publication Type] OR "meta-analysis"[Title] OR "cross-sectional"[Title/Abstract] OR "case reports"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "letter"[Publication Type] OR "case"[Title] OR "case-

control"[Title/Abstract] OR "observational"[Title] OR "cohort"[Title/Abstract] OR "longitudinal"[Title] OR "survey"[Title] OR "visual"[Title] OR "visually"[Title] OR "virtual"[Title] OR "therapy"[Title] OR "wheelchair"[Title/Abstract] OR "depressive symptom"[Title/Abstract] OR "depressive symptoms"[Title/Abstract] OR "depressed"[Title/Abstract] OR "depression"[Title] OR "anxiety"[Title] OR "anxious"[Title] OR "obstacle"[Title] OR "typology"[Title/Abstract] OR "muscle damage"[Title] OR "pain"[Title] OR "pains"[Title] OR "diabetes"[Title] OR "sclerosis"[Title] OR "poststroke"[Title] OR "post stroke"[Title] OR "online"[Title]

SDC 2.3.1 Tool used to access methodological study quality and bias [a]

Section/Topic	Item#	Checklist item	Score*	Page#
Title	1a	Identification as a randomized trial in the title		
Abstract ‡	1b	Specify a crossover or parallel design, and report all information outlined in Table 2.3.2		
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale		
	2b	Specific objectives or hypotheses		
Methods				
Trial design	3a†	Trials were randomized and provided rationale for a crossover design. Description of the design features including: (1) allocation ratio (equal vs. unequal, in parallel design) if applicable, (2) the number and duration of periods, (3) duration of washout period, and (4) consideration of carry over effect		
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		
Participants	4a	Eligibility criteria for participants		
	4b	Settings and locations where the data were collected		
Interventions ‡	5a†	The interventions for each group with sufficient details to allow replication, including (1) the different components of the interventions, (2) the precise details of both the experimental treatment and comparator, and if relevant, description of the similarity of interventions, (3) how and when they were actually administered, and when applicable, (4) the procedures for tailoring the interventions to individual participants.		
	5b†	Details of whether and how the interventions were standardized. Specifically, (1) attempts were made to control and/or monitor pre-trial conditions (e.g. diet, exercise), (2) measures of important baseline variables were incorporated into study design, and (3) a familiarization trial was conducted for studies involving a performance test.		
Outcomes	6a†	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed. Specifically, exclusively describe		

		the time point for pre and post measures of cognitive function, for example, immediately post-exercise means measures within how many time units.		
	6b	Any changes to trial outcomes after the trial commenced, with reasons		
Sample size	7a†	How sample size was determined, accounting for within participant variability		
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomization				
Sequence generation	8a	Method used to generate the random allocation sequence		
	8b	Type of randomization; details of any restriction (such as blocking and block size)		
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence§ (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned		
Implementation	10	Who generated the random allocation sequence, § who enrolled participants, and who assigned participants to the sequence of interventions		
Blinding ‡	11a†	If done, who was blinded after assignment to interventions and how? Specifically, was there blinding of all subjects, of all investigators involved in the trials, or both?		
	11b†	If done, were both the method of blinding and the evaluation of the successfulness of blinding described?		
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes which are appropriate for crossover design (that is, based on within participant comparison)		
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		
Results				
Participant flow (a diagram is strongly recommended)	13a	The numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome, separately for each sequence and period		

	13b	Number of participants excluded at each stage, with reasons, separately for each sequence and period		
Recruitment ‡	14a	Dates defining the periods of recruitment and follow-up		
	14b	Details were provided regarding why the trial ended or was stopped due to the inability of a subject to complete study requirements, adverse event, or otherwise.		
Baseline data	15a	A table showing baseline demographic and clinical characteristics by sequence and period, such as age, sample size, % gender		
	15b	Additional descriptive characteristics were provided, including (1) baseline cognition, or risk of dementia by using neuropsychological test (eg., Mini-Mental State Examination), (2) BMI (or height and weight), physical fitness/activity status with type/unit (e.g. VO2max, PA/wk, IPAQ, maximal power, other activity score) and value, and when applicable (3) resting measures of HR, SBP, DBP, Total-C, LDL-C, HDL-C, blood glucose, and medication information.		
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups		
Outcomes and estimation ‡	17a†	For each primary and secondary outcome, the following results (i.e., estimated effect size and its precision, e.g. 95% CI) should be reported: (1) within-subject ¶ and (2) between-condition(s) statistical comparisons. Results for each intervention in each period are recommended.		
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		
Harms	19	Describe all important harms or unintended effects in a way that accounts for the design (for specific guidance see CONSORT for harms)		
Discussion				

Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		
Generalizability	21	Generalizability (external validity, applicability) of the trial findings		
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		
Other information				
Registration	23	Registration number and name of trial registry		
Protocol	24	Where the full trial protocol can be accessed, if available		
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		

Note: CONSORT, Consolidated Standards of Reporting Trials. CI, Confidence interval. [a] The CONSORT statement extension to randomized controlled trials (Dwan et al., 2019) served as the foundation of this tool. Where applicable, we modified individual items to include study/intervention specific factors from the scale developed by Van Rosendal et al. (2010), designed to assessed bias resulting from subject selection, performance and data analysis in studies examining glycerol use in hyperhydration and rehydration and its impact on exercise capacity or performance. ‡ Modified original item from the CONSORT Statement extension to randomized crossover trials (Dwan et al., 2019). § Random sequence here refers to a list of random orders, typically generated via computer program. This should not be confused with the *sequence of interventions* in a randomized crossover trial (e.g., paper reports that a subject received intervention A before B). ¶ A within participant comparison takes into account the correlation between measurements for each participant because they act as their own control, therefore measurements are not independent.

Score:

* Individual items (except for those denoted by †) were scored as *Fully satisfied = 1, Not satisfied = 0, Cannot determine = CD, or Not applicable = NA*.

† Select items were scored as *Fully satisfied = 1, Partially Satisfied = 0.5, Not satisfied = 0, Cannot determine = CD, or Not applicable = NA*.

Explanation

Abstract – 1b

To receive score of 1, all 2 items must be accounted for. If only 1 item is reported, award score of 0.5.

Trial design – 3a

• apply bullet item *(1) allocation ratio* for parallel group design

• To receive score of 1, all bulleted items must be accounted for. If study identifies as randomized but provides no other information regarding the design features, award score of 0. Award score of 0.5 for all other combinations.

Interventions – 5a and 5b

• To receive score of 1, all bulleted items must be accounted for. If 1 or less items are reported, award score of 0. Award score of 0.5 for all other combinations.

- In interventions for acute exercise and control groups, the following components should be reported: exercise modality, intensity, duration, procedure, pattern (continuous or intermittent).

Outcomes – 6a

• To receive score of 1, all bulleted items must be accounted for. If authors report how and when outcomes were assessed but provide no measures of reproducibility, award score of 0.5.

- The cognitive outcome measures should include the following elements of assessments: 1) number of assessments, 2) cognitive domains, and 3) timing of pre and post exercise/control assessments, e.g., exclusively define the word "immediate" when applicable.

Sample size – 7a

• To receive score of 1, authors must report the method or approach used to determine the sample size and how they arrived at that particular value (i.e., justification of sample size). For example, did authors use data from previous study? Previous work in their laboratory? Etc.

• If authors report the method or approach used to determine sample size but provide no further detail about how they arrived at that particular N value or justification for it, award a score of 0.5.

Blinding – 11a

• In general, to receive score of 1, blinding of subjects and investigators must be reported. Note, a "double blind" study indicates that both subjects and investigators were blinded to conditions/treatments.

• If blinding is reported for subjects but not investigators (or vice versa), award score of 0.5.

Blinding successfulness – 11b

• In general, to receive score of 1, authors need to list the method or test used, the variable(s) evaluated pre- and/or post-experimental trial/condition, and the justification or support (e.g., statistical test & p-value) that their blinding method worked.

• If authors provide some of the information above but not all, and it is still unclear whether their method of blinding was successful (or not), award score of 0.5.

Baseline data – 15b

• To receive score of 1, all bullet items should be reported if applicable. Award score of 0.5 for all other combinations.

Outcomes and estimation – 17a

• To receive score of 1, bulleted items (1) and (2) must be reported. If only one bullet point is satisfied, award score of 0.5.

• Not receive point if the study only listed Mean and SD for significant ones.

SDC 2.3.2. Information to include in abstract of report of randomized crossover trial: extension of CONSORT for abstracts checklist *(Ioannidis et al., 2004)*

Item	**Description**
Title	Identification of study as a randomised crossover trial
Trial design	Description of the trial design (crossover trial and number of periods)
Methods:	
Participants	Eligibility criteria for participants and the settings where the data were collected
Interventions	Interventions intended for all participants
Objective	Specific objective or hypothesis
Outcome	Clearly defined primary outcome for this report
Randomisation	How participants were allocated to sequences
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to intervention
Results:	
Numbers randomised	Number of participants randomised to each sequence
Recruitment	Trial status (applicable to conference abstracts)
Numbers analysed	Number of participants analysed
Outcome	For the primary outcome, the estimated effect size and its precision based on within participant comparisons
Harms	Important adverse events or side effects
Conclusions	General interpretation of the results
Trial registration	Registration number and name of trial register
Funding	Source of funding

Reference

1. Dwan K, Li T, Altman DG, Elbourne D. CONSORT 2010 statement: Extension to randomised crossover trials. *BMJ.* 2019;366:l4378.
2. van Rosendal SP, Osborne MA, Fassett RG, Coombes JS. Guidelines for glycerol use in hyperhydration and rehydration associated with exercise. *Sports Medicine.* 2010;40(2):113-39.
3. Ioannidis JP, Evans SJ, Gotzsche PC, et al. CONSORT Group. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med.* 2004;141:781-8.
4. Hopewell S, Clarke M, Moher D, et al, CONSORT Group. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet.* 2008;371(9609).

SDC 2.3. Itemized and total study quality scores for included studies

Study	Total	Title/abs	Introduction		Methods														
	%MSQ	1a	1b	2a	2b	3a	3b	4a	4b	5a	5b	6a	6b	7a	7b	8a	8b	9	10	11a
Cordova et al., 2009	72.2	0	0	1	1	0.5	NA	1	1	1	1	1	NA	0	NA	1	0	0	0	NA
Kamijo et al., 2009	62.1	0	0	1	1	0.5	NA	1	1	1	0.5	1	NA	0	NA	0	0	0	0	NA
Barella et al., 2010	63.3	0	1	1	1	1	NA	1	0	1	1	1		0	NA	1	0	0	0	NA
Hyodo et al., 2012	63.8	0	0	1	1	0.5	NA	1	1	0.5	1	1	NA	0	NA	0	0	0	0	NA
Chang et al., 2015	77.8	0	1	1	1	1	NA	1	1	1	1	1	NA	1	NA	0	0	0	0	NA
Chu et al., 2015	63.8	0	0	1	1	1	NA	1	0	1	1	0.5	NA	0	NA	0	0	0	0	NA
Hsieh et al._1, 2016	75.9	0	0	1	1	1	NA	1	1	1	1	1	NA	1	NA	0	0	0	0	NA
Hsieh et al._2, 2016	65.5	0	0	1	1	1	NA	1	1	1	1	1	NA	0	NA	0	0	0	0	NA
Abe et al., 2018	79.3	0	0	1	1	1	NA	1	1	1	1	1	NA	0	NA	1	0	1	0	NA
Hsieh et al., 2018	72.4	0	0	1	1	1	NA	1	1	1	1	1	NA	1	NA	0	0	0	0	NA
Ji et al., 2019	63.8	0	0	1	1	1	NA	1	1	0.5	1	1	NA	0	NA	0	0	0	0	NA
Nouchi et al., 2020	92.2	1	0	1	1	1	NA	1	1	1	0.5	1	NA	1	NA	1	1	1	1	1
Stute et al., 2020	79.3	0	1	1	1	1	NA	1	1	1	1	1	NA	1	NA	0	0	0	0	NA
Boyle et al., 2021	58.6	0	1	1	1	1	NA	1	1	0.5	0.5	0.5	NA	1	NA	1	0	0	0	NA
McSween et al., 2021	90.3	1	0	1	1	1	NA	1	1	1	1	1	NA	0	NA	1	1	1	1	1
Olivo et al., 2021	95.3	1	0	1	1	1	NA	1	1	1	1	0.5	NA	1	NA	1	1	1	1	1

	Methods					Results									Discussion			Other		
	11b	12a	12b	13a	13b	14a	14b	15a	15b	16	17a	17b	18	19	20	21	22	23	24	25
Cordova et al., 2009	NA	1	1	1	NA	0	NA	1	1	1	1	NA	NA	NA	1	1	1	NA	NA	1
Kamijo et al., 2009	NA	1	1	1	1	0	NA	1	1	1	1	NA	1	NA	0	0	1	NA	NA	1
Barella et al., 2010	NA	1	1	1	0	0	0	1	1	1	1	NA	NA	NA	1	0	1	NA	NA	1
Hyodo et al., 2012	NA	1	1	1	1	0	NA	1	0.5	1	1	NA	1	NA	1	0	1	NA	NA	1
Chang et al., 2015	NA	1	1	1	NA	0	NA	1	1	1	1	NA	NA	NA	1	1	1	NA	NA	1
Chu et al., 2015	NA	1	1	1	0	0	NA	1	1	1	1	NA	1	NA	1	1	1	NA	NA	1

Hsieh et al._1, 2016	NA	1	1	1	1	0	NA	1	1	1	1	NA	1	NA	1	1	1	NA	NA	1
Hsieh et al._2, 2016	NA	1	1	1	0	0	NA	1	1	1	1	NA	1	NA	1	0	1	NA	NA	1
Abe et al., 2018	NA	1	1	1	1	0	NA	1	1	1	1	NA	1	NA	1	1	1	NA	NA	1
Hsieh et al., 2018	NA	1	1	1	0	0	NA	1	1	1	1	NA	1	NA	1	1	1	NA	NA	1
Ji et al., 2019	NA	1	1	1	0	0	NA	1	1	1	1	NA	1	NA	1	0	1	NA	NA	1
Nouchi et al., 2020	NA	1	1	1	1	0	NA	1	1	1	1	NA	1	NA	1	1	1	1	1	1
Stute et al., 2020	NA	1	1	1	1	0	NA	1	1	1	1	NA	1	NA	1	1	1	NA	NA	1
Boyle et al., 2021	NA	1	1	1	0	0	NA	0	0	1	0.5	NA	0	NA	1	1	1	NA	NA	0
McSween et al., 2021	0	1	1	1	1	1	NA	1	1	1	1	NA	1	NA	1	1	1	NA	NA	1
Olivo et al., 2021	NA	1	1	1	1	1	NA	1	1	1	1	NA	1	NA	1	1	1	1	1	1

Note: NA, not applicable; %MSQ, percentage of methodological study quality.

CHAPTER 3

COGNITIVE FUNCTION, ARTERIAL STIFFNESS, AND CENTRAL BLOOD PRESSURE FOLLOWING A SINGLE BOUT OF WALKING IN PHYSICALLY INACTIVE OLDER ADULTS

ABSTRACT

Purpose: The purpose of this study was to investigate the effects of a single bout of moderate-intensity walking on cognition and vascular function in physically inactive older adults aged ≥ 60 years. **Method:** Twenty-six healthy older adults (17 females, 67.8 ±11.3 years) who did not meet the current PA guidelines were recruited. Utilizing a repeated measures cross-over design, each participant performed two acute sessions: 1) exercise (30-min walking at a moderate intensity; 100 steps/min); and 2) control (30-min quiet sitting). Cognitive performance (Flanker, DCCS, and PCPS tests selected from NIH Toolbox) and vascular outcomes (central blood pressure [cMAP], carotid to femoral PWV [cfPWV], aortic augmentation standardized to a heart rate of 75 bpm [AIx75]) were measured before and immediately after acute exercise within 5 minutes. Separate two-way repeated measure ANOVAs were performed to determine differences in cognitive and cardiovascular outcomes between time points (post vs. pre) and conditions (walking vs. control). **Results:** All cognitive test scores increased immediately after walking ($p <$ 0.05), however, only DCCS score was significantly higher compared to the control condition

(mean difference [MD] with 95% confidence intervals [CIs]= 0.338 [0.07, 0.61], $p = 0.016$, Cohen's $d = 0.46$). In addition, cMAP was significantly increased after 30-min sitting (MD = 5.75 [2.19, 9.30] mmHg, $p = 0.03$; $d = 0.40$) but remained unaltered after walking ($p = 0.08$). Post-session cfPWV was significantly lower following walking vs. the control condition (MD = 0.55 [0.13, 0.96] m/s, $p = 0.012$; $d = 0.13$). There was a significant time × condition interaction for all variables except for AIx75. Other comparisons were not significant ($p > 0.05$). Following walking, the acute changes (%Δ) in cfPWV and cMAP were negatively associated with the changes in executive function and attention ($p < 0.05$). **Conclusion**: A single bout of cadence-controlled walking elicited an immediate increase in cognitive performance and reduction in arterial stiffness compared with a control condition in healthy older adults.

INTRODUCTION

Population aging has become a public health challenge. Age-related decline in cognitive function combined with lifestyle factors (e.g., smoking, sedentary behavior) leads to an increased risk of dementia and reduced quality of life (1). Worldwide, an estimated 55 million people were living with dementia in 2019, and this number is projected to reach 139 million by 2050 (2). The high prevalence of dementia and other geriatric diseases (e.g., cardiovascular disease) poses a large burden to the health care and social system. Regular physical activity (PA) has been increasingly recognized as an effective approach for improving cognition (3). Recent public health guidelines encourage older adults to accumulate a greater amount of PA to achieve health benefits, irrespective of duration (i.e., even shorter than 10-minute bouts) and intensity (e.g., the WHO's "*every move counts*" message) (3, 4). However, compared to other PA-related health benefits (e.g., cardiovascular), there is relatively less evidence regarding the PA-cognition relationship, for example, the specific dose of exercise that yields optimal benefits in cognitive function (3). As such, understanding the effect of a single brief bout of exercise (i.e., acute effects) on cognition and its potential association with other age-related deteriorations (e.g., arterial stiffness) may help develop specific daily PA recommendations for older adults. This is essential for those who are at risk of cognitive decline or impairment to maintain adequate cognitive health, adapt to environmental changes, and optimize their capacity for completing complex tasks in daily living.

Previous studies have demonstrated small and transient improvements in multiple cognitive domains, including executive function, memory, and attention (3, 5-8). However, conflicting findings exist in studies involving various cognitive outcomes (e.g., domain, assessment), sample characteristics (e.g., age, fitness), and exercise patterns (e.g., duration, modality) (9, 10). For example, Chang and colleagues reported a better performance in executive function following 20-minute moderate-to-vigorous intensity cycling compared to 10- or 45-min sessions (negligible effects) (11), whereas other studies failed to observe significant changes in executive function or processing speed with higher intensity (12) or longer duration (9, 10, 13, 14). In particular for healthy older adults, the evidence supporting the benefits of PA for improvements in cognition has been characterized as insufficient (15). Considering the associations between cognitive function with habitual PA and health status (16), well-designed randomized controlled trials (RCTs) are needed to control for these potential confounders. In addition, relevant studies commonly implement cycling or running within specific heart rate or oxygen uptake ranges to regulate exercise intensity (5, 14, 17). There is a lack of evidence regarding other exercise modalities and intensity expressions, for example, modulation of walking intensity using step-based metrics (cadence; steps/min) to facilitate practical application (18-21).

Furthermore, the underlying mechanisms and physiological pathways related to improvements in cognitive function following acute PA are poorly understood. Recent evidence has linked cardiovascular risk factors (e.g., hypertension) and the vascular pathogenesis of

cognitive aging (22, 23). One proposed mechanism suggests that impaired vascular function influences brain microcirculation and neuronal health, and therefore contributes to cognitive decline (24, 25). Indeed, central arterial stiffness (i.e., aorta and common carotid artery) in advanced aging may augment hemodynamic pulsatility in the delicate brain microcirculation, increasing strain in the cerebral arterioles and capillaries, and eventually, greater susceptibility to damage in the brain. Conversely, a single bout of exercise has been shown to have an immediate and favorable influence on brachial blood pressure (26) and arterial stiffness (27, 28) that can persist for up to 24 hours post-exercise. Nevertheless, evidence involving older adults is lacking, and it is unclear whether such vascular responses are associated with improvements in cognitive performance after acute exercise.

Therefore, the current study aimed to: 1) investigate the effects of a single bout of moderate-intensity walking on cognitive (i.e., executive function, attention, and processing speed) and vascular function (i.e., central blood pressure and arterial stiffness) in physically inactive but otherwise healthy older adults (aged ≥ 60 years); and 2) examine the associations between changes in cognitive performance and vascular function following acute walking activity. To our knowledge, this is the first study to examine the acute effects of exercise on cognitive and vascular function in healthy older adults. Results from the present study may help reveal the relationship between cognitive function and acute functional changes in arterial stiffness and central blood pressure produced by acute exercise.

METHODS

Participants

Twenty-six inactive older adults (aged ≥ 60 years old, 65% female) were recruited for this study. A total sample size of at least 24 participants was determined based on an *a priori* power analysis using G*Power (software version 3.1.9.6, Universität Kiel, Germany), with an effect size of 0.3, alpha (α) level of 0.05, and desired power (1-β) of 0.80. Study eligibility screening was administered via online survey portal (Qualtrics), and only eligible individuals were contacted to be considered for participation in this study. This screening process included two health screening questionnaires (American College of Sports Medicine [ACSM] preparticipation health screening guidelines (29), Physical Activity Readiness Questionnaire [PAR-Q+] (30)), and a self-reported record of any medical conditions that might impair cognition or restrict mobility (e.g., mild cognitive impairment, dementia, Alzheimer's disease, Parkinson's disease, stroke, depression, metabolic diseases). All participants were required to be generally healthy with the absence of any injury or illness, and must speak English as their first language (31). In addition, physical inactivity was assessed via self-report by the International Physical Activity Questionnaire (IPAQ) (32) and was defined as engaging in less than 150 minutes of moderate-to-vigorous PA per week. All participants signed a written informed consent form prior to data collection. The study was approved by the University of Alabama Institutional Review Board (protocol ID: 21-01-4237).

Study Design

The present study utilized a randomized cross-over design with repeated measures (Figure 3.1). Each participant underwent three laboratory visits (1 familiarization, 2 experimental sessions), with at least one week between individual visits to avoid carry-over effects. Each visit was scheduled at the same time of a day to control for diurnal variation in study measures. Visit 1 included informed consent, anthropometric measurements, and familiarization with all experimental tasks/measures. For example, participants were given instructions and familiarized with the cognitive tasks, measurements of vascular function, and treadmill walking at a moderate intensity. Visits 2 and 3 (experimental sessions) involved completion of either an exercise or control condition assigned in a counterbalanced, randomized order. Participants were instructed to fast for more than 2 hours and to abstain from alcohol and exercise routine for 24 hours and from caffeine for 12 hours. A 24-hour history questionnaire was completed upon arrival at each visit.

For the exercise session, participants walked on the treadmill at a moderate intensity (i.e., 100 steps/min) for 30 min (33, 34), which was accomplished by matching their cadence to a metronome set at 100 beats per minute (35). The 30-min exercise bout was chosen in accordance with current PA guidelines (i.e., ≥ 150 min/week moderate-to-vigorous PA [MVPA]), and the weekly target was broken down to 5 days * 30 min/day (36). Cognitive and vascular functions (described below) were assessed immediately before and after walking. Cognitive tests were

taken immediately after exercise within 5 minutes, and then participants were asked to lie down in a supine position and rest quietly for 5 minutes before measuring vascular function (i.e., arterial stiffness and central blood pressure). The average time between the completion of acute walking/sitting and the start of pulse wave analysis (after the 5-min resting) was approximately 23 minutes. The sitting session was sequentially the same as the walking session with pre-/post-measures; however, instead of walking, participants were asked to sit on a chair quietly and read books in a distraction-free room for 30 minutes. Writing, sleeping, standing, and technology use were prevented, and talking was kept to a minimum. All sessions were under supervision and with the assistance of the research team.

Measurements and Procedures

Anthropometrics

Standing height was measured without shoes to the nearest 0.1 cm with a manual stadiometer (SECA 67310, SECA©, Chino, CA), and weight was measured to the nearest 0.1 kg on a digital scale (Tanita BWB-800, Tanita©, Arlington Heights, IL). Measures were repeated to ensure accuracy, with a third measurement taken if the first two differ by > 0.3 cm or 0.5 kg. The two closest measurements were averaged and reported. Body mass index (BMI) was calculated from height and weight data, expressed as $kg \cdot m^{-2}$. Body composition was measured using bioimpedance spectroscopy (BIS; Imp™ SFB7, Impedimed Limited, Queensland, Australia). This technique uses a range of 256 frequencies that allow for the electrical current to pass

through and around cells (37). Prior to electrode placement, excess hair was removed from the electrode sites, and the sites were cleaned with alcohol swabs and allowed to dry. Participants were instructed to lie supine on a padded gurney with the arms ≥ 30° away from the body and with legs separated. In accordance with manufacturer guidelines, dual-tab electrodes were placed on the back of the right wrist and top of the right ankle. The measurement began after the necessary descriptive characteristics (height, weight, age, and sex) were entered into the BIS device.

Cognitive performance

The National Institutes of Health Toolbox (NIH Toolbox®) is a validated measurement tool for assessing neurological and behavioral function, which includes cognition, emotion, motor, and sensation (38). All measures of cognition in this study were administered using the NIH Toolbox iPad application. Flanker Inhibitory Control and Attention Test (Flanker), Dimensional Change Card Sort Test (DCCS), and Pattern Comparison Processing Speed Test (PCPS) were selected from the NIH Toolbox Cognition Battery (NIHTB-CB) to measure the changes in specific cognitive domains (i.e., executive function, attention, and processing speed) (39). Raw and computed scores were automatically calculated and exported by the software (40). The same combination of cognitive tests was delivered before and immediately after acute sessions in the same order (i.e., Flanker, DCCS, and PCPS tests). Instructions were presented on the iPad screen

at the beginning of each test. All participants were able to complete the cognitive assessment (3 tests) within 10 minutes (average completion time across all sessions: 8.15 ± 0.46 minutes).

The Flanker test is derived from the Attention Network Test and measures attention and executive function, specifically involving inhibitory control (41, 42). Participants were instructed to identify the direction of a central target arrow flanked by similar stimuli on the left and right. They were required to focus on a visual target in the center of the screen and then choose the direction that corresponds to the middle arrow. The task lasted approximately 4 minutes and included 20 trials (congruent and incongruent). Test scoring was based on a combination of accuracy and reaction time, with accuracy considered first. Higher scores indicate higher levels of ability to attend to relevant stimuli and inhibit attention to irrelevant stimuli.

The DCCS test measures the cognitive flexibility component of executive function, which represents the ability to switch among multiple task strategies and rules (43, 44). Two target pictures were presented that vary along two dimensions (e.g., shape and color). Participants were asked to match a series of bivalent test pictures (e.g., yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g., color), and then according to the other dimension (e.g., shape) after several trials. A word cue appeared on the screen with unpredictable order, and after several trials, the criterion switches between the two dimensions. The whole test lasted approximately 4 min to complete. Similarly, scoring was also based on a combination of accuracy and reaction time. Higher scores represent higher levels of cognitive flexibility.

The PCPS test is modeled after Salthouse's Pattern Comparison Task to measure processing speed (40, 45). Participants were asked to identify whether two side-by-side pictures were the same or not within 85 seconds, and responded to as many items as possible up to a maximum of 130. The test lasted around 3 minutes. Type, complexity, and the number of stimuli were varied to ensure adequate variability of performance across the age spectrum. The score was the number of correct items (0~130) completed in 85 seconds, and it can be used to evaluate simple improvement or decline over time. Higher scores indicate a faster processing speed within the normative standard being applied.

Vascular function

Participants were instructed to lie down in a supine position, resting quietly for 5 minutes before the measurements. This time period allowed for changes in central hemodynamics resulting from the change in posture (seated to supine) to equilibrate (46). Vascular function was measured using the SphygmoCor® XCEL System (AtCor Medical, Sydney, Australia) (47). First, participants were instrumented with a standard brachial cuff on the upper arm to measure brachial blood pressure and initiate pulse wave analysis to obtain central mean arterial pressure (cMAP) and aortic augmentation index (AIx). Note, the aortic AIx was standardized to a heart rate of 75 bpm (AIx75) by the software (i.e., AIx75 = AIx + 4.8*[heart rate - 75]/10) (48). Since aortic AIx can be influenced by heart rate, the use of AIx75 enables comparisons of results from individuals with different heart rates (e.g., after exercise) and between visits. With participants

still in supine position, carotid to femoral PWV (cfPWV) was measured using a carotid tonometer simultaneously with a leg cuff to capture pressure waveforms at the carotid and femoral sites. The distances between measurement sites were measured with a tape. cfPWV was calculated by using the difference in the distances between sites and the measured time delay between proximal and distal waveforms (49). Each parameter was measured three times with 1-minute intervals, and the average value was recorded as the final value.

Statistical Analysis

Descriptive statistics were generated for all outcome measures (i.e., mean ± SD for continuous variables; frequencies and percentages for categorical variables). To address the primary aim, separate two-way repeated measure ANOVAs were performed to determine differences in cognitive and cardiovascular outcomes between time points (post vs. pre) and conditions (walk vs. control). Significant condition × time interactions were further explored with Bonferroni-corrected pairwise comparisons. The magnitudes of pairwise differences were quantified using Cohen's *d* effect sizes (*d*) and were classified as small (0.1), medium (0.5), and large (0.8) (50). In addition, percent changes (i.e., %Δ = [post value – pre value]/pre value) across time were calculated for all outcomes. To further explore the effect of condition, paired *t*-tests with Bonferroni correction were conducted to compare the %Δ between the two conditions (walk vs. control).

In addition, Pearson correlation coefficients (r) were used to explore univariate associations between cognitive and cardiovascular outcomes at both resting state and following an acute bout of walking. Specifically, correlations (and p-values) between individual cognitive and vascular parameters were calculated by using two sets of values across each participant: 1) the average values of pre-session measurements across both conditions (considered as resting state), and 2) the acute changes (%Δ) of all variables for the walking condition. All data analyses were performed in R (version 4.0.2), with the α level set at 0.05.

RESULTS

Sample characteristics are summarized in Table 3.1. Twenty-three participants self-reported their race/ethnicity as White, and three as Asian. The pre- to post-session measurements on cognitive test scores and vascular outcomes, and results from statistical tests are reported in Table 3.2.

Cognitive Function

Two-way repeated measure ANOVAs (Table 3.3) showed significant time × condition interactions for all cognitive tests (p-values < 0.05), despite no main effect of condition (p -values > 0.05). Based on pairwise comparisons, Flanker and PCPS scores increased (post vs. pre) after walking (mean differences [MD] with 95% confidence intervals [CIs] = 0.29 [0.17, 0.41] and 4.96 [3.39, 6.53] points, p-values < 0.0001, Cohen's d = 0.41 and 0.59, respectively), but the

post-session scores were not significantly different from that in the control condition (p-values > 0.05). The post-exercise DCCS score was significantly higher compared to the control condition (MD = 0.338 [0.07, 0.61], p = 0.016, d = 0.46). Other comparisons in time and/or condition effects were not significant (p-values > 0.05). Individual's changes in cognitive test scores were plotted and displayed in Figure 3.2 (panels a~c).

Figure 3.3 (panel A) displays acute changes (%Δ) in cognitive function under the two experimental conditions. In terms of percent changes (%Δ), paired t-tests (Table 3.3) indicated that compared to the control condition, Flanker and DCCS scores were significantly improved after walking (p-values < 0.05, d = 0.68 and 0.76), whereas the changes in PCPS score were similar under both conditions (p >0.05). Furthermore, 73~96% vs. 61~84% of the sample had increased cognitive test scores after walking and control session, respectively.

Vascular Function

A significant main effect of time was identified in cMAP, aortic AIx75, and cfPWV (p -values < 0.05), while the time × condition interaction was significant in cMAP and cfPWV (p -values < 0.05), but not in AIx75 (p > 0.05). There was a significant main effect of condition on cMAP (p = 0.01), where cMAP was significantly increased after 30-min sitting (MD = 5.75 [2.19, 9.30] mmHg, p = 0.03; d = 0.40) but remained unaltered after walking (p = 0.08). Post-session cMAP was significantly lower after walking vs. control (MD = -4.34 [-7.56, -1.11] mmHg, p = 0.01; d = 0.30). Although the main effect of condition was not significant (p > 0.05),

post-session cfPWV was significantly lower following walking vs. the control condition (MD = 0.55 [0.13, 0.96] m/s, $p = 0.012$; $d = 0.13$). In addition, AIx75 was significantly decreased after walking (MD =2.42 %, $p = 0.019$; $d = 0.26$), but remained unchanged under the control condition ($p > 0.05$). No other significant comparisons in time and/or condition effects were observed (p-values > 0.05). Individual's changes in vascular function were plotted and displayed in Figure 3.2 (panels d~f).

Figure 3.3 (panel B) displays acute changes (%Δ) in vascular function under the two experimental conditions. Paired *t*-tests (Table 3.3) for these acute changes (%Δ) demonstrated that compared to the control condition, only the change in cfPWV was significantly different following walking vs. control ($p < 0.001$, $d = 1.11$), whereas changes in cMAP and aortic AIx were similar across both conditions (p-values > 0.05). Overall, 27~61% vs. 19~57% of the sample had decreased cMAP, AIx, and cfPWV after walking and control session, respectively.

Associations Between Acute Changes in Cognitive and Vascular Function

At resting state (baseline), significant positive correlations were observed within the three cognitive test scores and three cardiovascular outcomes, r ranges from 0.68 ~ 0.84 and 0.46 ~ 0.76 (p-values < 0.05); and only baseline Flanker test was significantly correlated with cMAP and cfPWV ($r = -0.47$ and -0.49, $p = 0.0165$ and 0.01, respectively). Interestingly, following a single bout of walking, significant negative correlations were only observed between the acute responses (%Δ) in DCCS score and cMAP ($r = -0.56$, $p = 0.003$), DCCS score and cfPWV ($r =$

-0.50, $p = 0.009$), and Flanker score and cfPWV ($r = -0.50$, $p = 0.009$). Full correlation matrices are provided in Table 3.3.

DISCUSSION

The present study sought to examine the effects of a single bout of cadence-controlled walking on cognitive and vascular function in healthy, physically inactive older adults. The data herein demonstrate that acute exercise (30-min cadence-controlled walking) results in: 1) significant increases in cognitive performance in executive function and attention (Flanker and DCCS test scores); 2) unaltered cMAP and a significant reduction in cfPWV; but 3) no differential effects on processing speed and aortic AIx75 compared to the control (sitting) condition. Moreover, following a single bout of walking, the acute changes (%Δ) in cfPWV and cMAP were negatively associated with the changes in executive function and attention. Overall, this study demonstrated that an acute bout of moderate-intensity (cadence-controlled) walking was associated with concomitant changes in specific domains of cognition and vascular function, highlighting potential mechanisms that may lead to improved cognition following acute exercise.

Effects of Acute Exercise on Cognitive and Vascular Function

Cognitive performance was improved by 3.69~11.5% following 30-min walking at a moderate intensity compared to baseline/pre-exercise measures. Differences in cognitive performance between conditions (exercise vs. control) seemed to be task/domain specific. For

executive function, our findings indicate significant changes in attention, inhibitory control, and cognitive flexibility following exercise only, which were further confirmed by comparing individual percent changes under the two conditions. We noticed improved processing speed after both exercise and control sessions without a condition difference, suggesting that the exercise stimulus may not have been sufficient to elicit beneficial changes in this task/domain. It may also suggest greater individual variability among participants' responses to this task - despite the use of a statistically robust within-subject repeated-measures design, we may have lacked sufficient power to detect an effect. Indeed, since the exercise-induced effects on cognition can be moderated by multiple factors (e.g., exercise modality) (15), it is likely that a higher exercise dose (longer duration and/or greater intensity than that was used in the current study) could elicit greater responses than control.

Previous studies found diverse results relating to different assessments and intensities. For example, Peiffer et al. (9) reported significantly enhanced Flanker task scores (post vs. pre, d = 0.29~0.46) immediately after a 20-min bout of moderate- to vigorous- intensity walking (50% and 70% $\dot{V}O_{2max}$), while Kamijo et al. (51) observed a faster Flanker reaction time (d = 0.69~0.92) after 20-min moderate-intensity cycling (30% $\dot{V}O_{2max}$), but similar response accuracy compared to control or light intensity sessions. Similar positive results were also reported from studies that applied other tasks (e.g., Stroop tests) to assess executive function subcomponents, including inhibition, set shifting, and working memory among healthy older

adults (3, 6, 15). However, the exercised-induced changes are frequently investigated in terms of time-dependent measures (6), whereas accuracy seems to be less sensitive to acute exercise in general (6, 8). Similar to Kamijo et al., Hatta and colleagues (21) noted an unaffected performance (numbers of errors) in the Wisconsin Card Sorting Test after 80–120 min of self-paced walking. Such null results on response accuracy may be due to a ceiling effect of accuracy measures or failure to choose appropriate tests that are complex enough to assess the changes in accuracy performance (6). Of note, the Flanker and DSSC test scores herein were computed (scaled) by the NIHTB algorithm that combines both accuracy and reaction time, which is distinct from other studies that analyzed them separately. Given the potential distinct effects on various cognitive outcomes (e.g., test, component), future studies are encouraged to include or compare both accuracy and time-related measures, or consider sophisticated cognitive tasks with a greater difficulty for correct responses to further explore the exercise-induced changes in cognitive function.

Herein, we found a significant increase in cMAP by 4.7 mmHg (~6%) after 30-min sitting, whereas a single bout of walking sustained a similar mean cMAP to the pre-session value. Indeed, prolonged sitting has been shown to induce blood pooling in lower limbs, reduce venous return and cardiac output, and elevate peripheral resistance and arterial stiffness, resulting in a small increase in MAP and systolic blood pressure (52). These changes over time may dampen cerebral blood flow and perfusion (blood volume in microvasculature), leading to impaired

cognitive function (53). Conversely, limited evidence shows that exercise prevents the decline in cerebral blood flow associated with prolonged sitting, and increases both cerebral perfusion and executive function acutely (53). Furthermore, although we did not observe a *hypotensive* effect after acute exercise as reported in previous studies (54), this between-condition difference still indicates a beneficial hemodynamic response that was not observed with sitting. Moreover, there is a dose-response relationship between the magnitude of post-exercise hypotension and exercise stimulus in relation to resting baseline blood pressure (BP), where both a higher dose (more intense exercise bout) and resting systolic and/or diastolic BP (e.g., ≥ 130 and/or ≥ 80 mmHg) have been shown to yield a greater post-exercise hypotensive response (3). In the current study, the exercise stimulus was relatively low (i.e., 30 min of moderate-intensity walking) and the resting BP of the sample was 117/85 mmHg or "elevated" (46), both of which may have contributed to the absence of post-exercise hypotension. It is possible that after a *hypertensive* stimulus that impacts cerebral autoregulation (e.g., acute exercise), the large extracranial arteries adapt to preserve and maintain a sufficient level of cerebral perfusion (55) close to homeostasis.

We noted reductions in indicators of arterial stiffness (cfPWV and AIx75) post-exercise, although the change in AIx75 was not significantly different from the control condition. This indicates a beneficial effect of acute exercise on alleviating arterial stiffening in older adults. One explanation is that exercise leads to increased blood flow and resultant shear stress in vessels supplying the working muscles, causing vasodilation, and thereafter reduced total peripheral

resistance and increased arterial compliance (27). To date, there are contradictory findings on the acute effect of exercise on arterial stiffness (27, 28), and most results are among healthy young adults and adults with hypertension. Unlike the beneficial effect found in the current study, following 30-min moderate-intensity exercise (e.g., cycling, walking), Lefferts et al. reported significantly higher PWV but no change in pulsatility indices in middle-aged adults (56), while Costa et al. found no changes in small and large arterial compliance (artery elasticity index) (57). Contrary to our findings (i.e., reduced PWV and AIx75 post-exercise), a review by Pierce and colleagues concluded that acute aerobic exercise might result in a significantly increased AIx75 (~3.58%) and unchanged PWV in young adults (28). However, another systematic review suggests that PWV remained unchanged immediately after exercise, but subsequently decreased 30 min after exercise in healthy, young to middle-aged individuals (58). Besides population characteristics (e.g., gender, age, hypertension), varying acute effects on arterial stiffness were observed in studies that assessed different arterial segments and time points at which the measure was performed post-exercise (27). For example, arterial stiffness of central and upper body peripheral arterial segments was found to be increased immediately post-exercise (0–5 min) and then (> 5 min) decreased to a level at or below resting values (27), whereas arterial stiffness of lower limbs decreased immediately post-exercise (0–5 min) and persisted into the recovery period post-exercise (> 5 min).

Interestingly, in the present study, two arterial stiffness indicators varied in opposite directions pre- vs. post-session under the control condition – the mean aortic AIx75 value was decreased, whereas the mean cfPWV value was elevated after 30-min sitting. Although previous evidence suggests a differential change in AIx75 than non-heart rate mediated indicators (e.g., AIx, cfPWV, left ventricular ejection time, and peripheral vasomotor tone) in response to acute exercise, the trends of acute changes in these indicators are inconsistent across studies (27, 28). Mutter et al. noted opposing effects of acute aerobic exercise on AIx and AIx75 (decrease vs. increase) (27), while Pierce et al. demonstrated reduced AIx but unaltered cfPWV after aerobic exercise (28). This difference might be explained by the distinction of AIx75, which is a corrected measure of wave reflection for HR at 75 bpm. While a reduction in AIx may be considered beneficial for health, the transient decrease in AIx may simply reflect increases in HR rather than actual reductions in wave reflection (27). As such, given the large influence of heart rate on AIx, researchers should cross compare their results cautiously, and consider including a correction for HR (AIx75) when evaluating changes in systemic stiffness at different time points after acute exercise.

Associations Between Cognitive Function and Arterial Stiffness

A novel finding is that the present study revealed a significant inverse relationship between executive function with arterial stiffness and central mean arterial pressure both at resting state and after acute exercise (correlation coefficients ranging from -0.47 to -0.56). This may indicate that immediate cognitive improvements are associated with a transient reduction in arterial

stiffening and hemodynamic changes in central arteries stemming from acute exercise. However, in congruence with cross-sectional findings from Mason et al. (59) and Kennedy et al. (60), cognitive processing speed was not associated with older adults' arterial stiffness based on our results. The links between exercise with cognition, arterial stiffness, and hemodynamic parameters (e.g., blood pressure and cerebral blood flow regulation) were mostly reported in cross-sectional and observational studies (25). It is posited that increased arterial stiffness and the subsequent excessive pulsatility, through mechanisms involving oxidative stress and inflammation, affect brain microcirculation and lead to blood-brain-barrier disruption (25). With compromised cerebral perfusion, the delivery of nutrients and the clearance of toxic products is disrupted, leading to neurodegeneration and cognitive dysfunction (61). On the other hand, exercise participation yields beneficial effects on cerebral vasoreactivity and cerebral perfusion, which may alleviate deterioration of cognition that is due to arterial stiffening with aging or diseases (25).

Nevertheless, evidence is still lacking concerning the relationship between vascular function and cognition, especially from well-designed RCTs with acute and chronic exercise intervention. To date, only two RCT studies focused on acute changes in both cognition and vascular function after a single bout of exercise. Palmiere et al. examined the acute effects of 30-min resistance exercise in healthy young adults, but they did not find any associations between changes in PWV and pulse pressure with changes in accuracy or reaction time for any cognitive tests (12). Lefferts

et al. suggested that the improved cognitive performance (Flanker reaction time) was not related to transient carotid stiffening in individuals with multiple sclerosis after 20-min of moderate-intensity (60% $\dot{V}O_{2max}$) walking (56). Partially similar to our findings, an intervention study by Guadagni et al. exhibited a negative association between executive function and cerebrovascular resistance index during sub-maximal cycling (40% $\dot{V}O_{2max}$) before and after 6-months of aerobic training (62). Contrary findings in the current study should be considered plausible for two reasons. First, the differential effects of exercise modality were frequently reported, and some reviews even noted opposite acute effects on domain-specific cognitive performance and vascular function following aerobic vs. resistance exercise (5). Second, considering age-related or pathological declines, it is likely that individuals within different age spans and/or with chronic health conditions may have varying responses to acute exercise or longer interventions over time (62). To address this research gap and assist the understanding of potential mechanisms (e.g., mediating effects), future work is necessary to investigate the effect of acute exercise-induced changes in hemodynamics (peripheral, central, and cerebrovascular) and arterial stiffness in relation to cognitive function while controlling for sufficient characterization of participants and exercise pattern.

Strengths of this study include a well-designed experimental protocol that had both control and exercise conditions with repeated measures, and the use of valid assessments of cognitive function that account for both accuracy and reaction time (41, 63). In addition, we implemented a

cadence-controlled walking protocol using a moderate-intensity cadence threshold that has been previously validated under both treadmill and overground environments (19). Considering 1) the wide-spread availability of wearable technologies and the feasibility of manipulating steps per minute in real life, and 2) the high popularity of walking activity among the general public (especially older adults) (64), favorable results in the present study may have practical implication for preserving cognition and vascular function for successful aging. Nevertheless, several limitations in the present study should be acknowledged. First, this study was conducted among healthy older adults who performed less than 150 min/week of MVPA. Thus, our results may not be applicable to other populations, such as young adults, and individuals who are physically active or with chronic diseases. Second, the small sample size of this study, although meeting the burden of statistical significance for the proposed research questions, was not adequate to explore potential sex differences and other confounding effects (e.g., obesity, hypertension). Last, we only focused on moderate intensity walking, future studies are encouraged to examine the dose-response association (i.e., various intensities and durations) between different types of exercise and acute changes in cognition in relation to vascular responses.

CONCLUSION

In conclusion, a single bout of cadence-controlled walking elicited an immediate increase in cognitive performance and reduction in arterial stiffness compared with a control condition in

healthy older adults. In addition, we observed a negative association between the exercise-induced changes in executive function with arterial stiffness and central arterial pressure. The findings from this study improve our understanding of the relationship between cognition and vascular function following acute exercise, and may also have practical implications for how older adults accumulate daily PA to obtain health benefits for successful aging.

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Table 3. 1 Sample characteristics

	Total (n = 26)	Females (n = 17)	Males (n = 9)
Age	67.81 (11.3)	65.4 (11.7)	72.3 (9.39)
Height (cm)	161.0 (22.1)	158.0 (23.6)	173.0 (6.71)
Weight (kg)	80.0 (24.6)	79.0 (26.6)	84.0 (15.4)
BMI (kg/m^2)	27.8 (5.38)	27.6 (5.81)	28.9 (3.34)
Body fat (%)	39.8 (6.36)	40.8 (6.02)	35.5 (6.67)
Systolic BP (mmHg)	117.3 (14.5)	115.6 (15.5)	124.4 (6.4)
Diastolic BP (mmHg)	84.1 (11.8)	82.9 (12.5)	89.3 (6.7)
Resting HR (bpm)	68.4 (6.9)	67.4 (7.4)	72.3 (2.4)
IPAQ Minutes/week MVPA	74.0 (57.1)	74.4 (58.8)	72.5 (57.2)

Note: Data are presented in mean (standard deviation). *Abbreviations:* BMI, body mass index; MVPA, moderate-to-vigorous physical activity.

Table 3. 2 Acute effects on cognitive and vascular function

	Repeated Measures ANOVA (Time × Condition)							Paired *t*-test (%Δ between conditions)			
	Control (Mean ± SD)		Walking (Mean ± SD)		*P*-values			%Δ (Mean ± SD)		%Δ, Walking vs. Control	
	Pre	Post	Pre	Post	T	C	T × C	Control	Walking	Mean difference (95% CIs)	*P*-values
Cognitive Function											
Flanker	8.16 (0.72)	8.24 (0.73)	8.14 (0.70)	8.43 (0.67)†	**<0.001**	0.41	**0.046**	1.11 (3.48)	3.69 (4.07)	2.57 (0.08, 5.06)	**0.044**
DCCS	8.38 (0.84)	8.38 (0.82)	8.29 (0.92)	**8.67 (0.89)***†	**0.016**	0.23	**0.006**	0.35 (6.10)	5.41 (7.20)	5.06 (1.54, 8.58)	**0.007**
PCPS	49.3 (7.00)	52.5 (6.93)†	48.1 (8.57)	53.0 (8.27)†	**<0.001**	0.90	**0.035**	6.15 (5.65)	11.5 (12.3)	5.37 (-0.48, 11.22)	0.07
Vascular Function											
cMAP (mmHg)	90.10 (9.67)	95.8 (14.7)†	89.9 (10.2)	**91.50 (11.0)***	**<0.001**	**0.012**	**0.049**	6.19 (9.71)	1.79 (4.95)	-4.40 (-8.96, 0.16)	0.058
Aortic AIx75 (%)	23.0 (8.12)	21.4 (11.0)	23.4 (9.12)	21.00 (9.42)†	**0.019**	0.98	0.564	-11.0 (36.7)	-9.89 (27.4)	1.08 (-13.62, 15.78)	0.88
cfPWV (m/s)	8.72 (2.09)	9.30 (2.27)†	8.81 (2.07)	**8.75 (2.17)***	**0.002**	0.14	**0.004**	6.86 (7.60)	-0.69 (5.90)	-7.55 (-11.58, -3.51)	**<0.001**

Note: Bold denotes $p < 0.05$. *Significantly different compared to the post-measure under control condition; †significantly different compared to pre-measure under the same condition. *Abbreviations:* Flanker, Flanker Inhibitory Control and Attention Test; DCCS, Dimensional Change Card Sort Test; PCPS, Pattern Comparison Processing Speed Test; cMAP, central mean arterial pressure; AIx75, augmentation index at a heart rate of 75 beats per minute; cfPWV, carotid to femoral pulse wave velocity.

Table 3. 3 Correlations between changes in cognitive and vascular function

Resting State (averaged pre-session measurements)					
	Flanker	DCCS	PCPS	cMAP	Aortic AIx75
DCCS	**0.83**				
PCPS	**0.83**	**0.67**			
cMAP (mmHg)	**-0.47**	-0.33	-0.26		
Aortic AIx75 (%)	-0.19	0.04	-0.13	**0.60**	
cfPWV (m/s)	**-0.49**	-0.34	-0.33	**0.76**	**0.52**
Acute Changes Post-Walking					
	%Δ Flanker	%Δ DCCS	%Δ PCPS	%Δ cMAP	%Δ Aortic AIx75
%Δ DCCS	0.19				
%Δ PCPS	0.15	0.046			
%Δ cMAP	-0.02	**-0.49**	-0.15		
%Δ Aortic AIx75	0.25	-0.06	-0.09	0.04	
%Δ cfPWV	**-0.50**	**-0.52**	0.15	0.35	-0.16

Note: Bold denotes $p < 0.05$. *Abbreviations:* Flanker, Flanker Inhibitory Control and Attention Test; DCCS, Dimensional Change Card Sort Test; PCPS, Pattern Comparison Processing Speed Test; cMAP, central mean arterial pressure; AIx75, augmentation index at a heart rate of 75 beats per minute; cfPWV, carotid to femoral pulse wave velocity.

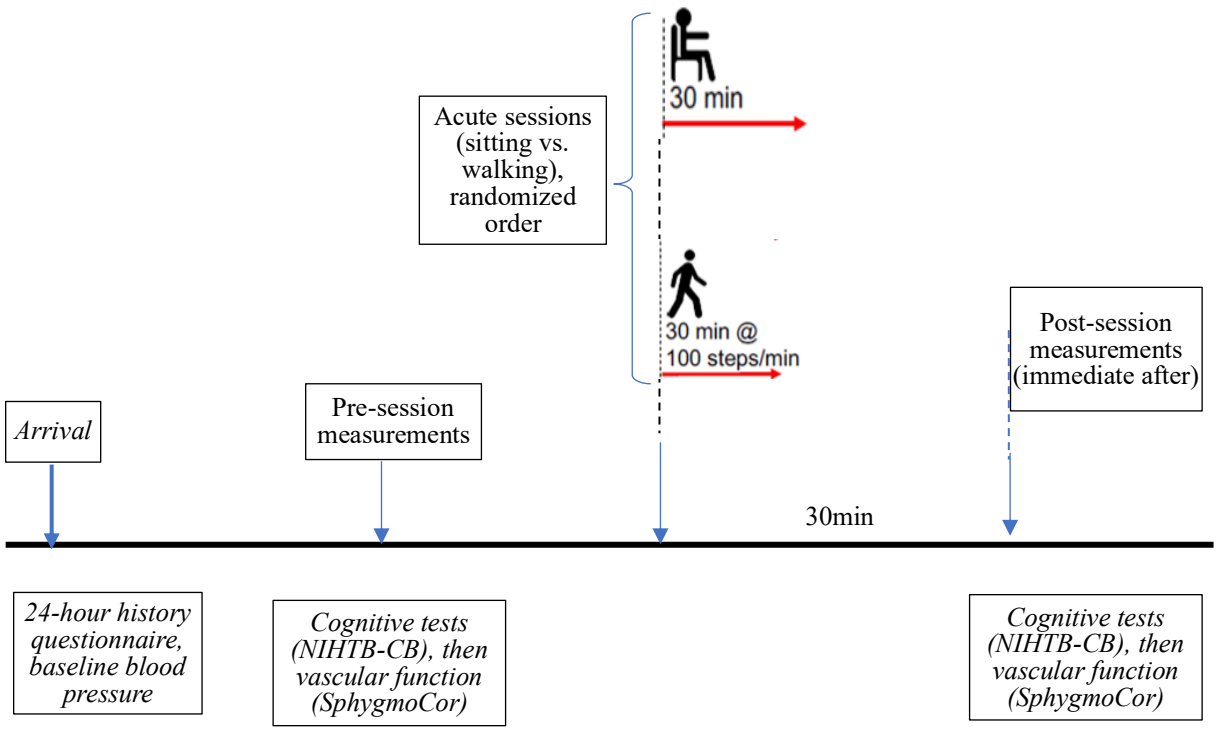

Figure 3. 1 Diagram of acute sessions. Each participant completed both the control and walking sessions on different days in a randomized cross-over design. Measurements were taken before and immediately after acute sessions within 5 minutes.

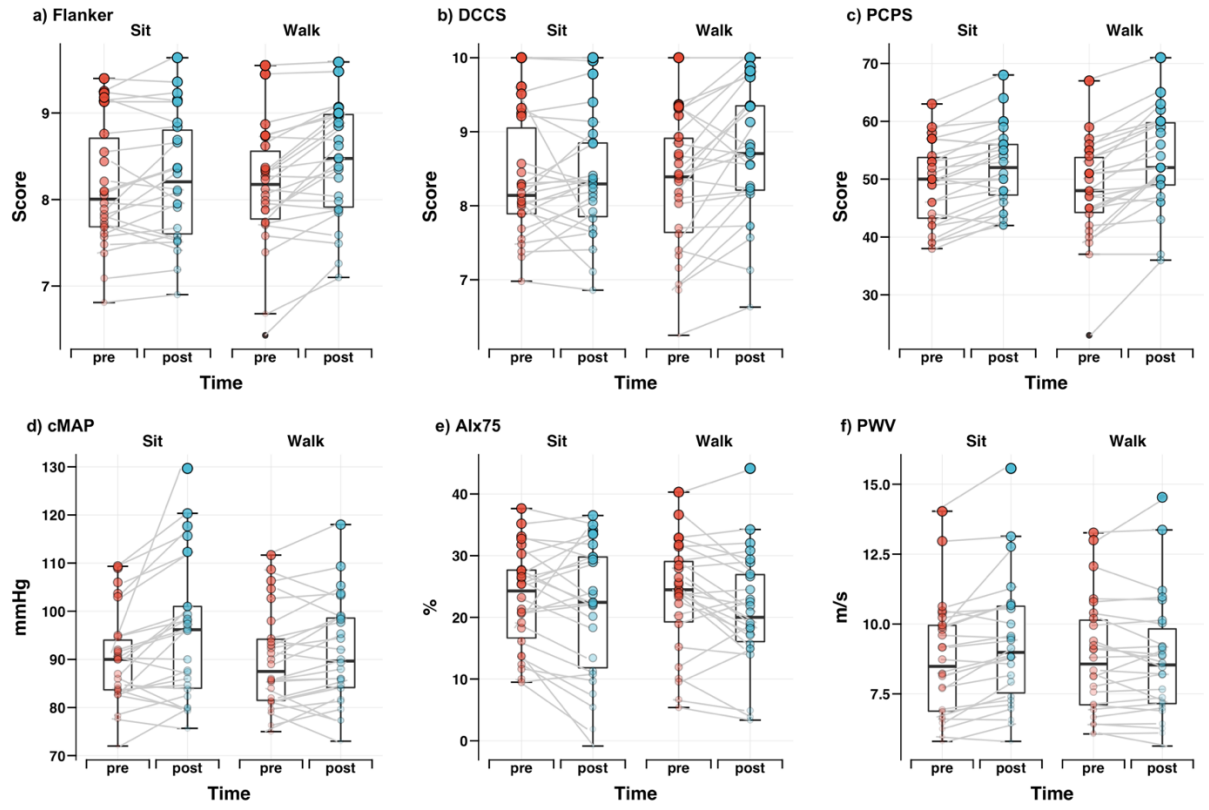

Figure 3. 2 Acute effects on cognitive and vascular function after sitting versus walking. Panels a~c) cognitive test scores, and panels d~f) vascular measurements. Boxplots with scatter plots display the distribution of outcomes, lines within boxes and error bars represent means and SDs, respectively. Dots linked with lines represent individuals' data points pre and post acute sessions. *Abbreviations:* Flanker, Flanker Inhibitory Control and Attention Test; DCCS, Dimensional Change Card Sort Test; PCPS, Pattern Comparison Processing Speed Test; cMAP, central mean arterial pressure; AIx75, augmentation index at a heart rate of 75 beats per minute; cfPWV, carotid to femoral pulse wave velocity.

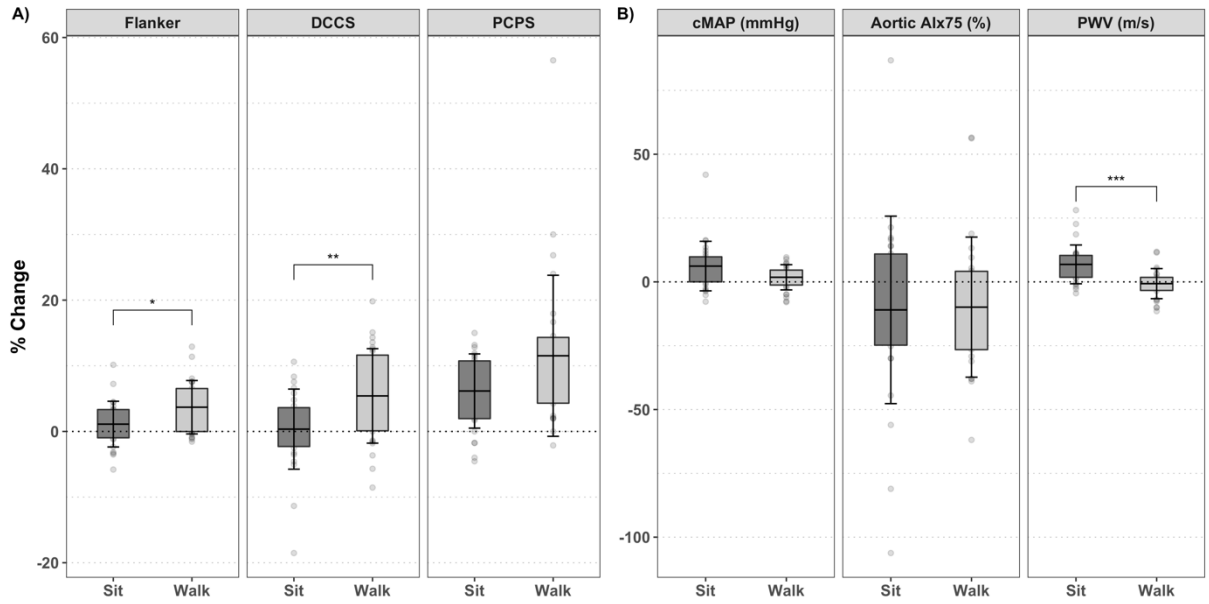

Figure 3. 3 Acute changes in cognitive and vascular function after sitting versus walking. Panels A) Cognitive test scores and B) Vascular measures. Boxplots with scatter plots display the distribution of outcomes, lines within boxes and error bars represent means and SDs, respectively. *Significant difference between conditions, *$p < 0.05$, *** $p < 0.0001$. *Abbreviations:* Flanker, Flanker Inhibitory Control and Attention Test; DCCS, Dimensional Change Card Sort Test; PCPS, Pattern Comparison Processing Speed Test; cMAP, central mean arterial pressure; AIx75, augmentation index at a heart rate of 75 beats per minute; cfPWV, carotid to femoral pulse wave velocity.

CHAPTER 4

THE IMPACT OF ONE-WEEK STEP REDUCTION ON COGNITIVE PERFORMANCE AND VASCULAR FUNCTION AMONG PHYSICALLY ACTIVE INDIVIDUALS: A BAYESIAN ANALYSIS

ABSTRACT

Purpose: The purpose of this study was to investigate the impact of short-term physical inactivity (i.e., one week) on cognitive performance (i.e., executive function, attention, working memory, and processing speed) and vascular function (i.e., central blood pressure [cMAP] and arterial stiffness) among physically active individuals aged 50 years or above. **Methods:** Fourteen physically active individuals (10 females, 65.21 ± 4.18 years) were required to maintain normal exercise and daily routines for one week, and then to reduce daily step count to below 5000 steps/day for the following week. Cognitive performance and vascular function were assessed at baseline (week 1) and after one week of step reduction (week 2). Data were analyzed using Bayesian random-effect models to provide probabilities of changes following step reduction. Pearson correlations were used to examine the relationship between cognitive and vascular function in response to step reduction. **Results:** Despite minimal changes in cognitive test scores and vascular outcomes, there were negligible differences between the baseline and step-reduction conditions across all variables, with a low probability of changes in cognitive and

vascular outcomes following step reduction (95% credible intervals include zero, $P_{(diff=0)}$ ranges from 0.28 to 0.61). Significant negative correlations were found between the percent changes (%Δ) in carotid to femoral pulse wave velocity with performance in executive function and processing speed (r = -0.81 and -0.65, respectively), whereas %Δs in central blood pressure and working memory were positively correlated (r = 0.63), all p-values < 0.05. **Conclusion:** One week of step reduction did not yield detrimental effects on cognitive performance and vascular function in physically active individuals aged 50 years or above. In other words, the dose of physical inactivity imposed on active individuals in the current study might not have been sufficient to negatively affect cognitive function among individuals who may have already accumulated health benefits from regular physical activity.

INTRODUCTION

The modern lifestyle continues shifting to a more "sedentary" way, characterized by prolonged sitting time and insufficient engagement in daily physical activity (PA) (1, 2). Despite wide-spread public health messaging for PA and its health benefits, there is still a large proportion of the population that remains physically inactive (2) and fails to meet the recommended target of at least 150-300 min/week of moderate-to-vigorous PA (MVPA) (3). Moreover, the current coronavirus (COVID-19) pandemic has also brought concerns about drastic decreases in daily incidental PA due to social isolation practices and work-from-home policies (4, 5). Individuals who experience challenges adhering to their original exercise routines (e.g., visiting the gym, playing team sports) might be more inclined to engage in excessive sedentary behavior during the pandemic. Global trends in physical inactivity combined with the lasting effect of the COVID-19 pandemic on behavior patterns may further compound the global burden of numerous health conditions (e.g., cardiovascular diseases, dementia) (5-7). As such, research examining the potential impact of sudden reduced PA or exercise cessation may provide insights into the role of short-term physical inactivity (i.e., not meeting the above PA guidelines) in health outcomes, especially among previously active individuals.

Physical inactivity has been regarded as an independent risk factor for common chronic diseases such as cardiovascular diseases (8), diabetes (9), and Alzheimer's disease (10), and may accelerate the age-related decline in cognitive function (11). Aichberger et al. (12) noted a higher

rate of cognitive decline in individuals (aged ≥ 50 years) who self-reported minimal MPA participation over a 2.5-year follow-up. Similarly, inactive community-dwelling older adults that engaged in no habitual MVPA were found to have a significantly worse performance in executive function than their active counterparts, regardless of sleep quality (13). However, the majority of existing evidence is obtained from observational and cross-sectional studies with self-report measures of physical activity/inactivity in various populations (14). Few studies have focused on the potential impact of short-term physical inactivity intervention on health or physiological outcomes (e.g., muscular function) (15-17). There is a lack of research investigating the relationship between reduced PA and other health outcomes, such as cognition and cardiovascular health (11). Well-designed experimental studies that follow individuals over a short time frame (e.g., one week) are needed to examine the specific impact of short-term physical inactivity on these additional health outcomes. Importantly, tracking changes in these outcomes over a one-week period aligns with public health guidelines that emphasize the weekly PA goals, i.e., ≥ 150-300 min/week of MVPA (9, 18).

Step reduction as a model of physical inactivity has previously been implemented to explore the impact of limited ambulation among both young and older adults, whereby participants were asked to simply reduce their daily PA to a low maximal daily step count (ranges from 750 to 5000 steps/day) (11, 19, 20). Compared to other models like bed rest or limb immobilization, step reduction may yield similar whole-body systemic effects without constituting complete

muscle disuse and changes in peripheral tissues (20), and therefore is a closer simulation of reduced PA under free-living conditions. Recently, several experimental studies have employed step reduction protocols to investigate the effects of short-term physical inactivity on metabolism (e.g., blood glucose profile) and muscular function (15-17, 21). Reducing steps to below 1500 steps/day for one or two weeks was found to significantly impair insulin sensitivity (16), attenuate postprandial lipid metabolism (17) and daily myofibrillar protein synthesis rates (22), and increase central adiposity (15). To date, only one study focused on the effects of sedentary intervention (1 week) on cognitive function and reported null results; however, it was conducted among college students and did not involve other relevant health outcomes (21). It remains unclear how short-term reductions in ambulatory activities might impact cognition and cardiovascular outcomes, and whether these potential effects might associate with each other (23-25). Indeed, considering the potential associations between cognitive performance with aging (26), vascular function (e.g., arterial stiffness) (27), and metabolic responses (e.g., glucose tolerance and insulin resistance) (24, 28-30), reduced PA might have differential effects on cognitive function in the older adult population.

Therefore, the current study aimed to: 1) investigate the impact of short-term physical inactivity (i.e., one week) on cognitive performance (i.e., executive function, attention, working memory, and processing speed) and vascular function (i.e., central blood pressure and arterial stiffness) among physically active individuals aged 50 years or above; and 2) examine the

associations between potential changes in cognitive performance and vascular responses to following reduced PA. A step-reduction model of walking below 5000 steps/day was determined according to the step-defined sedentary lifestyle index introduced by Tudor-Locke et al. (31). It was hypothesized that one week of step reduction could lead to decreased cognitive performance and worsened vascular function.

METHODS

Participants

Fourteen physically active individuals (aged ≥ 50 years old, 10 females) were recruited for this study. Eligibility screening was administered via online survey portal (Qualtrics), and only eligible individuals were considered for participating in the study. This screening process included two health screening questionnaires (American College of Sports Medicine [ACSM] preparticipation health screening guidelines (32), Physical Activity Readiness Questionnaire [PAR-Q+] (33)), and a self-reported record of any medical conditions that might impair cognition or restrict mobility. All participants were required to be generally healthy with the absence of any injury or illness, and must speak English as their first language. In addition, participants were required to be categorized as "high active" (i.e., Category 3 – *Any one of the following 2 criteria: "Vigorous-intensity activity on at least 3 days and accumulating at least 1500 MET-minutes/week, OR 7 or more days of any combination of walking, moderate- or*

vigorous-intensity activities accumulating at least 3000 MET-minutes/week.") by the International Physical Activity Questionnaire (IPAQ) (34). Individuals were excluded from participation if they had known mental disorders or other health conditions (e.g., mild cognitive impairment, dementia, Alzheimer's disease, Parkinson's disease, stroke, depression, and metabolic diseases). All participants signed a written informed consent form prior to data collection. The study was approved by the University of Alabama Institutional Review Board (protocol ID: 21-04-4544).

Study Design

The present study utilized a cross-over design with repeated measures. Each participant underwent three laboratory visits (familiarization, baseline, and post-intervention measures) over a two-week period, with a one-week interval between individual visits (see Figure 4.1). Each visit was scheduled at the same time of a day to control for diurnal variation in study measures. Participants were also instructed to fast for more than 2 hours and to abstain from alcohol and intense exercise for 24 hours and from caffeine for 12 hours prior to each visit. A 24-hour history questionnaire was completed upon arrival at each visit. Visit 1 included informed consent, familiarization, and anthropometric measurements. At the end of Visit 1, each participant was fitted with an accelerometer and wore it for 7 consecutive days (Week 1) to measure baseline habitual PA (see PA measures below). During Week 1, participants were required to maintain their normal daily and exercise routine so that the accelerometer data reflected their habitual PA.

Participants revisited the laboratory (Visit 2) at the end of Week 1 for baseline measures of cognitive and vascular function (see detailed description below).

At the end of Visit 2, participants were instructed to reduce their daily PA amount in the following week (Week 2), especially avoiding any planned exercise involving MVPA. A goal of walking less than 5000 steps/day (on average) was used as an upper limit of daily PA during the one week of step reduction (31). A new set of PA monitors (1 pedometer for self-monitoring steps and 1 accelerometer as the PA measure) with a log sheet was provided to assess participants' PA level and compliance with the step reduction protocol. Participants were able to self-monitor their daily step count using the visual feedback on the pedometer for reducing instances of exceeding the upper limit of 5000 steps/day on a given day. Other routines such as diet, working, and entertainment were maintained as usual. After one week of step reduction, participants visited the laboratory for the last time (Visit 3) to return all devices to the laboratory and completed the cognitive and vascular measurements again, following the same procedures as Visit 2. Participants were instructed to fast for more than 2 hours and to abstain from alcohol and intense exercise for 24 hours and from caffeine for 12 hours prior to each visit. A 24-hour history questionnaire was completed upon arrival at each visit.

Measurements and Procedures

Anthropometrics

Anthropometrics and body composition measures were taken during the first visit. Standing height was measured without shoes to the nearest 0.1 cm with a manual stadiometer (SECA 67310, SECA©, Chino, CA), and weight was measured to the nearest 0.1 kg on a digital scale (Tanita BWB-800, Tanita©, Arlington Heights, IL). Measures were repeated to ensure accuracy, with a third measurement taken if the first two differed by > 0.3 cm or 0.5 kg. The two closest measurements were averaged and reported. Body mass index (BMI) was calculated from height and weight data, expressed as $kg \cdot m^{-2}$.

Body composition was measured using bioimpedance spectroscopy (BIS; Imp™ SFB7, Impedimed Limited, Queensland, Australia), which uses a range of 256 frequencies that allow for the electrical current to pass through and around cells (35). Prior to electrode placement, excess hair was removed from the electrode sites, and the sites were cleaned with alcohol swabs and allowed to dry. Participants were instructed to lie supine on a padded gurney with the arms ≥ 30° away from the body and with legs separated. Following manufacturer guidelines, dual-tab electrodes were placed on the back of the right wrist and top of the right ankle. The measurement began after the necessary descriptive characteristics (height, weight, age, and sex) were entered into the BIS device.

Physical activity measure

Habitual PA was assessed using an accelerometer (ActiGraph, GT9X; ActiGraph Corporation, Pensacola, FL, USA). The ActiGraph GT9X is a small, lightweight triaxial device that measures body motion on three planes of movement. It was positioned on the right hip and secured using an elastic belt worn around the waist. Participants were instructed to wear the accelerometer during all waking hours, except when swimming or bathing, for 7 consecutive days for each one-week period. A wear log and instruction sheet were given to the participants to track their wear time and daily activities, such as bed and wake time, and times that the device is removed. All accelerometer data were downloaded in 60s epoch using ActiLife data analysis software (ActiGraph Link, ActiGraph Corporation, Pensacola, FL, USA). The Choi wear-time algorithm (36) was applied to identify non-wear time, and valid wear time was considered to be ≥10 hr/day for ≥4 days for each week.

During the step reduction week, participants also wore a pedometer (NL-1000, New-Lifestyles INC, Lee's Summit, MO, USA) simultaneously on the right hip with an elastic belt around the waist in order to provide visual feedback and self-monitor daily step count (37). To ensure an overall evaluation of PA level, we also instructed participants to record their exercise routine during Week 1, especially additional activities that were performed without wearing accelerometer (e.g., swimming).

Cognitive performance

The National Institutes of Health Toolbox (NIH Toolbox®) is a validated measurement tool for assessing neurological and behavioral function, which includes cognition, emotion, motor, and sensation (38). All measures of cognition in this study were administered using the NIH Toolbox iPad application. Flanker Inhibitory Control and Attention Test (Flanker), Dimensional Change Card Sort Test (DCCS), Pattern Comparison Processing Speed Test (PCPS), and List Sorting Working Memory (WM) were selected from the NIH Toolbox Cognition Battery (NIHTB-CB) to measure the changes in specific cognitive domains (i.e., executive function, attention, processing speed, and working memory) (39). Raw and computed scores were automatically calculated and exported by the software (40). The same combination of cognitive tests was delivered before and after one-week step reduction in the same order (i.e., Flanker, DCCS, PCPS, and WM tests). Instructions were presented on the iPad screen at the beginning of each test. All participants were able to complete the cognitive assessment (4 tests) within 20 minutes in the present study, the average completion time across all sessions was 16.21 ± 1.94 minutes.

The Flanker test is derived from the Attention Network Test and measures attention and executive function, specifically involving inhibitory control (41, 42). Participants were instructed to identify the direction of a central target arrow flanked by similar stimuli on the left and right. They were required to focus on a visual target in the center of the screen and then choose the

direction that corresponds to the middle arrow. The task lasted approximately 4 minutes and included 20 trials (congruent and incongruent). Test scoring was based on a combination of accuracy and reaction time, with accuracy considered first. Higher scores indicate higher levels of ability to attend to relevant stimuli and inhibit attention to irrelevant stimuli.

The DCCS test measures the cognitive flexibility component of executive function, which represents the ability to switch among multiple task strategies and rules (43, 44). Two target pictures were presented that vary along two dimensions (e.g., shape and color). Participants were asked to match a series of bivalent test pictures (e.g., yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g., color), and then according to the other dimension (e.g., shape) after several trials. A word cue appeared on the screen with unpredictable order, and after several trials, the criterion switches between the two dimensions. The whole test lasted approximately 4 min to complete. Similar to the Flanker test, scoring was also based on a combination of accuracy and reaction time. Higher scores represent higher levels of cognitive flexibility.

The PCPS test is modeled after Salthouse's Pattern Comparison Task to measure processing speed (40, 45). Participants were asked to identify whether two side-by-side pictures were the same or not within 85 seconds, and responded to as many items as possible up to a maximum of 130. The test lasted around 3 minutes. Type, complexity, and the number of stimuli were varied to ensure adequate variability of performance across the age spectrum. The score was the number

of correct items (0~130) completed in 85 seconds, and it can be used to evaluate simple improvement or decline over time. Higher scores indicate a faster processing speed within the normative standard being applied.

The WM test is adapted from Mungas' List Sorting task from the Spanish and English Neuropsychological Assessment Scales (46, 47), and measures working memory that requires immediate recall and sequencing of different visually and orally presented stimuli (40). Participants were instructed to sort a list of visual and auditory stimuli presented on the screen (e.g., pictures of different foods and animals) from smallest to largest, first within a single dimension (either animals or foods, called 1-List) and then on two dimensions (foods, then animals, called 2-List). The test took approximately 7 min to administer. Higher scores indicate higher levels of working memory within the normative standard being applied.

Vascular function

Participants were instructed to lie down in a supine position, resting quietly for 5 minutes before the measurements. This time period allowed for changes in central hemodynamics resulting from the change in posture (seated to supine) to equilibrate (48). Vascular function was measured using the SphygmoCor® XCEL System (AtCor Medical, Sydney, Australia) (49). First, participants were instrumented with a standard brachial cuff on the upper arm to measure brachial blood pressure (BP) and initiate pulse wave analysis to obtain central mean arterial pressure (cMAP) and aortic AIx. Note, the aortic AIx was standardized to a heart rate of 75 bpm

(AIx75) by the software (i.e., AIx75 = AIx + 4.8*(heart rate - 75)/10) (50). Since aortic AIx can be influenced by heart rate, the use of AIx75 enables comparisons of results from individuals with different heart rates (e.g., after exercise) and between visits. With participants still in supine position, carotid to femoral PWV (cfPWV) was measured using a carotid tonometer simultaneously with a leg cuff to capture pressure waveforms at the carotid and femoral sites. The distances between measurement sites were measured with a tape. cfPWV was calculated by using the difference in the distances between sites and the measured time delay between proximal and distal waveforms (51). Each parameter was measured three times with 1-minute intervals, and the average value was recorded as the final value.

Statistical Analysis

Descriptive statistics were generated for all outcome measures (i.e., mean and standard deviation (33) for continuous variables; frequencies and percentages for categorical variables). The magnitudes of differences before vs. post-intervention were quantified using Cohen's *d* effect sizes (*d*) and classified as small (0.1), medium (0.5), and large (0.8) (52). Pearson correlation coefficients (*r*) with significant tests (*p*-values) were used to explore univariate associations between changes (%Δ) in all cognitive and vascular outcomes following step reduction.

To address the primary aim, a Bayesian approach was used in the present study because of the following advantages. First, Bayesian analysis allows the incorporation of domain specific

knowledge and permits to draw direct probability statements about parameters (e.g., distribution of certain effects in a population) (53). Second, it provides estimates of uncertainty around parameter values that are more intuitively interpretable than results from traditional frequentist approaches (mostly based on long-run frequency, fixed random likelihood), which avoids concerns about the misinterpretation of *p*-values and statistical significance for decision making (54, 55). Third, given the promise of Bayesian methods to handle small samples (56), it may be particularly beneficial for certain types of studies that have relatively low sample sizes (e.g., sleep deprivation, PA reduction) (57). As such, the present study utilized Bayesian random-effect models to estimate the differences between baseline and post-intervention measures (i.e., changes before vs. after) following one week of step reduction.

Data analyses were performed in R (version 4.0.2) with the *MCMCglmm* package that uses Markov Chain Monte Carlo techniques for fitting multivariate generalized linear mixed models (58). One chain using 11,000 iterations with thinning of 1 was performed to reduce autocorrelation among samplers, and the model parameter estimates were summarized based on the posterior densities using the final 10,000 iterations after burn-in 1,000 (59). Due to the lack of existing literature on this topic, non-informative priors were incorporated into the Bayesian models. Specifically, diffuse priors were used for estimating random effects by specifying two scalar parameters of the inverse Wishart prior as V = 1 and nu = 0.002 (where V and nu represent expected variances and degree of belief parameter, respectively) following the practice of

Hadfield (58). All models were checked for convergence by visual diagnosis of posterior distributions (i.e., the conditional distribution of the estimated value after taking into account the current data) (60) and trace plots of posterior samples. Results from the Bayesian models are presented as the estimated difference with 95% credible intervals (95% CIs; i.e., there is a 95% probability that the true estimate would lie within the interval, given the evidence provided by the observed data) (61), and the probability that the posterior distribution of the estimated difference includes zero ($P_{(diff=0)}$).

RESULTS

Sample characteristics are summarized in Table 4.1. Thirteen participants self-reported their race/ethnicity as White, and one as Asian. The education level of the sample was as follow: three Bachelor's degree, six Master's or professional degree, and five doctorate degree. Average baseline step count (mean [standard deviation]) was 7023 (1888) steps/day, however, most participants (n = 8) reported routine exercises (at least 2 days, 1 hour/day) in addition to walking during Week 1, including resistance training (n = 3), stationary cycling (n = 2), swimming (n = 2), yoga (n = 2), dancing (n = 1). Regarding step reduction in Week 2, all participants complied with the protocol and walked below the required 5000 steps/day limit (on average, measured by accelerometer).

The means with standard deviations (SDs) of cognitive scores and vascular outcomes before vs. after step reduction are displayed in Table 4.2. Based on the average percent changes (%Δ) from baseline, there were small decreases in cognitive scores across the sample. In addition, over half of the sample had decreased cognitive test scores (50~57%) and increased values of vascular outcomes (50~64%). The means and SDs of each variable and individuals' data were also plotted in Figure 4.2. Although the changes (%Δ) in cognitive scores and vascular outcomes were towards certain directions (e.g., negative values in the former), the SDs of those mean values were relatively large (Table 4.2), indicating large variances of these changes and individual differences (Figure 4.2).

Results from the Bayesian analysis are shown in Table 4.2, and the posterior distribution of estimated differences between before vs. after step reduction are displayed in Figure 4.3. Overall, Bayesian models fitted with non-informative priors suggest minimal differences between the baseline and step-reduction conditions, with a low probability of changes in cognitive and vascular outcomes following step reduction ($P_{(diff=0)}$ ranges from 0.28~0.61; see Table 4.2). The impact of step reduction was uncertain with all 95% credible intervals including zero. The direction of the estimated differences from Bayesian models was similar to that of the %Δ values based on participants' data, where all cognitive scores decreased and vascular outcomes increased, except for aortic AIx75. However, the opposite direction of change in AIx75 from the Bayesian estimation seemed to be plausible; the 95% CIs of estimated differences included zero,

and therefore, the true changes in outcomes (including aortic AIx75) following step reduction for the population could be either negative, zero, or positive (i.e., decreased, unchanged, or increased). To further confirm the null effects, we conducted a series of Bayesian-approach regression analyses to determine if the changes in cognitive and vascular outcomes were associated with age, sex, educational level, BMI, body fat, or resting BP. We found negligible effects of these factors on changes in cognitive or vascular outcomes (probabilities of beta coefficient exclude zero, range from 0.18 to 0.71). All models converged well, and trace plots of parameter values against the iteration number can be found in supplemental document SDC 4.1.

Associations Between Acute Changes in Cognitive and Vascular Function

Before step reduction (at baseline), significant positive correlations were observed among several cognitive tests (Flanker and DCCS, PCPS and WM, DCCS and PCPS), r ranges from 0.57 ~ 0.71 (p-values < 0.05); whereas correlations between other variables were not significant. After one-week step reduction, changes (%Δ) in Flanker, DCCS and PCPS scores significantly correlated with each other (r ranges from 0.65 ~ 0.83, p-values < 0.05). Moreover, %Δ in cfPWV was negatively correlated with %Δs in DCCS and PCPS scores (r = -0.81 and -0.65, p = 0.0004 and 0.012, respectively); whereas %Δs in cMAP and WM score were positively correlated (r = 0.63, and p = 0.017). Full correlation matrices are provided in Table 4.3.

DISSCUSSION

The present study sought to examine the impact of one-week step reduction on cognitive and vascular function in physically active individuals aged 50 years or above. Overall, participants were able to follow the step reduction protocol and demonstrated good compliance in reducing PA for one week. Based on results from the Bayesian analysis, we observed minimal changes in cognitive performance across multiple domains, arterial stiffness, and central BP following step reduction, indicating that reducing PA for one week may not yield detrimental effects on cognitive and vascular functions in physically active individuals. Despite the null results from Bayesian models, following one week of step reduction, the percent change in arterial stiffness (cfPWV) was negatively associated with the performance in executive function and processing speed, whereas the changes in central BP and working memory performance were positively correlated.

Despite a slightly decreasing trend in the test scores, such changes in the overall cognitive performance were considered negligible (less than -3% from baseline). This null result was against our prior assumption of a potential negative impact of PA reduction based on existing evidence of the positive PA-cognition relationship. Previous studies have shown a significant improvement in cognitive function after a single bout of exercise (e.g., 30-min walking) (1) and short-term PA intervention (e.g., weeks to months of aerobic training) (62). Furthermore, the dose-response relationship between PA and numerous health outcomes was also exhibited in

large-scale cross-sectional investigations (9), with PA assessed mostly by self-report and few accelerometer-based approaches. For example, Loprinzi et al. (63) reported that older adults engaged in 6000 to 7999 MET-min-month of MVPA associated with the best executive function performance (DSST score) compared to other groups with lower or higher amounts of MVPA. Likewise, the beneficial effects of PA and exercise on cardiovascular health are also well-documented, such as lowering blood pressure (64), improving cardiorespiratory fitness (65), and alleviating arterial stiffness with aging (66). On the other hand, cross-sectional evidence suggests that habitual physical inactivity and sedentary behavior combined with age-related declines may further contribute to higher risks of common chronic diseases (11, 67) and consequently, lower physical independence and quality of life in later age (9). It was plausible to assume that a reduction in the amount of PA accumulated over the course of a week would negatively influence cognitive or cardiovascular outcomes, especially in older adults who are suffering from corresponding functional deteriorations. Instead of promoting PA acutely or chronically, as has been observed in numerous other studies, we chose "the opposite" manipulation by enforcing a low step count (on average below ~4000 steps/day herein) for a relatively short time period (i.e., one week). However, this level of step-reduction did not lead to an evident decline in cognitive performance. One possible explanation is that individuals with an active lifestyle might have already accrued PA-related benefits (e.g., better cognitive reserve), and these benefits might have counteracted any negative effects of step reduction. Since the majority of previous physical

inactivity-cognition research is observational or cross-sectional in nature, future work is needed to explore the effect of PA reduction over a relatively longer time frame (where applicable) using step-reduction or other sedentary interventions. Furthermore, studies should evaluate whether any changes in cognition are ameliorated with the recovery of exercise participation.

Our results aligned with the only study focused on step reduction and cognition by Edwards et al. (21). They also reported non-significant changes in cognition after PA reduction among young adults, but some cognitive test scores (e.g., Spatial Slider test score, related to planning) slightly increased in the intervention group after one-week of sedentary intervention (21). Such increases might be due to a practice effect over time, but this could not be tested without knowing the cognitive change in the control group over time (i.e., only measured at baseline). Indeed, despite the lower test scores post-intervention in the present study, the SDs of percent changes were relatively larger than the mean values, which suggests large inter-individual variability (Table 4.2 and Figure 4.2). However, we did not detect any confounding effects of covariates such as age, BMI, and body fat. Individual's cognition can be influenced by many other factors, such as emotion and sleep quality (68). Future work should explore other potential mediators that lead to this individual difference in cognitive and vascular responses induced by physical inactivity.

To date, the underlying mechanisms of exercise-induced enhancement in cognition are still unclear. Some studies have highlighted increases of growth factor (e.g., brain-derived

neurotrophic factor, vascular endothelial growth factor, insulin-like growth factor I) secretion with exercise, might be involved with downstream signaling to enhance hippocampal plasticity and related benefits in cognition (11, 69, 70). Conversely, physical inactivity combined with the aging process might further restrict the capability of participating in higher intensity PA. Consequently, without the protective effect of exercise, vascular dysfunction (e.g., arterial stiffness) might accelerate brain structure changes (e.g., cerebral small vessel disease, lower brain volume) (71, 72) over time, and lower the chance of attaining reversibility of neurogenesis, plasticity, and cognitive benefits in older adults (11). Notably, the current study attempted to provide insights regarding the relationship between cognition with central BP and arterial stiffness in response to short-term PA reduction. Although the results herein suggested significant associations between the changes in certain cognitive domains and vascular outcomes, this might vary due to the selection of a different population (e.g., younger or less active adults), given the restricted and relatively small sample in the present study. As alluded to above, considering the unfavorable effects of step reduction on myofibrillar protein synthesis and glycemic control and their potential associations with cognition (24, 27-30), cognitive performance after PA reduction could be indirectly impacted by those neurophysiological pathways. Well-designed experimental studies are encouraged to address potential causal effects between PA or inactivity with cognition, central hemodynamics, and arterial stiffness.

To the best of our knowledge, this is the first study investigating the effect of short-term physical inactivity on cognitive and vascular functions among middle-aged and older adults. Results from this study may help understand the effect of reduced PA given the current increasing prevalence of physical inactivity. Strengths of this study include: 1) the use of an applicable step reduction protocol based on the previously defined graduate step count index (31), which effectively reduced PA level (measured by accelerometry) for one week; and 2) conducting data analysis using Bayesian approach that is beneficial for handling small sample sizes and making inferences based on interpretable results. Nevertheless, several limitations should be acknowledged. First, due to the "PA-restriction" nature and rigorous eligibility criteria of this study, we were only able to recruit a small sample of active participants who had no chronic diseases that might impact their cognition and/or mobility. In fact, over half of the eligible individuals who passed the online screening declined to participate in the study because they were unable or unwilling to skip their exercise routine for one week (e.g., work, training purposes). Second, habitual PA quantified by the average daily step count might be underestimated by the accelerometer utilized in the present study. We initially enrolled individuals as long as they were rated as "active" based on self-report PA (IPAQ-SF), and anticipated that this would translate to a high step count (e.g., over 7500 steps/day based on Tudor-Locke's graduated step index) (73). However, the average step count of ~7000 step/count was lower than expected. Indeed, based on the exercise routine recorded by participants, it is

likely that those additional activities were underestimated by ActiGraph (e.g., resistance training) or performed without wearing it (not water-proof; e.g., swimming). Last, since we only included individuals who were 50 years old (mostly females), results from the current study may have limited generalizability to other populations.

CONCLUSION

In conclusion, one week of step reduction did not result in detrimental effects on cognitive performance and vascular function in physically active individuals aged 50 years or above. In addition, the current study revealed a significant association between changes in cognitive and vascular functions following step reduction; however, the results demonstrated evident individual differences, and as such, should be interpreted with caution. These findings may have practical implications for people who need to temporarily reduce or stop exercise routine due to busy schedules, injury, illness, etc., but still want to maintain optimal cognitive function for complex tasks and activities of daily living.

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Table 4. 1 Sample characteristics

	Total (n = 14)	Females (n = 10)	Male (n = 4)
Age	65.2 (4.2)	69.0 (8.0)	55.8 (8.7)
Height (cm)	161.7 (23.8)	156.3 (26.3)	87.0 (17.0)
Weight (kg)	83.0 (27.4)	81.4 (31.2)	175.4 (5.0)
BMI (kg/m^2)	28.0 (4.5)	28.0 (4.8)	28.1 (4.5)
Body fat (%)	37.6 (6.6)	39.5 (6.0)	33.0 (6.4)
Systolic BP (mmHg)	115.0 (11.3)	116.4 (12.1)	111.5 (9.7)
Diastolic BP (mmHg)	68.1 (8.4)	67.7 (8.3)	69.2 (9.9)
Resting HR (bpm)	70.6 (8.1)	70.3 (6.8)	71.5 (12.2)
IPAQ MET-min/week Total	2835.0 (813.5)	2719.4 (774.5)	3124.1 (955.2)
Step/day, Week 1[b]	7023.1 (1888.3)	6852.4 (1813.2)	7588.7 (2444.5)
Step/day, Week 2[b]	3855.3 (839.5)	3859.5 (866.1)	3838.5 (1037.3)

Note: Data are presented as mean (SD). [a] No statistical differences between Visit 1 and Visit 2. [b] Measured by accelerometer, averaged across all valid days. *Abbreviations:* BMI, body mass index; BP, blood pressure; HR, heart rate; IPAQ: International Physical Activity Questionnaire; MET, metabolic equivalent; MVPA, moderate-to-vigorous physical activity.

Table 4. 2 Summary of descriptive statistics and Bayesian analysis results

	Descriptive statistics				Results from Bayesian analysis (Uniform Prior)	
	Before (mean [SD])	After (mean [SD])	% Change (mean [SD])	ES (*d*)	Estimated difference (95% CIs), before vs. after	$P_{(diff=0)}$
Cognitive Function						
Flanker	8.15 (0.53)	7.94 (0.86)	-2.39 (10.35)	0.29	-0.21 (-0.71, 0.29)	0.61
DCCS	8.39 (0.74)	8.31 (1.04)	-1.00 (8.40)	0.08	-0.08 (-0.50, 0.34)	0.33
PCPS	43.93 (7.09)	42.86 (9.12)	-2.72 (12.93)	0.12	-1.08 (-4.30, 2.16)	0.53
WM	17.43 (2.65)	17.07 (3.17)	-1.59 (15.08)	0.12	-0.36 (-2.02, 1.46)	0.36
Vascular Function						
cMAP (mmHg)	90.69 (8.80)	91.92 (9.87)	1.52 (8.10)	-0.04	1.26 (-3.30, 5.40)	0.46
Aortic AIx75 (%)	22.29 (7.22)	21.42 (6.05)	4.28 (35.45)	0.13	-0.87 (-6.05. 4.09)	0.28
cfPWV (m/s)	8.32 (2.13)	8.40 (2.01)	1.38 (7.11)	-0.13	0.08 (-0.21, 0.40)	0.42

Abbreviations: 95% CIs, 95% credible intervals; AIx75, augmentation index at a heart rate of 75 beats per minute; cfPWV, carotid to femoral pulse wave velocity; cMAP, central mean arterial pressure; DCCS, Dimensional Change Card Sort Test; ES, effect size; Flanker, Flanker Inhibitory Control and Attention Test; PCPS, Pattern Comparison Processing Speed Test; $P_{(diff=0)}$, the probability of the posterior distribution of the difference includes zero; WM, List Sorting Working Memory Test.

Table 4. 3 Correlations between changes in cognitive and vascular function

Before step reduction (Visit 2, baseline)						
	Flanker	DCCS	PCPS	WM	cMAP	Aortic AIx75
DCCS	**0.66**					
PCPS	**0.71**	**0.62**				
WM	0.32	0.15	**0.57**			
cMAP	-0.09	0.10	-0.02	-0.11		
Aortic AIx75	-0.43	-0.39	-0.14	-0.06	0.28	
cfPWV	-0.30	-0.49	-0.15	-0.28	0.34	0.51
Changes after step reduction (Visit 3 vs. Visit 2)						
	%Δ Flanker	%Δ DCCS	%Δ PCPS	%Δ WM	%Δ cMAP	%Δ Aortic AIx75
%Δ DCCS	**0.65**					
%Δ PCPS	**0.83**	**0.71**				
%Δ WM	0.32	0.40	0.18			
%Δ cMAP	-0.08	-0.14	-0.31	**0.63**		
%Δ Aortic AIx75	-0.21	-0.27	-0.07	0.31	0.12	
%Δ cfPWV	-0.52	**-0.81**	**-0.65**	-0.21	0.31	0.23

Note: Bold denotes $p < 0.05$. *Abbreviations*: AIx75, augmentation index at a heart rate of 75 beats per minute; cfPWV, carotid to femoral pulse wave velocity; cMAP, central mean arterial pressure; DCCS, Dimensional Change Card Sort Test; Flanker, Flanker Inhibitory Control and Attention Test; PCPS, Pattern Comparison Processing Speed Test; WM, List Sorting Working Memory Test.

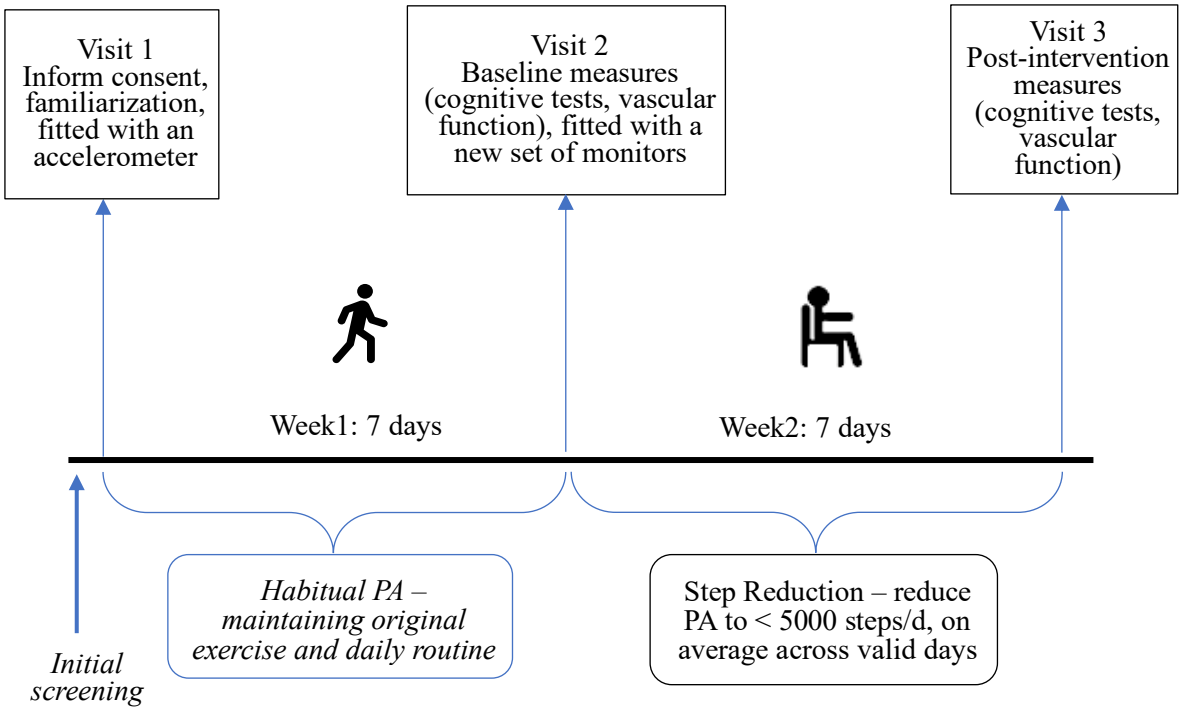


Figure 4. 1 Experimental design and order of procedures involving step reduction.

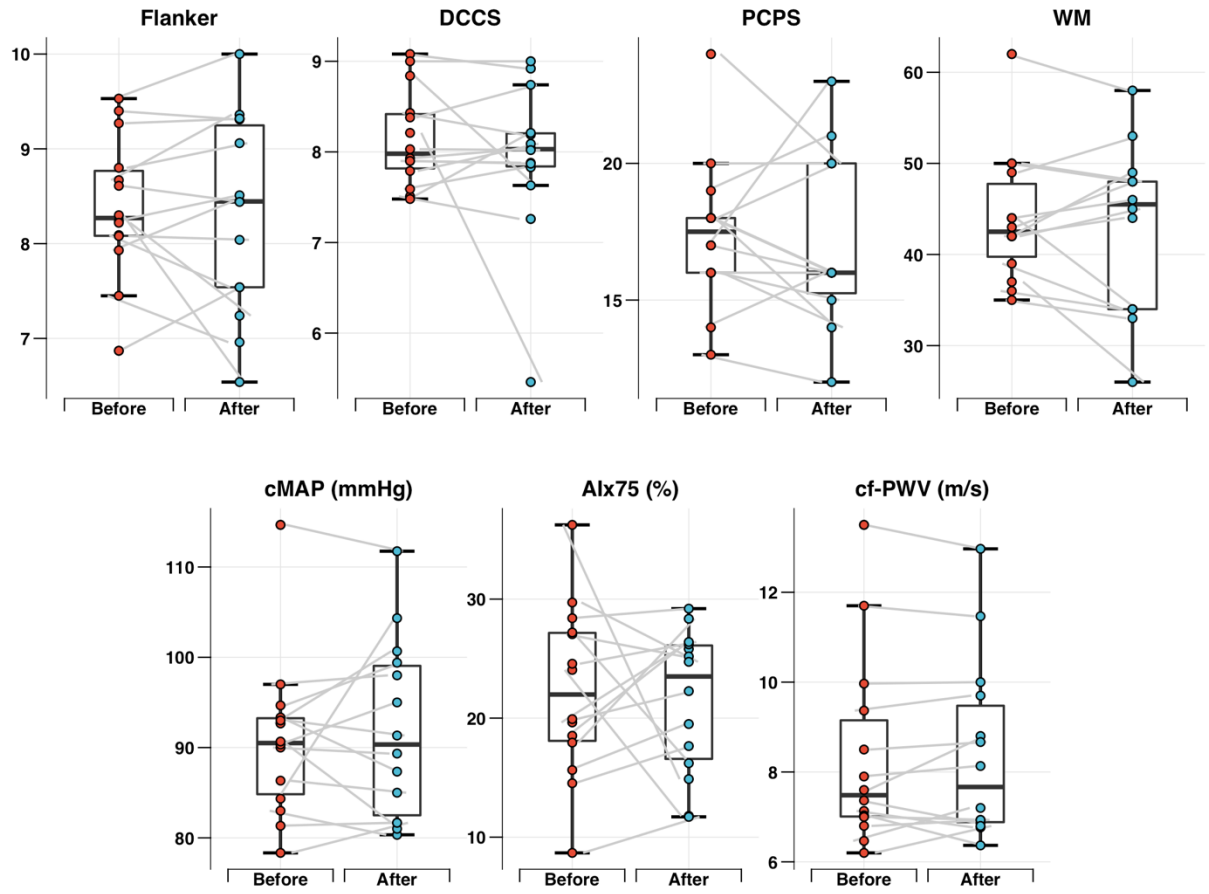


Figure 4. 2 Impact of one-week step reduction on cognitive and vascular function. Boxplots with scatter plots display the distribution of outcomes, black lines within boxes and error bars represent means and SDs, grey lines link individuals' data points before and after step reduction, respectively. *Abbreviations*: AIx75, augmentation index at a heart rate of 75 beats per minute; cfPWV, carotid to femoral pulse wave velocity; cMAP, central mean arterial pressure; DCCS, Dimensional Change Card Sort Test; Flanker, Flanker Inhibitory Control and Attention Test; PCPS, Pattern Comparison Processing Speed Test; WM, List Sorting Working Memory Test.

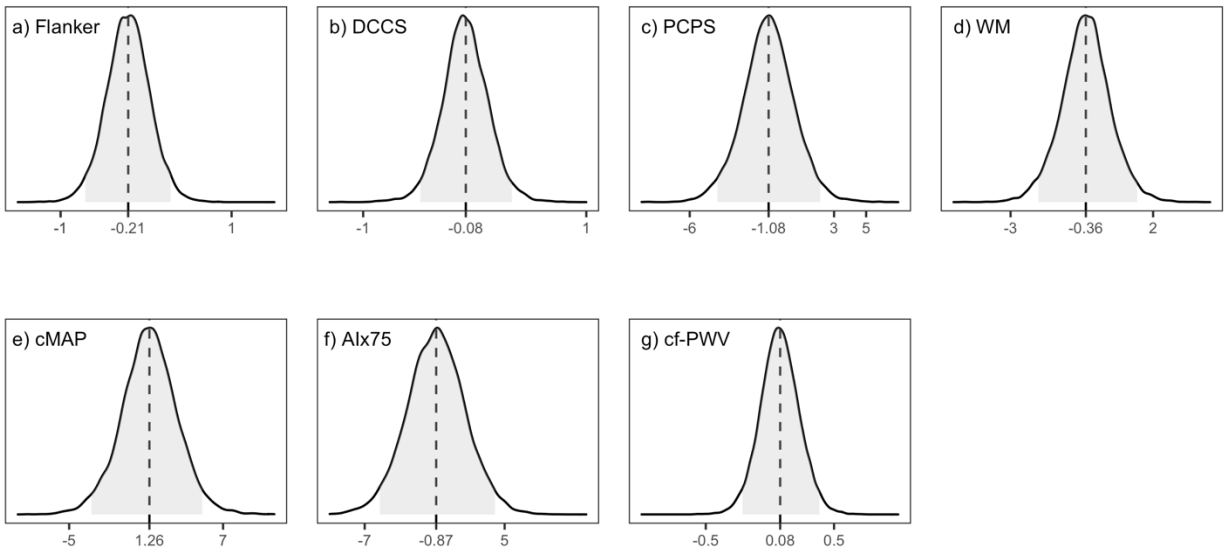
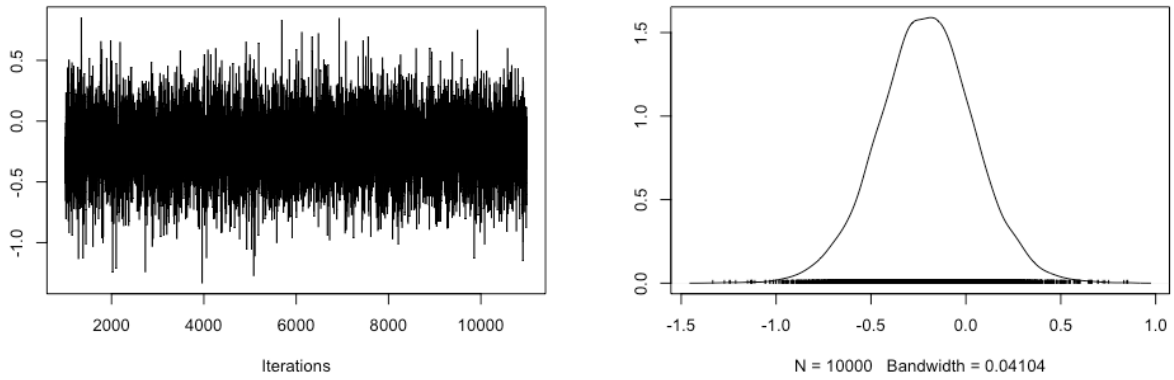


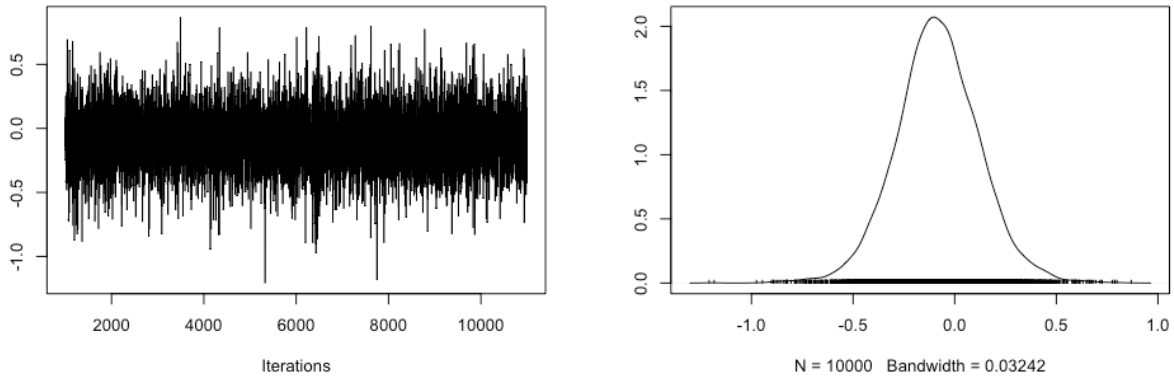
Figure 4. 3 Estimated changes in cognitive and vascular outcomes after step reduction. Plots display the posterior distributions of estimated differences (before vs. after) in cognitive (a~d) and vascular (e~g) outcomes. Dashed lines indicate estimated value, shaded areas exhibit 95% credible intervals. *Abbreviations*: AIx75, augmentation index at a heart rate of 75 beats per minute; cfPWV, carotid to femoral pulse wave velocity; cMAP, central mean arterial pressure; DCCS, Dimensional Change Card Sort Test; Flanker, Flanker Inhibitory Control and Attention Test; PCPS, Pattern Comparison Processing Speed Test; WM, List Sorting Working Memory Test.

SDC 4.1. Trace and density plots of posterior samples for each variable

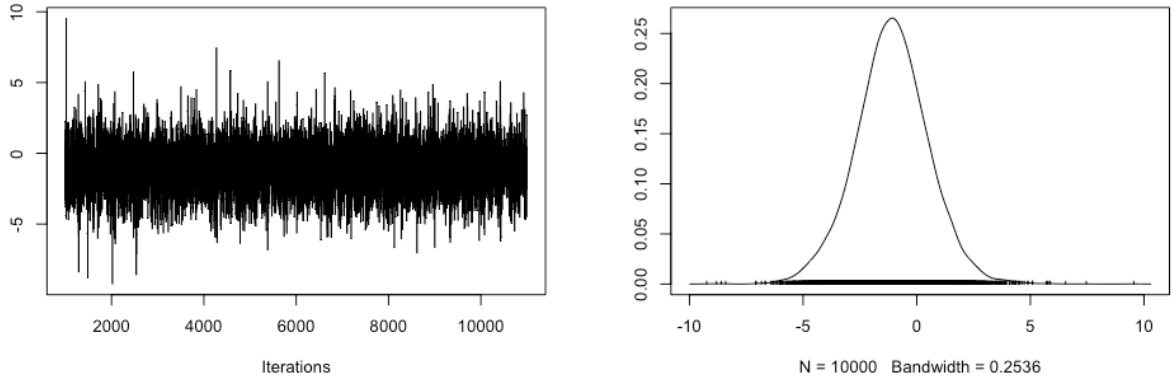
Flanker



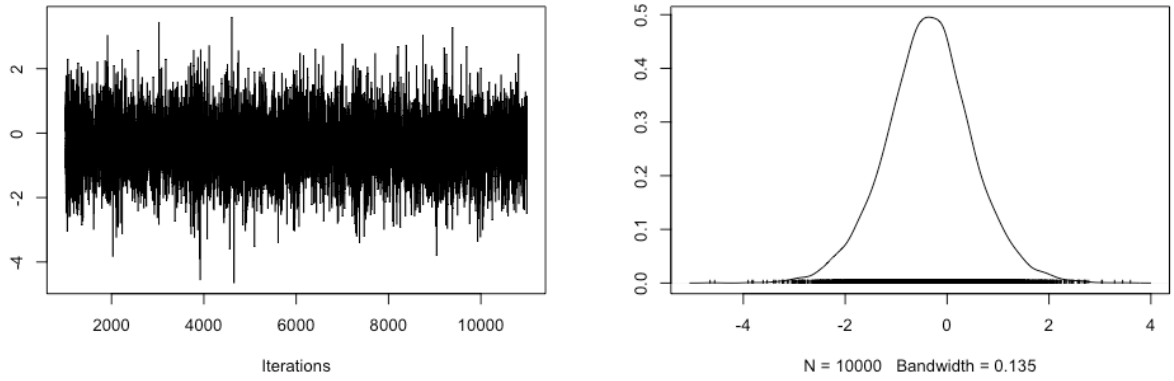
DCCS



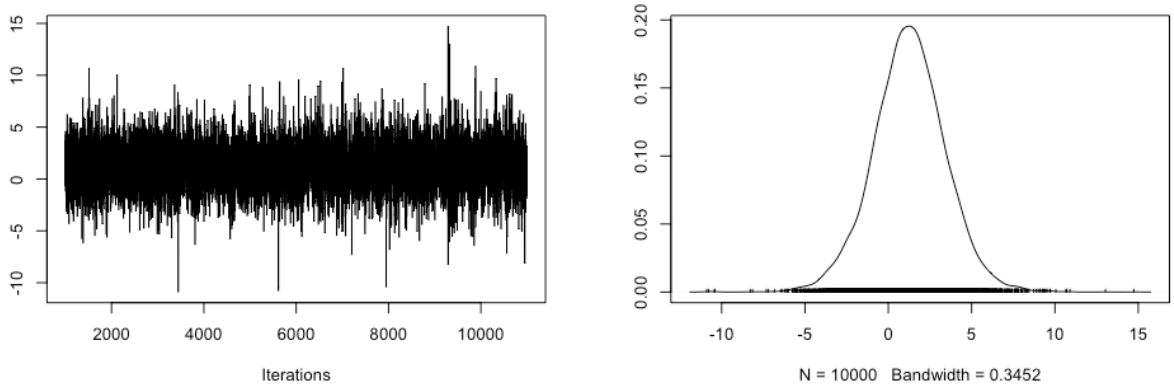
PCPS



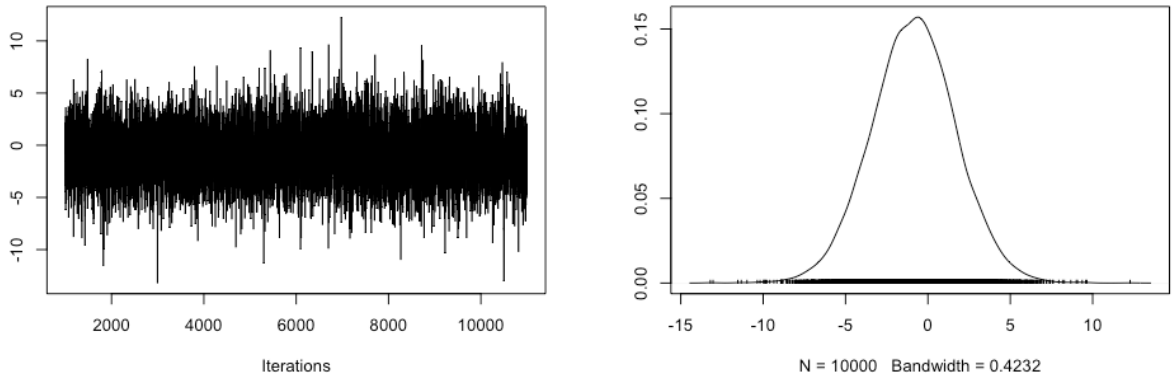
WM



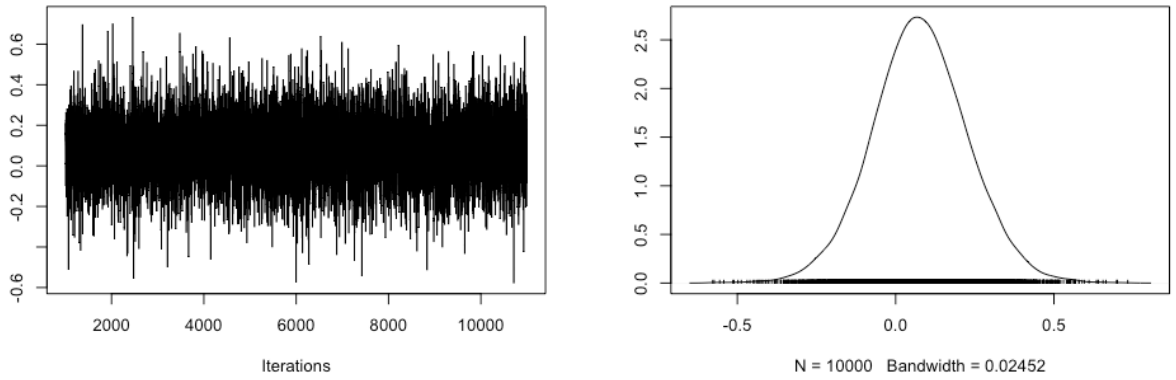
cMAP



AIx75



cfPWV



Abbreviations: AIx75, augmentation index at a heart rate of 75 beats per minute; cfPWV, carotid to femoral pulse wave velocity; cMAP, central mean arterial pressure; DCCS, Dimensional Change Card Sort Test; Flanker, Flanker Inhibitory Control and Attention Test; PCPS, Pattern Comparison Processing Speed Test; WM, List Sorting Working Memory Test.

CHAPTER 5

CONCLUSION

Regular physical activity (PA) has been increasingly recognized as an effective approach for improving and maintaining both cognitive function and physical independence that contribute to successful aging (1). Although previous research suggests a small improvement in cognitive function following acute exercise (2), the results were inconsistent regarding differential effects on multiple cognitive domains and within studies that utilized various exercise modalities (2-6). There is also a lack of evidence on the PA-cognition relationship among healthy older adults who were physically active or inactive. Moreover, it is unknown how short-term reduction in PA would impact cognitive function and its association with vascular function. To address these evidence gaps, we conducted three studies to examine the effects of acute exercise and short-term PA reduction on cognitive function, especially in the older adult population.

The first study systematically reviewed and meta-analyzed the existing literature concerning the acute effects of exercise on cognitive function in healthy older adults. The standardized mean difference (SMD) of 90 effects from 16 randomized controlled trials indicated a small but significant improvement in cognitive performance immediately following acute exercise compared to the non-exercise control condition (SMD = 0.17, $p = 0.003$). Interestingly, moderator analysis revealed a significantly higher effect in the time vs. accuracy-related

components of cognitive measurements (SMD = 0.24 vs. 0.11; $p < 0.05$). Although greater effect sizes were observed based on study design (cross-over design), exercise type (cycling), intensity (moderate) and duration (> 20 min), and cognitive domain (executive function), no differential effects were found within levels of those moderators ($p > 0.05$). The findings suggest that a single bout of exercise improves cognitive function in healthy older adults. This may have practical implications for the prescription of daily PA for older adults to accumulate exercise-induced benefits on cognitive function.

The second study sought to investigate the effects of a single bout of moderate-intensity walking on cognition and vascular function in physically inactive older adults aged 60 years or above. Separate repeated-measures ANOVAs were used to compare potential differences in cognitive test scores and vascular outcomes pre- vs. post-acute sessions under control (30-min quiet sitting) and exercise (30-min walking at 100 steps/min) conditions. Compared to the control condition, acute exercise was found to significantly improve cognitive performance in executive function and attention, and also reduced carotid to femoral pulse wave velocity ([cfPWV], $p < 0.05$). Central mean arterial blood pressure (cMAP) was unaltered pre vs. post exercise ($p > 0.05$), and no differential effects were found on processing speed and aortic augmentation index (AIx75, standardized to a heart rate of 75 beats/min) between the two conditions ($p > 0.05$). Following walking, acute changes (%Δ) in cfPWV and cMAP were negatively associated with the changes in executive function and attention ($p < 0.05$). The

findings from this study help improve our understanding of the relationship between cognition and vascular function in response to acute exercise.

The purpose of study 3 was to examine the impact of short-term physical inactivity (one week) on cognitive performance and vascular function among physically active individuals aged 50 years or above. Due to the small sample size, a Bayesian approach was used to estimate differences before and after step reduction (to below 5000 steps/day on average). Results herein indicated minimal changes in all variables (e.g., -0.08 to -0.36 in cognitive test scores), indicating that one week of reduction in PA did not yield detrimental effects on cognitive performance and vascular function among previously active individuals. Significant correlations were observed between changes in cognitive performance with cfPWV and cMAP in response to one week of step reduction.

Overall, this dissertation expands upon existing evidence regarding the relationship between short-term PA and cognitive function. The favorable effects of acute exercise on cognitive function in older adults were observed in both the systematic review and experimental studies. Notably, our results are the first to reveal a significant association between arterial stiffness and cognitive performance in response to short-term acute exercise or PA reduction. Given the accessibility and utility of walking activity as a PA modality, and the emphasis herein on the use of step-based metrics, the findings presented in this dissertation may have practical implications for how daily PA is prescribed to achieve health benefits for successful aging.

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APPENDIX: IRB LETTER

THE UNIVERSITY OF ALABAMA® | Research & Economic Development
Office for Research Compliance

March 8, 2022

Peixuan Zheng
Department of Kinesiology
College of Education
The University of Alabama
Box 870312

Re: IRB #21-01-4237-B "Changes in active cognitive function following a single bout of moderate-intensity (cadence-controlled) walking"

Dear Peixuan Zheng:

The University of Alabama Institutional Review Board has granted approval for your renewal application. Your renewal application has been given expedited approval according to 45 CFR part 46. Approval has been given under expedited review categories 4 and 7 as outlined below:

(4) Collection of data through non-invasive procedures (not including general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves; and

(7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

The approval for your application will lapse on March 7, 2023. If your research will continue beyond this date, please submit a continuing review to the IRB as required by University policy before the lapse. Please note, any modifications made in research design, methodology, or procedures must be submitted to and approved by the IRB before implementation. Please submit a final report form when the study is complete.

Good luck with your research.

Sincerely,

[redacted]
Director & Research Compliance Officer

166 Rose Administration Building | Box 870127 | Tuscaloosa, AL 35401 | 205-348-8461 | rscompliance@ua.edu

THE UNIVERSITY OF ALABAMA® | Research & Economic Development
Office for Research Compliance

May 11, 2022

To: Peixuan Zheng
Department of Kinesiology
College of Education

From: [redacted]
Director & Research Compliance Officer

Re: **Notice of Approval**

IRB Application #:	e-Protocol 21-04-4544-R1
Project Title:	"The Impact of One-Week Step Reduction on Cognitive Function Among Physically Active Individuals"
Submission Type:	Renewal
Approval Date:	May 11, 2022
Expiration Date:	May 10, 2023
Funding Source:	None
Review Category:	EXPEDITED
Approved Documents:	Informed Consent, Recruitment Flyer/Script

Dear Peixuan :

The University of Alabama Institutional Review Board has approved your proposed research . Therefore, your renewal application has been approved according to 45 CFR part 46 *as outlined below:*

(4) Collection of data through non-invasive procedures (not including general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves; and

(7)Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

The approval for your application will lapse, as noted above. If your research will continue beyond this date, please submit the Continuing Review to the IRB as University policy requires before the lapse. Please note any modifications made in research design, methodology, or procedures must be submitted to and approved by the IRB before implementation. Please submit a final report form when the study is complete.

All the best with your research.

166 Rose Administration | Box 870127 | Tuscaloosa, AL 35487-0127 | 205-348-8461
Fax 205-348-7189 | Toll Free 1-877-820-3066 | rscompliance@research.ua.edu