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Multiple-Modality Exercise And Mind-Motor Training To Improve Cardiovascular Health And Fitness In Older Adults At Risk For Cognitive Impairment: A Randomized Controlled Trial

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Abstract

Background: The effects of multiple-modality exercise on arterial stiffening and cardiovascular fitness has not been fully explored. Objectives: To explore the influence of a 24-week multiple-modality exercise program associated with a mind-motor training in cardiovascular health and fitness in community-dwelling older adults, compared to multiple-modality exercise (M2) alone. **Methods**: Participants (n=127, aged 67.5 [7.3] years, 71% females) were randomized to either M4 or M2 groups. Both groups received multiple-modality exercise intervention (60 min/day, 3 days/week for 24-weeks); however, the M4 group underwent additional 15 min of mind-motor training, whereas the M2 group received 15 min of balance training. Participants were assessed at 24-weeks and after a 28-week non-contact follow-up (52-weeks). **Results**: at 52-weeks, the M4 group demonstrated a

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Abbreviations: M2, multiple-modality group; M4, multiple-modality, mind-motor group; SSE, square-stepping exercise; AE, aerobic exercise; ST, strength training; STEP, The Step Test and Exercise Prescription; BMI, body mass index; HR, resting heart rate; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental Status Examination; CAC, carotid arterial compliance; IMT, intima-media thickness; VO2max, maximal oxygen consumption; 24 h SBP, systolic blood pressure; 24 h DBP, diastolic blood pressure; Day SBP, daytime systolic blood pressure; Day DBP daytime diastolic blood pressure; Night SBP, nighttime systolic blood pressure; Night DBP nighttime diastolic blood pressure; Rec-FD, frequency and duration of recreational physical activity.

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greater VO2max (ml/kg/min) compared to the M2 group (mean difference: 2.39, 95% CI: 0.61 to 4.16, p=0.009). Within-group analysis indicated that the M4 group demonstrated a positive change in VO2max at 24-weeks (mean change: 1.93, 95% CI: 0.82 to 3.05, p=0.001) and 52-weeks (4.02, 95% CI: 2.71 to 5.32, p=0.001). Similarly, the M2 group increased VO2max at 24-weeks (2.28, 95% CI: 1.23 to 3.32, p<0.001) and 52-weeks (1.63, 95% CI: 0.43 to 2.83, p = 0.008). Additionally, the M2 group decreased 24 h SBP (mmHg) at 24-weeks (-2.31, 95% CI: -4.61 to -0.01, p=0.049); whereas the M4 group improved 24 h DBP (-1.6, 95% CI: -3.03 to -0.17, p=0.028) at 52-weeks. **Conclusion**: Mind-motor training associated with multiple-modality exercise can positively impact cardiovascular fitness to the same extent as multiple-modality exercise alone.

Keywords: Randomized controlled trial; Exercise; Mind-motor training; Cardiovascular health; Group-based program; Older adults.

1. Introduction

Ischemic heart disease and stroke account for approximately 25% of deaths worldwide per year.(“WHO | Projections of mortality and causes of death, 2015 and 2030,” 2014) The World Health Organization (WHO) estimates that by 2030, 34.8% of the world population will be affected by the progressive expansion of cardiovascular diseases (CVD).(“WHO | Projections of mortality and causes of death, 2015 and 2030,” 2014) Older adults are at increased risk for CVD,(Remsberg & Siervogel, 2003) and this risk can be partially attributed to age-related arterial stiffening, reduced arterial compliance and reduced cardiovascular fitness.(Sakuragi & Abhayaratna, 2010; Tanaka, DeSouza, & Seals, 1998)

Arterial stiffness is associated with coronary disease, stroke and heart failure, and is a precursor to isolated systolic hypertension later in life.(Boutouyrie et al., 2002) Moreover, arterial stiffening and associated hypertension reduce cerebrovascular reactivity and cerebral flow, and predispose older adults to pathological changes in cerebral structure and further cognitive deterioration(Dai et al., 2008; Kilander, Nyman, Boberg, Hansson, & Lithell, 1998; Kivipelto et al., 2001; Launer et al., 1995); in fact, 5% of Alzheimer’s disease cases worldwide have been attributed to hypertension.[10] Consequently, age-related arterial stiffening is an independent risk factor for cognitive impairment,(Norton et al., 2014) as well as, cardiovascular events and all-cause mortality in older adults.(Boutouyrie et al., 2002; Vlachopoulos, Aznaouridis, & Stefanadis, 2010; Zieman, Melenovsky, & Kass, 2005) Furthermore, impairment of cardiovascular function is accompanied by worsening in cardiovascular fitness (i.e., maximal oxygen consumption, VO2max)(Fleg et al., 2005; Jackson, Sui, Hébert, Church, & Blair, 2009); in fact, after 70 years of age, VO2max decreases by 17% per decade.(Fleg et al., 2005) Low VO2max is also an indicator of increased risk for CVD and all-cause mortality in this population,(Fleg et al., 2005; G. Huang et al., 2015; Lakka et al., 2003; Vanhees, De Sutter, et al., 2012; Vanhees, Rauch, et al., 2012) and it is inversely associated with healthy cognitive functioning.(Freudenberger et al., 2016)

In the past decades, several studies have reported a positive relationship between high physical activity levels and improved arterial compliance (i.e., increased arterial elasticity).(Cameron & Dart, 1994; Cameron, Rajkumar, Kingwell, Jennings, & Dart, 1999; Monahan, Dinenno, et al., 2001; Monahan, Tanaka, Dinenno, & Seals, 2001; Otsuki et al., 2006; Tanaka et al., 2000, 1998) Regular aerobic-based exercise is a non-pharmacological strategy that seems to attenuate and partially reverse age-induced arterial stiffening by increasing arterial compliance(Cameron & Dart, 1994; Lu, Hui-Chan, & Tsang, 2013a, 2013b; Maeda et al., 2008; Miyaki et al., 2009; Nickel, Acree, & Gardner, 2011; Parnell, Holst, & Kaye, 2002; Seals, Desouza, Donato, & Tanaka, 2008; Sugawara et al., 2009; Sugawara, Inoue, Hayashi, Yokoi, & Kono, 2004; Tanaka et al., 2000; Vanhees, Rauch, et al., 2012; Villareal, Smith, Sinacore, Shah, & Mittendorfer, 2011) and VO2max,(G. Huang et al., 2015; Vanhees, De Sutter, et al., 2012; Vanhees, Rauch, et al., 2012) thereby, leading to improved health outcomes. Although, resistance training also promotes improvements in VO2max,(Brentano et al., 2008; GR, JP, & MM, 2004; Hepple et al., 2015; D. Lovell, 2010; D. I. Lovell, Cuneo, & Gass, 2009; Ozaki, Loenneke, Thiebaud, & Abe, 2013; Phillips et al., 2012; Vincent, Braith, Feldman, Kallas, & Lowenthal, 2002) research to date suggests that this modality does not seem to promote any positive impact on arterial compliance.(Bertovic et al., 1999; Cortez-Cooper et al., 2008; Miyachi et al., 2003, 2004)

Understanding that current guidelines for exercise prescriptions have stressed the importance of multiple-modality approaches for enhancing health and quality of life in older adults,(Chodzko-Zajko et al., 2009) investigations exploring the effects of multiple-modality exercise programs on cardiovascular health and fitness are imperative. In general, multiple-modality exercise programs encompass as their main structural components aerobic exercise (AE), strength training (ST), flexibility and balance exercises.(Carvalho, Marques, & Mota, 2009; Chodzko-Zajko et al., 2009; Howe, Rochester, Neil, Skelton, & Ballinger, 2011) Accordingly, older adults seem to benefit more from these multiple-modality exercise approaches in comparison to programs focusing on either AE or ST alone.(Gregory, Gill, & Petrella, 2013) Furthermore, when a mind-motor exercise component is included (e.g., dual-task training), the associated benefits impact not only cardiovascular health, muscle strength and balance, but may also promote additive benefit to cognitive outcomes.(Gregory et al., 2013) Despite this promising evidence, it remains unclear what specific type of exercise intervention would most effectively address cardiovascular, functional and cognitive concerns in older populations. As such, rigorously designed randomized controlled trials (RCTs) are necessary.

Square-stepping exercise (SSE) is a novel, group-based, low-intensity exercise program that has been shown to be associated with improvements in lower extremity functional fitness and reduced fall risk factors in older adults at high risk of falling.(Shigematsu et al., 2008) The SSE intervention is characterized as a visuospatial working memory task, with a stepping response on a gridded floor mat, and thus, may be considered as a type of mind-motor exercise.(Gill et al., 2016) Recent evidence has suggested that SSE may improve global cognitive functioning and certain specific cognitive domains (i.e., memory, executive functioning, attention and mental flexibility).(Gill et al., 2016; Shigematsu, 2014; Teixeira et al., 2013) Nonetheless, the influence of SSE on cardiovascular health and fitness has not been strictly evaluated.

In this study, we explored the secondary outcomes from a recently completed RCT.(Gregory et al., 2016) Specifically, we investigated the influence of a group-based, multiple-modality exercise combined with a novel form of mind-motor training (i.e., SSE), compared to multiple-modality exercise alone on arterial stiffening, arterial compliance, VO2max and ambulatory blood pressure in community-dwelling older adults at risk for cognitive impairment. We hypothesized that the addition of a mind-motor training component to the multiple-modality exercise intervention would lead to improvements in the aforementioned cardiovascular outcomes to a greater extent compared to the multiple-modality exercise alone.

2. Materials and Methods

2.1. Participants

Community-dwelling older adults living in Woodstock, ON, Canada, were invited to participate in this study. Details about participant recruitment can be found elsewhere.(Gregory et al., 2016) Briefly, older adults aged 55 years or older were recruited through advertisements, health fairs and posters at local businesses. The inclusion criteria encompassed the following items: a) be aged 55 years or older; b) answer ‘yes’ to the question: “do you feel like your memory or thinking skills have gotten worse recently?"; and c) have preserved Instrumental Activities of Daily Living (i.e., reached maximum score in the Lawton-Brody Instrumental Activities of Daily Living scale [8/8]). The exclusion criteria were: a) severe cognitive impairment (i.e., self-reported diagnosis of dementia and/or score < 24 on the Mini-Mental State Examination); b) major depression (i.e., score ≥ 16 on the Centre for Epidemiologic Studies Depression scale combined with clinical judgment by the study physician); c) recent history of severe cardiovascular conditions (e.g., stroke, myocardial infarction, end stage congestive heart failure, etc.); d) significant orthopedic condition (e.g., severe osteoarthritis); e) any neurological and/or psychiatric disorders; f) resting blood pressure > 180/100 mmHg and/or < 100/60 mmHg (unsafe for exercise); g) unable to comprehend study letter of information; and lastly, i) any other reasons that could significantly impact participation in the exercise program.

2.2. Study Design

This two-arm RCT was a 24-week intervention program with a 28-week no-contact follow-up. Participants were randomized (1:1) to either a multiple-modality, mind motor exercise intervention group (M4) or to a multiple-modality exercise comparison group (M2). This study was registered with ClinicalTrials.gov on 29 April 2014 (Identifier: NCT02136368) The Western University Health Sciences Research Ethics Board approved this project. All participants provided written informed consent prior to taking part in the study.

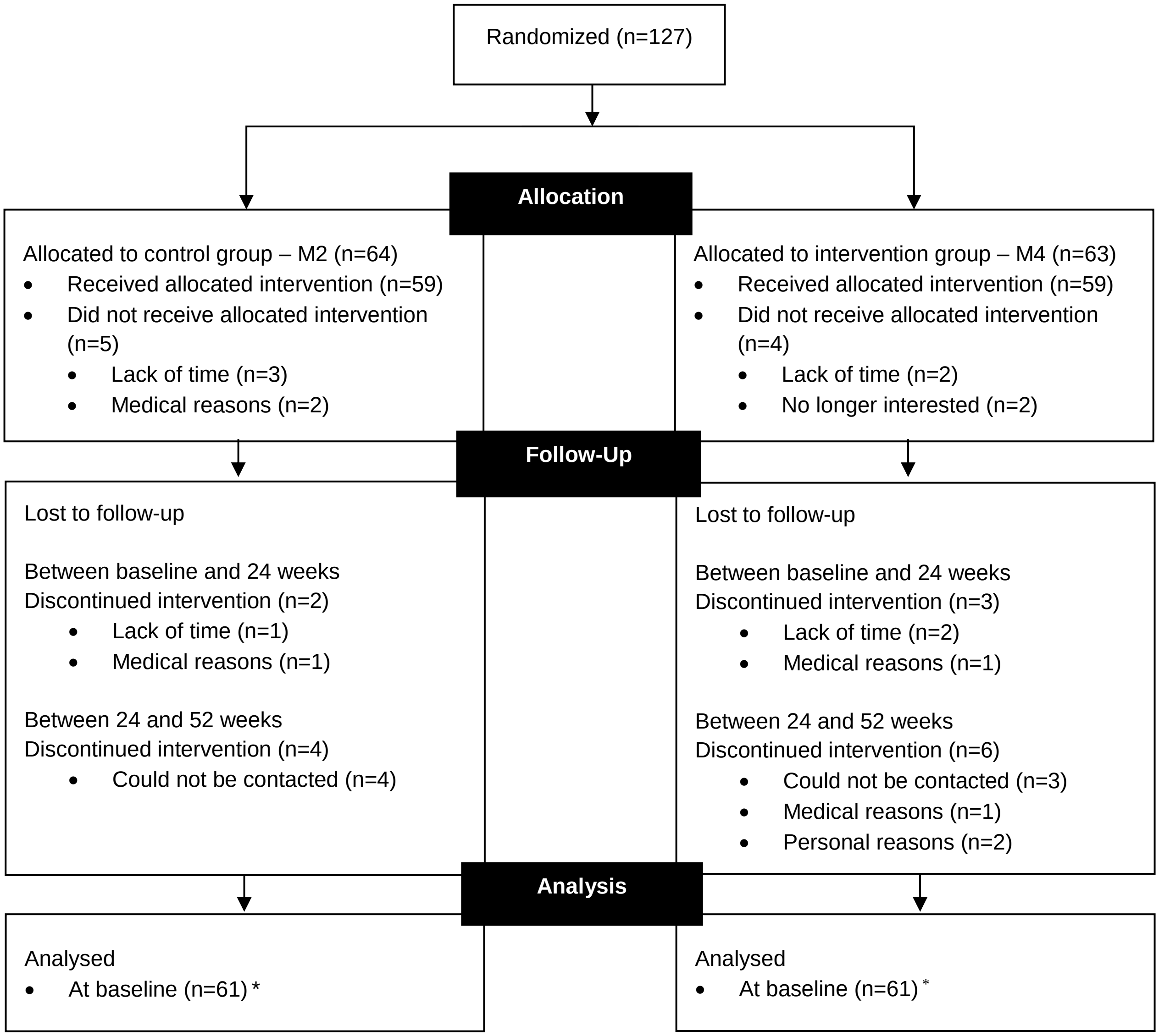

Figure 1. Diagram illustrating flow of participants in the 24-week randomized controlled trial with a 28-week follow-up period. *4 participants were excluded from analysis because the assessments could not be completed (M2, n=2; M4 n=2).

2.3. Exercise Intervention

Participants exercised 60 minutes per day, 3 days per week, for 24 weeks at the community location. The exercise program was carried out by certified Seniors' Fitness Instructors (Canadian Centre for Activity and Aging), who received adequate training on the SSE protocol before the beginning of the program. Both groups equally received standardized exercise training, described as follows: 5 min aerobic warm-up, 20 min moderate-to-vigorous-intensity AE, 5 min aerobic cool down, followed by 10 min ST. In addition to the standardized exercise training, the M4 group underwent 15 min of mind-motor training (i.e. SSE), whereas the M2 group underwent 15 min of training that involved balance, range of motion and breathing exercises (i.e., types of exercise with evidence that they benefit cognition). Error! Reference source not found. illustrates the training protocol in detail. Aerobic exercise intensity was prescribed via target heart rates (HR) determined prior to the beginning of the program. During the AE portion of each session, participants were encouraged to keep their HR at 65-85% of predicted maximum heart rate (HRmax) and/or at a rating of 5-8 on the 10-point modified Borg Rating of Perceived Exertion (RPE) scale. Monitoring of target HR during each session was conducted part way through and after the aerobic component. Participants were instructed to record HR and RPE immediately after each monitoring in a training log provided by the research team. The Step Test and Exercise Prescription (STEP™) tool(Stuckey, Knight, & Petrella, 2012) was used to predict HRmax (see methods section **2.5.3** for details). Target HR were recalculated at 12-weeks via the STEP™ to adjust for progression in the aerobic training.

2.3.1. The Square Stepping Exercise (SSE) Protocol

The SSE is a group-based activity performed on a gridded floor mat (2.5 m × 1 m), containing 10 rows with 4 equalized squares per row.(Shigematsu, 2014) The training protocol entails the reproduction of complex foot placements (i.e., stepping patterns) on the mat, previously performed by an instructor. Participants are expected to visualize and memorize the stepping pattern demonstrated by the instructor on the mat, and subsequently, attempt to reproduce the same stepping pattern. There are more than 200 stepping patterns, which are classified in 3 categories (i.e., beginner, intermediate and advanced) involving lateral, backwards, forward and diagonal steps across the mat. The complexity of the patterns are given based on the amount of steps per pattern (varying from 2 to 16 steps), as well as, foot placement ordering and directions. In order to promote a positive social atmosphere, participants were encouraged to assist each other during this component of the class. To keep tracking of participants' progression throughout the program, instructors recorded information of the last pattern performed at the end of each session; thus, participants started at the pattern where they left off at previous class, advancing through the SSE pattern categories gradually, over the 24-week intervention period.

Table 1. Detailed description of the 24-week exercise intervention.

M2: Multiple-modality exercise group (comparison group)	**M4: Multiple-modality, mind-motor exercise group** (intervention group)
Warm-up (5 minutes) • Light aerobics • Dynamic range of motion of the major joints	**Warm-up (5 minutes)** • Light aerobics • Dynamic range of motion of the major joints
Aerobic Exercise (20 Minutes) • Large rhythmical endurance activities (e.g., walking, marching, • sequenced aerobics) • Keep HR continuously in target zone (i.e., not interval training) • Moderate to vigorous intensity • RPE: 5–8 on scale of 0–10 • Participants to check HR ½ way through and at end of AE.	**Aerobic Exercise (20 Minutes)** • Large rhythmical endurance activities (e.g., walking, marching, • sequenced aerobics) • Keep HR continuously in target zone (i.e., not interval training) • Moderate to vigorous intensity • RPE: 5–8 on scale of 0–10 • Participants to check HR ½ way through and at end of AE.
Aerobic Cool Down (5 minutes) • Safely bringing heart rates down	**Aerobic Cool Down (5 minutes)** • Safely bringing heart rates down
Strength Training (10 minutes) • Therabands, wall or chair exercises, core strengthening • Day 1 – Upper body focus • Day 2– Lower body focus • Day 3 – Core focus	**Strength Training (10 minutes)** • Therabands, wall or chair exercises, core strengthening • Day 1 – Upper body focus • Day 2– Lower body focus • Day 3 – Core focus
Balance, Range of Motion & Breathing (15 minutes) • Keep HR below target zone • Dynamic, static and functional balance • Breathing and relaxation exercises • Finger exercises • Range of motion (e.g., arm circles)	**Mind-Motor Training (15 minutes)** • Keep HR below target zone • Progressive, group-based, Square Stepping Exercise (SSE) • Stretching (5 minutes) Stretching (5 minutes)
Total: 60 min exercise intervention	Total: 60 min exercise intervention

Abbreviations: HR Heart Rate; RPE Rating Perceived Exertion. Table adapted from Gregory et al. BMC Geriatrics (2016) 16:17.(Gregory et al., 2016) (Original Publisher is Biomed Central).

2.4. Study Outcomes

In this study, we examined the secondary outcomes from a larger RCT(Gregory et al., 2016), which encompassed changes between and within groups at 24 weeks (intervention endpoint) and 52 weeks (study endpoint) in carotid arterial compliance (CAC), intima-media thickness (IMT), predicted maximal oxygen consumption (VO2max), 24 h systolic blood pressure (24 h SBP), and 24 h diastolic blood pressure (24 h DBP), daytime systolic blood pressure (Day SBP), daytime diastolic blood pressure (Day DBP), nighttime systolic blood pressure (Night SBP), and nighttime diastolic blood pressure (Night DBP).

2.5. Assessments

Participants attended to assessments at the Salvation Army Church in Woodstock and at the research centre at Parkwood Hospital, in London, Ontario, Canada. Baseline assessments included collection of the following information: age, sex, race, medical history, weight, height, body mass index (BMI), resting heart rate (HR), CAC, IMT, VO2max, 24 h SBP, 24 h DBP, Day SBP, Day DBP, Night SBP, and Night DBP. In addition, the Mini-Mental Status Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) were administered to assess cognitive status; and the Phone-FITT(Gill, Jones, Zou, & Speechley, 2008) questionnaire was applied to monitor frequency and duration of recreational physical activity (Rec-FD). Baseline assessments were performed after obtaining written informed consent and prior to randomization.

2.5.1. 24-hour Ambulatory Blood Pressure Monitoring

On the first day of assessments in Woodstock, ON, Canada, participants were fitted with a 24-hour ambulatory blood pressure and heart rate monitor (Model 90207, Spacelabs Inc., Redmond, WA, USA). A total of 40 readings were assigned to be recorded over a 24-hour period, with one measurement collected in intervals of 30 min between 6:00 and 22:00 (daytime), and a once every 60 min between 22:00 and 6:00 (nighttime). Individuals were instructed to relax the arm and remain still during the measurement. Should an error had occurred, the monitor performed a second attempt two minutes later. An activity log was provided to record any events that could impact blood pressure and heart rate, such as physical activity or stressful situations over the

24-hour period. A minimum of 28 successful readings (70%) were required for statistical analysis.

2.5.2. Common Carotid Arterial Ultrasonography

On the second day of assessments, in London, ON, Canada, participants underwent common carotid arterial ultrasonography. Participants were instructed to: not to engage vigorous physical activity or drink alcohol for 24 hours, avoid caffeine intake and smoking for 12 hours, and fast for 4 hours preceding the ultrasound measurement. Participants were instrumented with a standard three lead electrocardiogram and underwent 10 min supine rest in a quiet, temperature controlled room. With the participant's head rotated to the left, a 10 MHz transducer was placed longitudinally along the right carotid artery, 1-2 cm proximal to the carotid sinus, in order to obtain two-dimensional B-mode ultrasound images (Vingmed System 5, GE Ultrasound A/S, Horten, Norway). Right common carotid arterial diameters were measured in triplicate from wall to wall, and from wall to intima media layer at end diastole and peak systole, and a Doppler ultrasound was used to collect pulse wave for 60 s. After acquisition of the ultrasound images, carotid pulse pressure was inferred from supine brachial arterial blood pressure (BPM-100, BPTru™ Medical Devices, Coquitlam, BC, Canada). Anatomic land marking was used to ensure that all ultrasound images were obtained from the same portions of the carotid artery and to ensure accurate comparisons across time.

To determine CAC (mm/mmHg^2×10^{-1}), we applied the following equation: CAC = $[\pi \cdot (Dmax/2)^2 - \pi \cdot (Dmin/2)^2] / \Delta P$, where *Dmax* is the systolic carotid arterial diameter, *Dmin* is the diastolic carotid arterial diameter and *ΔP* is the automated supine brachial pulse pressure.(Sugawara et al., 2004) By subtracting the carotid arterial lumen diameter from the arterial diameter at diastole, we were able to determine IMT (mm). Two technicians were designated to perform and analyze all ultrasound images, with the same technician performing all measurements on a given participant whenever it was possible. To ensure inter-rater consistency of measurements, the level of agreement between technicians was tested by analyzing interclass correlation coefficient (ICC), using data collected by both technicians on 15 participants. A two-way random effects model was applied to calculate the ICC, which indicated a high level of agreement between assessors for average measures (ICC: 0.88, 95% confidence interval: 0.70 to 0.94, $p < 0.001$).

2.5.3. Predicted Maximal Oxygen Consumption (VO2max)

Following the common carotid arterial ultrasonography, participants performed the predicted VO2max test via STEP™ tool.(Stuckey et al., 2012) The test involved participants walking up and down a set of 2 standardized steps (20 cm), twenty times. Participants were instructed to perform the task at a self-selected pace and were supervised by an assessor throughout the test. The time to perform the task and heart rate, immediately after test completion, were recorded and applied to the equation: VO2max = 3.9 + (1511/time) · (O_2 pulse · 0.124) – (age · 0.032) – (sex · 0.633), where *time* is the time to complete the task (s); *O_2 pulse* is the quotient of body mass (kg) divided by heart rate (bpm); *age* is the participant's age (yr); and *sex* is *1* for male and *2* female.(Stuckey et al., 2012)

2.6. Sample Size Calculations

The sample size included in this study was calculated based on the primary outcome from the larger RCT (i.e., difference between groups at 24 weeks in global cognitive functioning).(Gregory et al., 2016) Briefly, results from a previous meta-analysis indicated that exercise could improve cognition with an moderate effect size ($d = 0.48$).(Colcombe & Kramer, 2003) Although our study has a different design (e.g., intervention and outcome), we decided to take this number into account. Therefore, a sample size of 52 participants per group would have an 80% power at the 5% significance level to detect a moderate effect size of 0.55. Taking into account a dropout rate of 20% during the 24-week intervention period, our final sample size was estimated at 130 participants, 65 in each group.

2.7. Statistical Analysis

Analyses were performed according to an intent-to-treat approach, including all randomized participants (according to their random allocation), regardless of compliance with the program and follow-up assessments. Descriptive exploratory statistics were conducted to assess data normality and homogeneity of distributions. Assumptions for each parametric test were properly tested prior to data treatment and variables were transformed as necessary. We applied linear mixed models for repeated measurements to assess differences between groups in mean change from baseline at 24 and 52 weeks.(Fitzmaurice, Laird, & Ware, 2011) The terms included in the model were: group (treatment), time and group (treatment) × time. Time was modeled categorically using two indicator variables representing each time point. Furthermore, the model was also used to analyze differences within M4 and M2 groups from baseline to 24 and 52 weeks. Significant changes were assessed using an alpha of 0.05; therefore, any two-sided p-values less than 0.05 were claimed as significant. Interpretation of study results were primarily based on mean estimation and associated 95% confidence interval (CI). The analyses were performed using the IBM® SPSS® Statistics, Version 23 for Windows 10.

3. Results

3.1. Enrollment, Randomization and Adherence

This study was conducted between January 13, 2014 and March 14, 2016. Participants were enrolled in 4 waves of assessments and intervention over a period of 14 months. During the screening process, 169 individuals were assessed for eligibility; 11 did not meet the inclusion criteria and 31 declined to participate. Thus, 127 participants were included and randomized to either the M2 (n=64) or M4 (n=63) groups, **Figure 1**.

After baseline assessments, 9 participants did not receive the allocated intervention. Between baseline and 24 weeks, 5 participants did not complete the study, and at 52 weeks, 10 participants did not attend to follow-up assessments. At 24 weeks, 81% (n=102) of participants had completed the study and the average attendance to the exercise sessions was 71% (51 out of 72 sessions).

3.2. Baseline Characteristics and Demographic Information

Baseline data regarding participant characteristics, demographic & clinical information, and study outcomes are presented in **Table 2**. Briefly, approximately 70% (90) participants were female, predominantly white (97.6%), and on average, participants were in their late 60s, with no signs of dementia (MMSE ≥ 29) or severe cognitive impairment (MoCA ≥ 25). Furthermore, the major medical conditions among participants were hypertension (~53%), hypercholesterolemia (~40%) and type 2 Diabetes (~9.5%). As expected, baseline demographics and clinical characteristics were balanced among groups.

Table 2. Baseline demographics and clinical characteristics

Variables	**M2 (n=61)**	**M4 (n=61)**
Demographics		
Age, yr, mean (SD)	67.4 (7.2)	67.6 (7.5)
Females, *n* (%)	46 (71.9)	44 (69.8)
Weight, kg, mean (SD)	80.8 (17.7)	80 (13.8)
Height, m, mean (SD)	1.65 (0.1)	1.65 (0.1)
BMI, kg/m^2, mean (SD)	29.7 (6.2)	29 (4.1)
HR, bpm, mean (SD)	71.7 (7)	72.38 (9.3)
MoCA, score, mean (SD)	25.6 (2.4)	25.3 (2.7)
MMSE, score, mean (SD)	29.2 (1)	29 (1.2)
Rec-FD, score, mean (SD)	3.21 (1.67)	2.97 (1.64)
Race, *n* (%)		
Caucasian	62 (98.4)	61 (96.8)
Black	1 (1.6)	1 (1.6)
South African	-	1 (1.6)
Medical history, *n* (%)		
Hypertension	32 (50)	36 (57.1)
Hypercholesterolemia	23 (35.9)	28 (44.4)
Type 2 diabetes	5 (7.8)	7 (11.1)
Myocardial infarction	4 (6.3)	5 (7.9)
Atrial fibrillation	-	3 (4.8)
Angina/coronary artery disease	1 (1.6)	2 (3.2)
Aneurysm	1 (1.6)	2 (3.2)
Former smoker	28 (44.4)	29 (46)
Current smoker	1 (1.6)	1 (1.6)
Outcomes		
CAC, $mm^2/mmHg\times10^{-1}$, mean (SD)	0.92 (0.37)	0.87 (0.29)
IMT, mm, mean (SD)	0.69 (0.16)	0.66 (0.14)
VO2max, ml/kg/min, mean (SD)	26.8 (8)	27.1 (7.9)
24 h SBP, mmHg, mean (SD)	129.6 (15.5)	126.43 (11.4)
24 h DBP, mmHg, mean (SD)	74.4 (8.4)	72.34 (8.2)
Day SBP, mmHg, mean (SD)	132 (15.6)	128.6 (11.37)
Day DBP, mmHg, mean (SD)	76.27 (8.55)	74.16 (8.55)
Night SBP, mmHg, mean (SD)	120.21 (17.4)	116.43 (18.95)
Night DBP, mmHg, mean (SD)	66.75 (9.1)	65.12 (8.32)

Abbreviations: M2, multiple-modality group; M4, multiple-modality, mind-motor group; BMI, body mass index; HR, resting heart rate; MoCA, Montreal Cognitive Assessment; MMSE, Mini-Mental Status Examination; CAC, carotid arterial compliance; IMT, intima-media thickness; VO2max, maximal oxygen consumption; 24 h SBP, systolic blood pressure; 24 h DBP, diastolic blood pressure; Day SBP, daytime systolic blood pressure; Day DBP daytime diastolic blood pressure; Night SBP, nighttime systolic blood pressure; Night DBP nighttime diastolic blood pressure; Rec-FD, frequency and duration of recreational physical activity.

2.1. Results of Comparisons between and within Groups

After the intervention period (i.e., at 24 weeks), no differences between groups were observed in any of the study outcomes. At 52 weeks, the M4 group demonstrated a greater VO2max compared to the M2 group (mean difference between groups: 2.39

ml/kg/min, 95% CI: 0.61 to 4.16, p = 0.009, **Figure 2 a**), with no differences in the remaining outcomes (see **Figures 2 and 3)**.

Although there were minimal to no differences between groups for the variables examined at either 24 or 52 weeks, there were numerous within-group changes over time (see **Table 3)**. In summary, the M4 group demonstrated a positive change in VO2max at 24 weeks (1.93 ml/kg/min, 95% CI: 0.82 to 3.05, p = 0.001) and 52 weeks (4.02 ml/kg/min, 95% CI: 2.71 to 5.32, p = 0.001) compared to baseline. Similarly, the M2 group increased VO2max at 24 weeks (2.28 ml/kg/min, 95% CI: 1.23 to 3.32, p = 0.000) and at 52 weeks (1.63 ml/kg/min, 95% CI: 0.43 to 2.83, p = 0.008) compared to baseline.

The M2 group also decreased 24 h SBP at 24 weeks compared to baseline (-2.31 mmHg, 95% CI: -4.61 to -0.01, p = 0.049); while the M4 group did not present any differences at any time points. On the other hand, the M4 group improved 24 h DBP compared to baseline (-1.6 mmHg, 95% CI: -3.03 to -0.17, p = 0.028) at 52 weeks; however, no changes were seen within the M2 group at any time points. Further, the M2 group showed increased Rec-FD at 24 weeks (0.48 score, 95% CI: 0.009 to 0.96, p = 0.46) whereas the M4 demonstrated similar results only at 52-weeks (0.71 score, 95% CI: 0.14 to 1.28). Additionally, no significant changes within groups were observed over time for CAC, IMT, Day SBP, Day DBP, Night SBP and Night DBP.

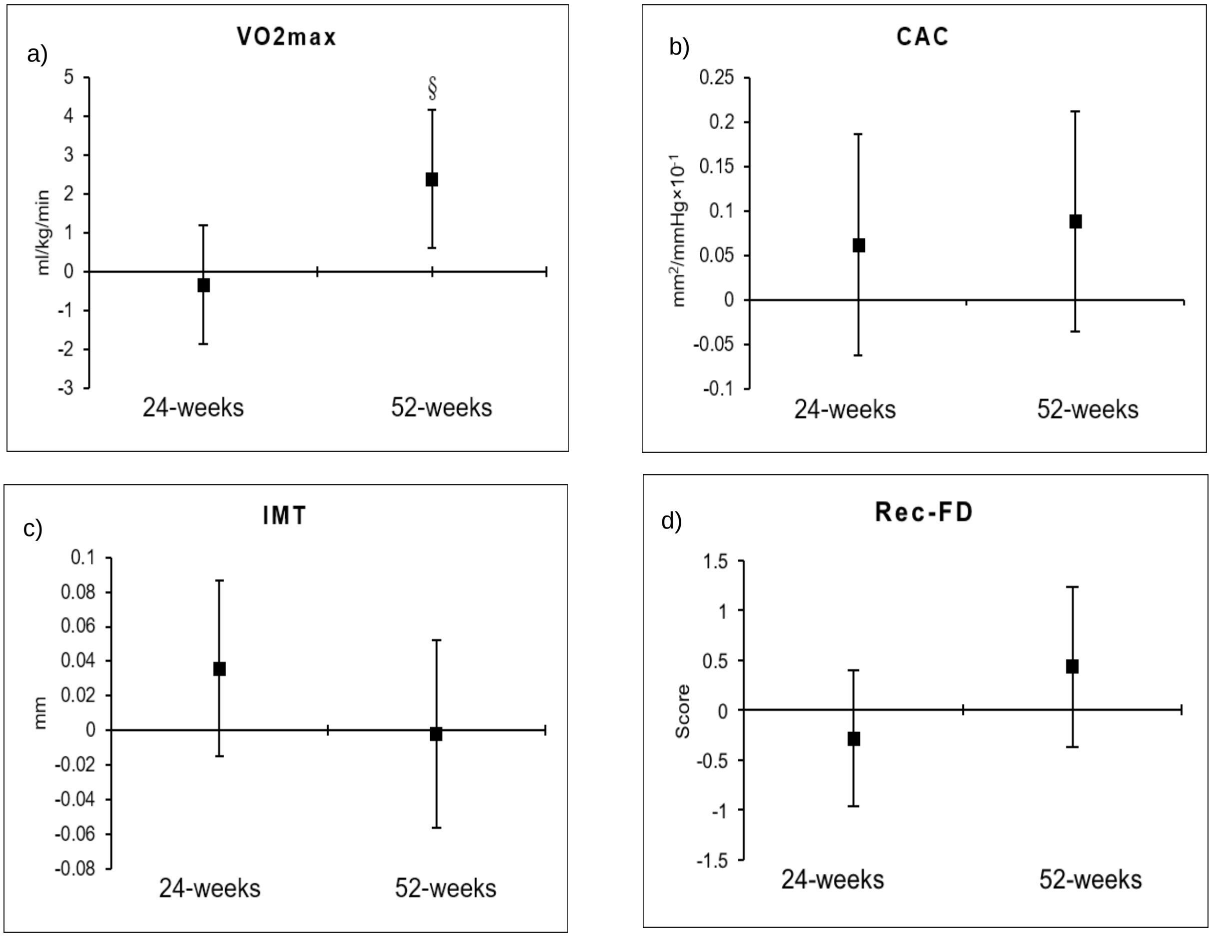

Figure 2. Difference between groups in mean change at 24 and 52 weeks using the M2 group as reference for: a) VO2max, b) CAC, c) IMT, and d) Rec-FD. Solid squares represent point estimates and bars represent associated 95% confidence intervals.

§Significant changes between groups at 52 weeks ($p = 0.009$) for VO2max.

Abbreviations: VO2max, predicted maximal oxygen consumption; CAC, carotid arterial compliance; IMT, intima-media thickness; and Rec-FD, frequency and duration of recreational physical activities.

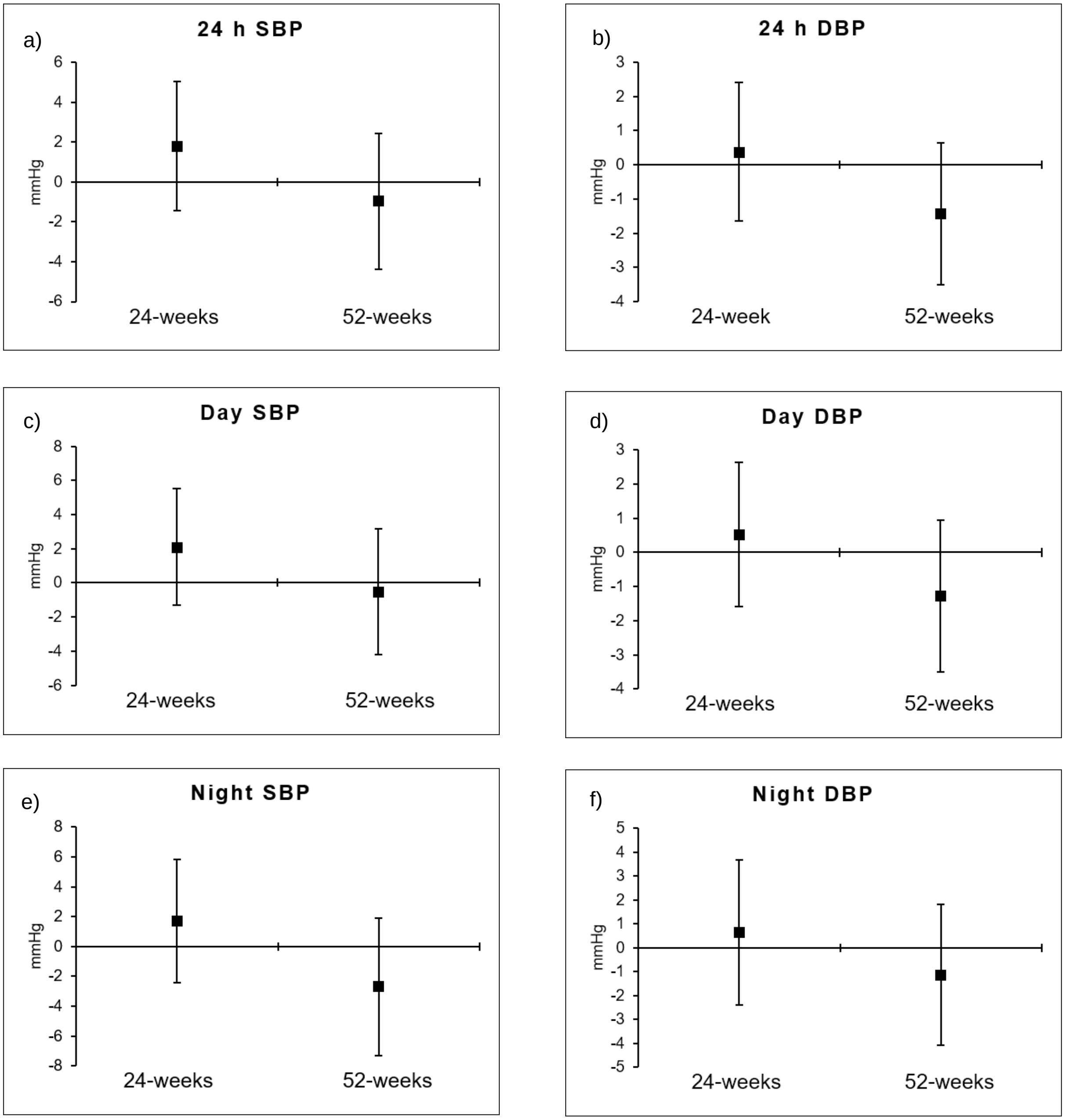

Figure 3. Difference between groups in mean change at 24 and 52 weeks using the M2 group as reference for: a) 24 h SBP, b) 24 h DBP, c) Day SBP, d) Day DBP, e) Night SBP, f) Night DBP. Solid squares represent point estimates and bars represent associated 95% confidence intervals.

Abbreviations: 24 h SBP, systolic blood pressure; 24 h DBP, diastolic blood pressure; Day SBP, daytime systolic blood pressure; Day DBP daytime diastolic blood pressure; Night SBP, nighttime systolic blood pressure; Night DBP nighttime diastolic blood pressure.

Table 3. Estimate and 95% CI of changes from baseline within M2 and M4 groups. [A]

Outcomes	**M2 (n=61)**		**M4 (n=61)**	
	Estimate	**95% CI**	**Estimate**	**95% CI**
CAC, $mm^2/mmHg \times 10^{-1}$				
24 weeks	0.005	-0.09 to 0.1	0.09	-0.005 to 0.19
52 weeks	-0.01	-0.09 to 0.07	0.4	-0.03 to 0.13
IMT, mm				
24 weeks	-0.005	-0.04 to 0.03	0.03	-0.005 to 0.06
52 weeks	0.01	-0.02 to 0.049	0.009	-0.02 to 0.04
VO2max, ml/kg/min §				
24 weeks	2.28	1.23 to 3.32	1.93	0.82 to 3.05
52 weeks	1.63	0.43 to 2.83	4.02	2.71 to 5.32
Rec-FD, score				
24 weeks	0.48	0.009 to 0.96 π	0.2	-0.27 to 0.69
52 weeks	0.28	-0.28 to 0.84	0.71	0.14 to 1.28 ¥
24 h SBP, mmHg				
24 weeks	-2.31	-4.61 to -0.01 †	-0.5	-2.76 to 1.75
52 weeks	-0.6	-3.06 to 1.86	-1.56	-3.91 to 0.78
24 h DBP, mmHg				
24 weeks	-1.05	-2.49 to 0.39	-0.67	-2.09 to 0.75
52 weeks	-0.17	-1.66 to 1.32	-1.6	-3.03 to -0.17 ‡
Day SBP, mmHg				
24 weeks	-2.58	-5.03 to -0.14	-0.48	-2.88 to 1.92
52 weeks	-0.8	-3.47 to 1.87	-1.33	-3.88 to 1.21
Day DBP, mmHg				
24 weeks	-1.12	-2.63 to 0.38	-0.6	-2.09 to 0.87
52 weeks	-0.07	-1.68 to 1.54	-1.35	-2.89 to 0.18
Night SBP, mmHg				
24 weeks	-1.89	-4.85 to 1.05	-0.19	-3.08 to 2.7
52 weeks	-0.41	-2.88 to 3.72	-2.26	-5.45 to 0.92
Night DBP, mmHg				
24 weeks	-0.89	-3.04 to 1.26	-.25	-2.38 to 1.87
52 weeks	-0.45	-2.57 to 1.66	-1.59	-3.64 to 0.44

Abbreviations: M2, multiple-modality group; M4, multiple-modality, mind-motor group; CAC, carotid arterial compliance; IMT, intima-media thickness; VO2max, maximal oxygen consumption; SPB, systolic blood pressure; DBP, diastolic blood pressure; 24 h DBP, diastolic blood pressure; Day SBP, daytime systolic blood pressure; Day DBP daytime diastolic blood pressure; Night SBP, nighttime systolic blood pressure; Night DBP daytime diastolic blood pressure; Rec-FD, frequency and duration of recreational activity.

Improvements from baseline in § VO2max (both groups, at 24 and 52 weeks), π Recreational FD (M2 at 24 weeks), ¥ Recreational FD (M4 at 52 weeks), † 24 h SBP (M2 group at 24 weeks), and ‡ 24 h DBP (M4 group at 52 weeks).

[A] Calculated from linear mixed effects regression models that included group (M2 or M4), time (baseline, 24 and 52 weeks), and group × time interaction terms. A total of ten models were run—corresponding to each mobility outcome listed in the first column.

4. Discussion

The objective of this study was to investigate the influence of multiple-modality exercise combined with mind-motor training (M4), compared to multiple-modality exercise alone (M4), on cardiovascular outcomes in a sample of community-dwelling older adults with self-reported cognitive complaints. In this study, we found that differences between groups were observed only at 52 weeks for VO2max, where the M4 group showed a greater improvement compared to the M2 group. In within-group analyses, both groups demonstrated positive changes from baseline in VO2max (M4 = 7.14%, M2 = 8.5%) to 24 weeks; however, no differences between groups were seen. Positive changes from baseline were also observed in the M2 group for 24 h SBP (1.78%) at 24 weeks, accompanied by ~16.5% increase in Rec-FD; whereas, the M4 group demonstrated improvements at 52 weeks in 24 h DBP (-2.21%) from baseline with a nearly 27% augmentation in Rec-FD. The changes observed in 24 h SBP and DBP did not lead to significant differences between groups at either 24 or 52 weeks, similar to the changes in Rec-FD.

Thus, the findings of the current study suggest that the addition of a mind-motor component to the standardized multiple-modality exercise intervention does not seem to promote any superior improvements in cardiovascular health fitness when compared to multiple-modality exercise alone. Furthermore, multiple-modality exercise showed positive changes in 24 h SBP and VO2max in community-dwelling older adults. The clinical and practical relevance of our findings are noteworthy, as increased VO2max (i.e., improved fitness) both groups and reduced systolic blood pressure in the M2 group is directly associated with reduced risk for all-cause and cardiovascular disease mortality in this population.(Ashor, Lara, Siervo, Celis-Morales, & Mathers, 2014; Blair et al., 1989; G. Huang et al., 2015; Guoyuan Huang, Gibson, Tran, & Osness, 2005; Joyner, 2000; Vanhees, De Sutter, et al., 2012)

4.1. Improvements in VO2max

The major finding of this study was the improvement in VO2max after the 24-week intervention period in both groups. Our results are in accordance with previous studies with regards to the increase in VO2max following an aerobic-based exercise intervention.(G. Huang et al., 2015; Guoyuan Huang, Gibson, et al., 2005; Vanhees, De Sutter, et al., 2012) In fact, a 16-week AE program (30 min/day at ≥ 60% VO2max, 3 days/week) has been shown to promote enhancement of aerobic capacity by 16-20% (approximately 3.8 ml/kl/min) among healthy older subjects.(Chodzko-Zajko et al., 2009; G. Huang et al., 2015; Guoyuan Huang, Gibson, et al., 2005; Guoyuan Huang, Shi, Davis-Brezette, & Osness, 2005) Furthermore, the addition of a ST component may have provided an additive benefit to VO2max in both groups. Previous work reported increased VO2max after a period of ST in older adults. In a study by Lovell et al., lower limb ST improved VO2max in 8% in elderly men.(D. I. Lovell et al., 2009) In another study, Hepple et al.(Hepple et al., 2015) reported an increase in VO2max by 7.9% in healthy older men who engaged in a 9-week ST program, followed by 9 weeks of AE training on a cycle ergometer, compared to an 18-week AE program at the same frequency and intensity. Likewise, two studies noticed a superior improvement in aerobic capacity in older adults who underwent ST.(Brentano et al., 2008; Vincent et al., 2002)

A higher cardiac output, characterized by an augmentation in blood flow, associated with increased capitalization and improvements in respiratory chain function, are considered possible mechanisms by which AE training leads to improvement in VO2max.(Freudenberger et al., 2016),(Bassett & Howley, 2000) Also, several physiological adaptations to ST may be accounted for improvements in aerobic capacity in older adults, such as augmentation of capillary density, myoglobin concentration, mitochondria content and enzyme activity in the working muscle.(Brentano et al., 2008; Cadore et al., 2010; Ozaki et al., 2013; Phillips et al., 2012) These physiological adaptations may lead to increase in arterial-venous oxygen difference (a-vO2), which associated with elevated exercise-induced blood flow, are the key-factors that of ST-induced improvements in VO2max.(Brentano et al., 2008; D. Lovell, 2010; Ozaki et al., 2013; Phillips et al., 2012)

Although aerobic- and resistance-based exercise interventions have been associated with increase in VO2max in older adults, the influence of multiple-modality exercise training in cardiorespiratory fitness measured via VO2max has not been largely explored. Indeed, some studies have investigated impact of multiple-modality exercise approach on cardiovascular fitness in the elderly(Capodaglio et al., 2005; Carvalho et al., 2009; Gudlaugsson et al., 2012; Nelson et al., 2004; Ratel et al., 2012; Rubenstein & et al., 2000; Sousa, Mendes, Abrantes, Sampaio, & Oliveira, 2013; F. Toraman & Şahin, 2004; N F Toraman & Ayceman, 2005; N Füsun Toraman, Erman, & Agyar, 2004); however, only a few have used VO2max as an outcome measure.(Ratel et al., 2012; Villareal et al., 2011) For example, Villareal et al.(Villareal et al., 2011) investigated the effects of a multicomponent exercise program (90 min/day, 3 days/week, for 12 weeks) to improve physical function in frail obese older adults. After the intervention period, 15% improvement in aerobic capacity (VO2max) was seen in the intervention group compared to the control group. In the same direction, Ratel and colleagues(Ratel et al., 2012) noticed 13% improvement in older adults following a 16-week program of similar characteristics. Regardless of the minor differences between the intervention methodology applied in the current study and the work conducted by Villareal et al.(Villareal et al., 2011) and Ratel et al.(Ratel et al., 2012), our results corroborate their findings.

Besides the work conducted by Villareal and colleagues,(Villareal et al., 2011) other studies investigating effects of multiple-modality exercise intervention in older adults have used an alternative assessment of cardiovascular fitness and aerobic capacity, i.e., the 6-min walking test (6MWT).(Capodaglio et al., 2005; Carvalho et al., 2009; Gudlaugsson et al., 2012; Nelson et al., 2004; Rubenstein & et al., 2000; Sousa et al., 2013; F. Toraman & Şahin, 2004; N F Toraman & Ayceman, 2005; N Füsun Toraman et al., 2004) Rubenstein et al.(Rubenstein & et al., 2000) administered a multiple-modality exercise intervention program in elderly men composed by ST, AE and 5 min of balance training once a week, for 12-weeks. Their findings indicated 10.42% improvement in the 6MWT following the program. Likewise, a 9-week multicomponent exercise training conducted by Toraman et al.(F. Toraman & Şahin, 2004; N F Toraman & Ayceman, 2005) led to 17.48% and 10.43% improvement in the same test in older adults aged at 67 and 80, respectively. The intervention program encompassed AE, followed by ST and flexibility exercises.(F. Toraman & Şahin, 2004)

Lastly, it is important to stress that the administration of different methodologies to assess cardiovascular fitness (VO2max via the STEP™ vs. 6MWT) between our study and the largest portion of the aforementioned studies limits the extent of our comparisons and understanding. However, not many studies involving older adults have explored the effects of multicomponent exercise interventions on cardiovascular fitness via VO2max, thereby, more RTCs are necessary.

4.2. Carotid Arterial Compliance and Blood Pressure

This study had hypothesized that positive changes in CAC and IMT would have occurred as result of the 24-week program. Further, we hypothesized that the M4 group would demonstrate improvements in a greater extent compared to the M2 group—however our results indicated otherwise.

Aerobic-based exercise interventions have successfully increased systemic and local CAC,(Maeda et al., 2008, 2009; Miyaki et al., 2009; Moreau, Donato, Seals, DeSouza, & Tanaka, 2003; Pescatello et al., 2004; Seals et al., 2008; Sugawara et al., 2009, 2004, Tanaka et al., 2000, 1998) which reflects in improved arterial health and reduced risk factors for cardiovascular diseases and all-cause mortality in older adults.(Seals et al., 2008) Although in the current study participants exercised aerobically at similar intensity (60-85% HRmax), exercise duration (20 min/day) and frequency (3 days/week) were remarkably inferior to those reported in previous studies.(Maeda et al., 2008, 2009; Miyaki et al., 2009; Seals et al., 2008; Sugawara et al., 2004; Tanaka et al., 2000) These factors suggest that exercise volume (duration and frequency), despite of intensity, might be a key-factor to improve arterial compliance in older adults.(Sugawara et al., 2004) However, a recent systematic review and meta-analysis(Ashor et al., 2014) indicated that AE intensity was rather more associated with improved arterial stiffness than exercise duration and frequency. Furthermore, the authors also noticed a tendency for a positive dose-response relationship between exercise intensity and cardiovascular health, meaning that high-intensity physical activity could benefit more cardiovascular health outcomes than low-intensity exercise.(Ashor et al., 2014)

Effects of combined AE and ST in CAC have not been fully explored. A study conducted by Cortez-Cooper et al. (Cortez-Cooper et al., 2008) investigated the effects of a 13-week ST program in relatively healthy older adults. In the same study, another group at equal age exercised in a combined intervention, integrating 2 days/week of similar ST plus aerobic training. After the intervention period, no changes were observed in CAC in either ST or combined exercise groups. Indeed, there is some evidence suggesting decrease in central arterial compliance associated with strength-based exercise interventions in young men.(Bertovic et al., 1999; Miyachi et al., 2003, 2004)

Aerobic exercise seems to attenuate age-related arterial stiffness and increase arterial compliance through improvements in artery function and structure.(Maeda et al., 2008, 2009; Sugawara et al., 2004) These improvements are understood as reduction of endogenous enothelin-1 plasma concentration and angiotensin-2 (endothelium-derived vasoconstrictors), and increased nitric oxide production (endothelium-derived vasodilator).(Maeda et al., 2008, 2009; Sugawara et al., 2004) Animal models have also demonstrated that the arteries of exercised animals had lower collagen and higher elastin than non-exercised ones, representing improved distensibility capacity of the vessel wall, leading to a better cardiovascular outcome.(Ashor et al., 2014) Nonetheless, the mechanisms underlying reduction in CAC as a result of ST in older adults remain unclear. Myichi and colleagues(Miyachi et al., 2004) proposed that ST-induced arterial stiffening in young men might be a consequence of acute intermittent elevations in arterial blood pressure during each exercise repetition, leading to changes in the arterial structure and function (e.g., endothelium dysfunction).(Miyachi et al., 2003, 2004) They also argue that, as ST is a strong stimulus to increase sympathetic nervous system activity, CAC might be affected by chronic restraint on the arterial wall via greater sympathetic adrenergic vasoconstrictor tone, hence, increasing arterial stiffness.(Failla et al., 1999; Miyachi et al., 2003, 2004)

From this perspective, it is possible to assume that the multi-modal aspect of the exercise training administered in our study (i.e., relatively low AE volume associated with a ST component) may have restricted improvements in CAC immediately after the training program in both groups. Our results are analogous to the findings described previously in the study conducted by Cortez-Cooper and colleagues.(Cortez-Cooper et al., 2008) Accordingly, in the systematic review and meta-analysis performed by Ashor et al.,(Ashor et al., 2014) studies investigating the influence of combined exercise interventions did not lead to any improvement in arterial stiffness.

Although in the current study only the M2 group demonstrated small reduction of 24 h SBP (2.31 mmHg) immediately after the exercise program, this finding is in accordance with previous research.(Pescatello et al., 2004) Undeniably, aerobic- and resistance-based exercise intervention reduces arterial blood pressure in normotensive and those with hypertension in the general population.(Kelley & Kelley, 2000; Pescatello et al., 2004) In older adults, however, there have been conflicting results from RTCs regarding the effectiveness of exercise training in reducing blood pressure.(Pescatello et al., 2004) In overall, AE interventions seem to be one of the most powerful non-pharmacological strategies to attenuate arterial blood pressure and reduce cardiovascular risk in this population.(Kelley & Kelley, 2000; Kelley & Sharpe Kelley, 2001) Although, our findings indicated modest reduction of approximately 1.8% in 24 h SBP following the exercise program, the minimal decline in arterial blood pressure has been associated with 5-14% reduced CVD incidence and 4% all-cause mortality.(Kelley & Kelley, 2000; Kelley & Sharpe Kelley, 2001; Pescatello et al., 2004; Sakuragi & Abhayaratna, 2010; Zieman et al., 2005)

To conclude, as previously stated, arterial stiffness is a precursor of isolated systolic hypertension later in life and is highly associated with the pathophysiological mechanisms for stroke and coronary heart disease in older adults.(Sakuragi & Abhayaratna, 2010; Zieman et al., 2005) A reduced systolic blood pressure—as seen in the M2 group— might be an indicator of improved cardiovascular functioning and health and improved arterial compliance, following a multiple-modality exercise program; even though the findings of this study did not indicate direct improvements in CAC or IMT measurements.

4.3. Follow-up Results

It is remarkable that after the 28-week non-contact follow-up, the M4 group demonstrated improvement VO2max and reduced 24 h DBP. Firstly, this suggests that the M4 group potentially remained more physically active following the intervention. This assumption can be supported taking into account the slightly change—although significant—in 24 h DBP (-2.31%) and greater VO2max improvement (14.83%) at 52 weeks. Actually, everyone who participated in our study received orientation to continue exercising after the intervention endpoint; however, no additional support or orientation was provided by the researchers, and no contact was made with the participants until their final assessments. In fact, after concluding the primary analyses in this study, we decided to look for changes in the levels of recreational physical activities (Rec-FD; e.g., walking, bicycling, swimming) at 24 and 52 weeks using the Phone-FITT questionnaire. As such, we noticed that the M4 group had shown nearly 27% increment in Rec-FD after the follow-up assessments compared to baseline. Secondly, we could attribute these superior changes in the M4 group to the mind-motor component that was administered in the sessions; nonetheless, this assumption is unlikely be true, especially due the following reasons: a) no differences between groups were observed immediately after intervention in any of the variables (except 24 h DBP in M2), which suggests that both programs had equal or no impact on the study outcomes; b) participants in the M4 group were not provided with the SSE mat to keep practicing during the follow-up period, therefore, no influence of the mind-motor training during the 28-week follow-up can be inferred.

4.4. Study Limitations

The absence of a non-intervention control group is a major limitation of this study, as we could have seen significant difference in the remaining variables if the between-group comparisons had included a group of participants who had not taken part in any of the intervention programs. Another limitation relates to the CAC and IMT measurements; although participants were provided with very specific instructions 24 hours prior to the carotid arterial ultrasonography, compliance to these recommendations was not monitored or enforced. There were also limitations regarding the power of our statistical analyses, particularly due to the fact that our sample size was calculated based on an effect size associated with a different outcome (i.e., global cognitive functioning)—this could be the reason why in some instance, no differences between and within groups were found in the remaining variables. Also, AE intensity was controlled based on target HR defined prior to the intervention and participants were oriented to monitor their own target HR; as such, the AE intensity relied on participants voluntarily and accurately assessing their HR, which could have created room for underestimations. Finally, we recruited high functioning, community-dwelling older adults with self-reported subjective cognitive complaints, living in Woodstock, ON, Canada, predominantly Caucasian and females. Thus, our findings may not be generalized to other populations, including older adults with severe cognitive and/or mobility disorders, different ethnic and cultural backgrounds, social and economic status.

5. Conclusion

This study investigated the influence of multiple-modality exercise combined with mind-motor training compared to multiple-modality exercise alone on cardiovascular outcomes, in older adults at risk for cognitive impairment. Our results suggest that the addition of a mind-motor component to the standardized multiple-modality exercise intervention does not seem to promote additional benefits on cardiovascular outcomes in comparison to multiple-modality exercise alone. Furthermore, multiple-modality exercise seems to promote additive benefits to systolic blood pressure in community-dwelling older adults. The clinical and practical relevance of our findings are noteworthy, as improved VO2max and decreased SBP is directly associated with reduced risk for cognitive impairment, as well as, all-cause and cardiovascular disease mortality in this population. Nonetheless, more rigorously RCTs should be conducted in order to explore whether the benefits of multiple-modality exercise programs encompassing mind-motor training components (e.g., SSE) can promote benefits beyond to cardiovascular fitness, such as global cognitive functioning in older adults living with or without cognitive impairment and dementia.

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Conflict of interest

The study authors have no relevant conflicts of interest to report.

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