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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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1 **Multiple-modality exercise and mind-motor training to improve cardiovascular health**
2 **and fitness in older adults at risk for cognitive impairment: a randomized controlled**
3 **trial**

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Abstract

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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

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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1 greater VO₂max (ml/kg/min) compared to the M2 group (mean difference: 2.39, 95% CI: 0.
2 61 to 4.16, p=0.009). Within-group analysis indicated that the M4 group demonstrated a
3 positive change in VO₂max at 24-weeks (mean change: 1.93, 95% CI: 0.82 to 3.05,
4 p=0.001) and 52-weeks (4.02, 95% CI: 2.71 to 5.32, p=0.001). Similarly, the M2 group
5 increased VO₂max at 24-weeks (2.28, 95% CI: 1.23 to 3.32, p<0.001) and 52-weeks (1.63,
6 95% CI: 0.43 to 2.83, p = 0.008). Additionally, the M2 group decreased 24 h SBP (mmHg) at
7 24-weeks (-2.31, 95% CI: -4.61 to -0.01, p=0.049); whereas the M4 group improved 24 h
8 DBP (-1.6, 95% CI: -3.03 to -0.17, p=0.028) at 52-weeks. **Conclusion:** Mind-motor training
9 associated with multiple-modality exercise can positively impact cardiovascular fitness to the
10 same extent as multiple-modality exercise alone.

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

13

1 **1. Introduction**

2 Ischemic heart disease and stroke account for approximately 25% of deaths
3 worldwide per year. (“WHO | Projections of mortality and causes of death, 2015 and
4 2030,” 2014) The World Health Organization (WHO) estimates that by 2030, 34.8% of
5 the world population will be affected by the progressive expansion of cardiovascular
6 diseases (CVD). (“WHO | Projections of mortality and causes of death, 2015 and 2030,”
7 2014) Older adults are at increased risk for CVD, (Remsberg & Siervogel, 2003) and this
8 risk can be partially attributed to age-related arterial stiffening, reduced arterial
9 compliance and reduced cardiovascular fitness. (Sakuragi & Abhayaratna, 2010;
10 Tanaka, DeSouza, & Seals, 1998)

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

29 In the past decades, several studies have reported a positive relationship
30 between high physical activity levels and improved arterial compliance (i.e., increased

1 arterial elasticity).(Cameron & Dart, 1994; Cameron, Rajkumar, Kingwell, Jennings, &
2 Dart, 1999; Monahan, Dinunno, et al., 2001; Monahan, Tanaka, Dinunno, & Seals, 2001;
3 Otsuki et al., 2006; Tanaka et al., 2000, 1998) Regular aerobic-based exercise is a non-
4 pharmacological strategy that seems to attenuate and partially reverse age-induced
5 arterial stiffening by increasing arterial compliance(Cameron & Dart, 1994; Lu, Hui-
6 Chan, & Tsang, 2013a, 2013b; Maeda et al., 2008; Miyaki et al., 2009; Nickel, Acree, &
7 Gardner, 2011; Parnell, Holst, & Kaye, 2002; Seals, Desouza, Donato, & Tanaka, 2008;
8 Sugawara et al., 2009; Sugawara, Inoue, Hayashi, Yokoi, & Kono, 2004; Tanaka et al.,
9 2000; Vanhees, Rauch, et al., 2012; Villareal, Smith, Sinacore, Shah, & Mittendorfer,
10 2011) and VO₂max,(G. Huang et al., 2015; Vanhees, De Sutter, et al., 2012; Vanhees,
11 Rauch, et al., 2012) thereby, leading to improved health outcomes. Although, resistance
12 training also promotes improvements in VO₂max,(Brentano et al., 2008; GR, JP, & MM,
13 2004; Hepple et al., 2015; D. Lovell, 2010; D. I. Lovell, Cuneo, & Gass, 2009; Ozaki,
14 Loenneke, Thiebaud, & Abe, 2013; Phillips et al., 2012; Vincent, Braith, Feldman,
15 Kallas, & Lowenthal, 2002) research to date suggests that this modality does not seem
16 to promote any positive impact on arterial compliance.(Bertovic et al., 1999; Cortez-
17 Cooper et al., 2008; Miyachi et al., 2003, 2004)

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

1 most effectively address cardiovascular, functional and cognitive concerns in older
2 populations. As such, rigorously designed randomized controlled trials (RCTs) are
3 necessary.

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

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

23 **2. Materials and Methods**

24 **2.1. Participants**

25 Community-dwelling older adults living in Woodstock, ON, Canada, were invited
26 to participate in this study. Details about participant recruitment can be found
27 elsewhere.(Gregory et al., 2016) Briefly, older adults aged 55 years or older were
28 recruited through advertisements, health fairs and posters at local businesses. The
29 inclusion criteria encompassed the following items: a) be aged 55 years or older; b)
30 answer 'yes' to the question: "do you feel like your memory or thinking skills have gotten

1 worse recently?"; and c) have preserved Instrumental Activities of Daily Living (i.e.,
2 reached maximum score in the Lawton-Brody Instrumental Activities of Daily Living
3 scale [8/8]). The exclusion criteria were: a) severe cognitive impairment (i.e., self-
4 reported diagnosis of dementia and/or score < 24 on the Mini-Mental State
5 Examination); b) major depression (i.e., score \geq 16 on the Centre for Epidemiologic
6 Studies Depression scale combined with clinical judgment by the study physician); c)
7 recent history of severe cardiovascular conditions (e.g., stroke, myocardial infarction,
8 end stage congestive heart failure, etc.); d) significant orthopedic condition (e.g., severe
9 osteoarthritis); e) any neurological and/or psychiatric disorders; f) resting blood pressure
10 > 180/100 mmHg and/or < 100/60 mmHg (unsafe for exercise); g) unable to
11 comprehend study letter of information; and lastly, i) any other reasons that could
12 significantly impact participation in the exercise program.

13 **2.2. Study Design**

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

21

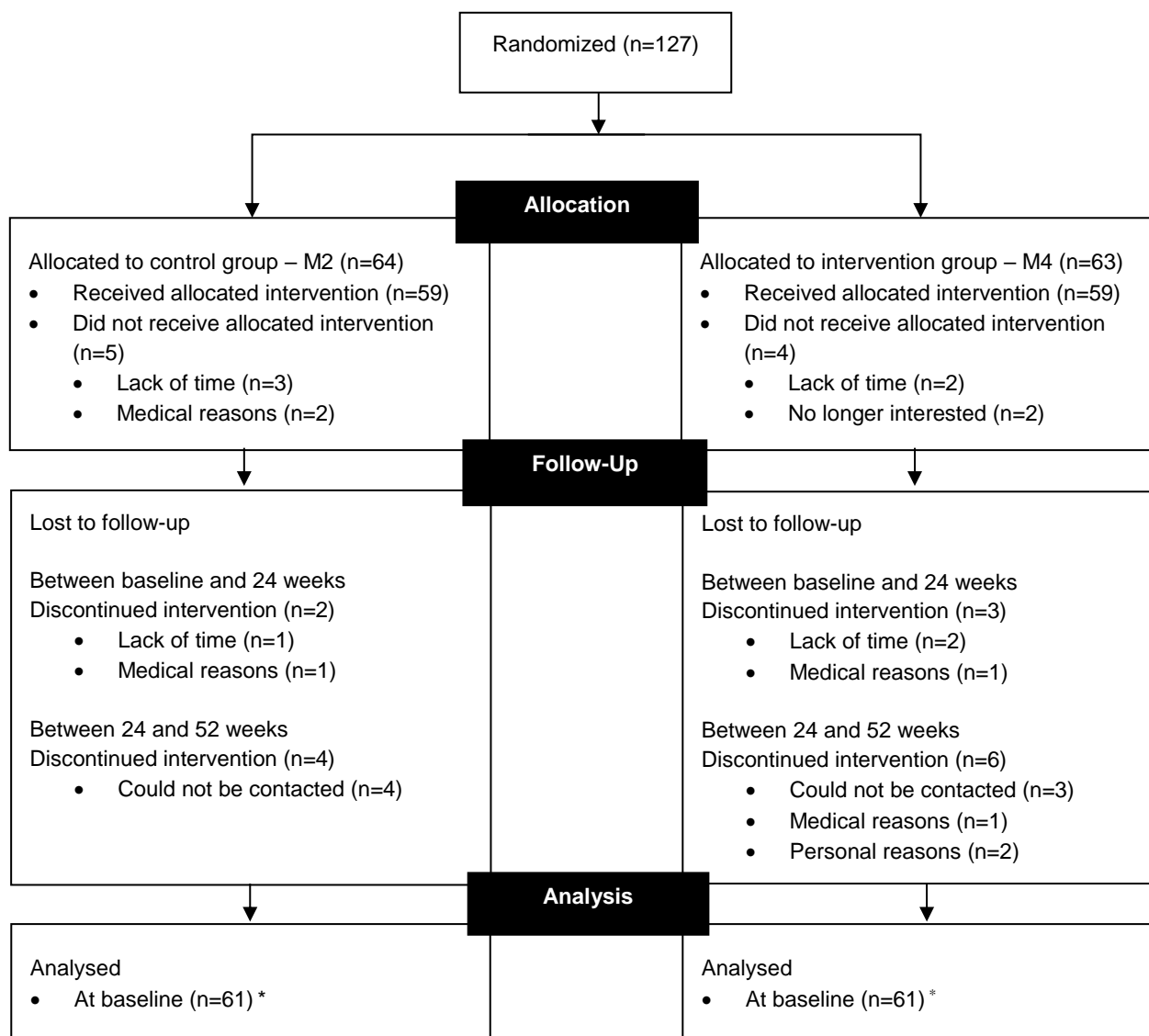


Figure 1. Diagram illustrating flow of participants in the 24-week randomized controlled trial with a 28-week follow-up period. *4 participants were excluded from analysis because the assessments could not be completed (M2, n=2; M4 n=2).

1

2 2.3. Exercise Intervention

3 Participants exercised 60 minutes per day, 3 days per week, for 24 weeks at the
 4 community location. The exercise program was carried out by certified Seniors' Fitness
 5 Instructors (Canadian Centre for Activity and Aging), who received adequate training on
 6 the SSE protocol before the beginning of the program. Both groups equally received
 7 standardized exercise training, described as follows: 5 min aerobic warm-up, 20 min
 8 moderate-to-vigorous-intensity AE, 5 min aerobic cool down, followed by 10 min ST. In

1 addition to the standardized exercise training, the M4 group underwent 15 min of mind-
2 motor training (i.e. SSE), whereas the M2 group underwent 15 min of training that
3 involved balance, range of motion and breathing exercises (i.e., types of exercise with
4 evidence that they benefit cognition). Error! Reference source not found. illustrates the
5 training protocol in detail. Aerobic exercise intensity was prescribed via target heart rates
6 (HR) determined prior to the beginning of the program. During the AE portion of each
7 session, participants were encouraged to keep their HR at 65-85% of predicted
8 maximum heart rate (HRmax) and/or at a rating of 5-8 on the 10-point modified Borg
9 Rating of Perceived Exertion (RPE) scale. Monitoring of target HR during each session
10 was conducted part way through and after the aerobic component. Participants were
11 instructed to record HR and RPE immediately after each monitoring in a training log
12 provided by the research team. The Step Test and Exercise Prescription (STEP™)
13 tool(Stuckey, Knight, & Petrella, 2012) was used to predict HRmax (see methods section
14 **2.5.3** for details). Target HR were recalculated at 12-weeks via the STEP™ to adjust for
15 progression in the aerobic training.

16 **2.3.1. The Square Stepping Exercise (SSE) Protocol**

17 The SSE is a group-based activity performed on a gridded floor mat (2.5 m × 1
18 m), containing 10 rows with 4 equalized squares per row.(Shigematsu, 2014) The
19 training protocol entails the reproduction of complex foot placements (i.e., stepping
20 patterns) on the mat, previously performed by an instructor. Participants are expected to
21 visualize and memorize the stepping pattern demonstrated by the instructor on the mat,
22 and subsequently, attempt to reproduce the same stepping pattern. There are more than
23 200 stepping patterns, which are classified in 3 categories (i.e., beginner, intermediate
24 and advanced) involving lateral, backwards, forward and diagonal steps across the mat.
25 The complexity of the patterns are given based on the amount of steps per pattern
26 (varying from 2 to 16 steps), as well as, foot placement ordering and directions. In order
27 to promote a positive social atmosphere, participants were encouraged to assist each
28 other during this component of the class. To keep tracking of participants' progression
29 throughout the program, instructors recorded information of the last pattern performed at
30 the end of each session; thus, participants started at the pattern where they left off at

- 1 previous class, advancing through the SSE pattern categories gradually, over the 24-
 2 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)
<p>Warm-up (5 minutes)</p> <ul style="list-style-type: none"> • Light aerobics • Dynamic range of motion of the major joints 	<p>Warm-up (5 minutes)</p> <ul style="list-style-type: none"> • Light aerobics • Dynamic range of motion of the major joints
<p>Aerobic Exercise (20 Minutes)</p> <ul style="list-style-type: none"> • 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. 	<p>Aerobic Exercise (20 Minutes)</p> <ul style="list-style-type: none"> • 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.
<p>Aerobic Cool Down (5 minutes)</p> <ul style="list-style-type: none"> • Safely bringing heart rates down 	<p>Aerobic Cool Down (5 minutes)</p> <ul style="list-style-type: none"> • Safely bringing heart rates down
<p>Strength Training (10 minutes)</p> <ul style="list-style-type: none"> • Therabands, wall or chair exercises, core strengthening • Day 1 – Upper body focus • Day 2– Lower body focus • Day 3 – Core focus 	<p>Strength Training (10 minutes)</p> <ul style="list-style-type: none"> • Therabands, wall or chair exercises, core strengthening • Day 1 – Upper body focus • Day 2– Lower body focus • Day 3 – Core focus
<p>Balance, Range of Motion & Breathing (15 minutes)</p> <ul style="list-style-type: none"> • Keep HR below target zone • Dynamic, static and functional balance • Breathing and relaxation exercises • Finger exercises • Range of motion (e.g., arm circles) 	<p>Mind-Motor Training (15 minutes)</p> <ul style="list-style-type: none"> • Keep HR below target zone • Progressive, group-based, Square Stepping Exercise (SSE) • Stretching (5 minutes) Stretching (5 minutes)
<p>Total: 60 min exercise intervention</p>	<p>Total: 60 min exercise intervention</p>

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).

1 **2.4. Study Outcomes**

2 In this study, we examined the secondary outcomes from a larger RCT(Gregory
3 et al., 2016), which encompassed changes between and within groups at 24 weeks
4 (intervention endpoint) and 52 weeks (study endpoint) in carotid arterial compliance
5 (CAC), intima-media thickness (IMT), predicted maximal oxygen consumption
6 (VO2max), 24 h systolic blood pressure (24 h SBP), and 24 h diastolic blood pressure
7 (24 h DBP), daytime systolic blood pressure (Day SBP), daytime diastolic blood
8 pressure (Day DBP), nighttime systolic blood pressure (Night SBP), and nighttime
9 diastolic blood pressure (Night DBP).

10 **2.5. Assessments**

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

21 **2.5.1. 24-hour Ambulatory Blood Pressure Monitoring**

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

1 24-hour period. A minimum of 28 successful readings (70%) were required for statistical
2 analysis.

3 **2.5.2. Common Carotid Arterial Ultrasonography**

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

21 To determine CAC ($\text{mm}/\text{mmHg}^2 \times 10^{-1}$), we applied the following equation: $\text{CAC} =$
22 $[\pi \cdot (D_{\text{max}}/2)^2 - \pi \cdot (D_{\text{min}}/2)^2] / \Delta P$, where D_{max} is the systolic carotid arterial
23 diameter, D_{min} is the diastolic carotid arterial diameter and ΔP is the automated supine
24 brachial pulse pressure. (Sugawara et al., 2004) By subtracting the carotid arterial lumen
25 diameter from the arterial diameter at diastole, we were able to determine IMT (mm).
26 Two technicians were designated to perform and analyze all ultrasound images, with the
27 same technician performing all measurements on a given participant whenever it was
28 possible. To ensure inter-rater consistency of measurements, the level of agreement
29 between technicians was tested by analyzing interclass correlation coefficient (ICC),
30 using data collected by both technicians on 15 participants. A two-way random effects

1 model was applied to calculate the ICC, which indicated a high level of agreement
2 between assessors for average measures (ICC: 0.88, 95% confidence interval: 0.70 to
3 0.94, $p < 0.001$).

4 **2.5.3. Predicted Maximal Oxygen Consumption (VO₂max)**

5 Following the common carotid arterial ultrasonography, participants performed
6 the predicted VO₂max test via STEP™ tool.(Stuckey et al., 2012) The test involved
7 participants walking up and down a set of 2 standardized steps (20 cm), twenty times.
8 Participants were instructed to perform the task at a self-selected pace and were
9 supervised by an assessor throughout the test. The time to perform the task and heart
10 rate, immediately after test completion, were recorded and applied to the equation:
11 $VO_{2max} = 3.9 + (1511/time) \cdot (O_2 \text{ pulse} \cdot 0.124) - (age \cdot 0.032) - (sex \cdot 0.633)$, where
12 *time* is the time to complete the task (s); *O₂ pulse* is the quotient of body mass (kg)
13 divided by heart rate (bpm); *age* is the participant's age (yr); and *sex* is 1 for male and 2
14 female.(Stuckey et al., 2012)

15 **2.6. Sample Size Calculations**

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

26 **2.7. Statistical Analysis**

27 Analyses were performed according to an intent-to-treat approach, including all
28 randomized participants (according to their random allocation), regardless of compliance
29 with the program and follow-up assessments. Descriptive exploratory statistics were

1 conducted to assess data normality and homogeneity of distributions. Assumptions for
2 each parametric test were properly tested prior to data treatment and variables were
3 transformed as necessary. We applied linear mixed models for repeated measurements
4 to assess differences between groups in mean change from baseline at 24 and 52
5 weeks.(Fitzmaurice, Laird, & Ware, 2011) The terms included in the model were: group
6 (treatment), time and group (treatment) × time. Time was modeled categorically using
7 two indicator variables representing each time point. Furthermore, the model was also
8 used to analyze differences within M4 and M2 groups from baseline to 24 and 52 weeks.
9 Significant changes were assessed using an alpha of 0.05; therefore, any two-sided p-
10 values less than 0.05 were claimed as significant. Interpretation of study results were
11 primarily based on mean estimation and associated 95% confidence interval (CI). The
12 analyses were performed using the IBM® SPSS® Statistics, Version 23 for Windows 10.

13 **3. Results**

14 **3.1. Enrollment, Randomization and Adherence**

15 This study was conducted between January 13, 2014 and March 14, 2016.
16 Participants were enrolled in 4 waves of assessments and intervention over a period of
17 14 months. During the screening process, 169 individuals were assessed for eligibility;
18 11 did not meet the inclusion criteria and 31 declined to participate. Thus, 127
19 participants were included and randomized to either the M2 (n=64) or M4 (n=63) groups,
20 **Figure 1.**

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

26 **3.2. Baseline Characteristics and Demographic Information**

27 Baseline data regarding participant characteristics, demographic & clinical
28 information, and study outcomes are presented in **Table 2.** Briefly, approximately 70%
29 (90) participants were female, predominantly white (97.6%), and on average,

1 participants were in their late 60s, with no signs of dementia (MMSE \geq 29) or severe
2 cognitive impairment (MoCA \geq 25). Furthermore, the major medical conditions among
3 participants were hypertension (~53%), hypercholesterolemia (~40%) and type 2
4 Diabetes (~9.5%). As expected, baseline demographics and clinical characteristics were
5 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, <i>n</i> (%)	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, <i>n</i> (%)		
Caucasian	62 (98.4)	61 (96.8)
Black	1 (1.6)	1 (1.6)
South African	-	1 (1.6)
Medical history, <i>n</i> (%)		
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×10 ⁻¹ , mean (SD)	0.92 (0.37)	0.87 (0.29)
IMT, mm, mean (SD)	0.69 (0.16)	0.66 (0.14)
VO ₂ max, 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.

1

2 2.1. Results of Comparisons between and within Groups

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

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

3 Although there were minimal to no differences between groups for the variables
4 examined at either 24 or 52 weeks, there were numerous within-group changes over
5 time (see **Table 3**). In summary, the M4 group demonstrated a positive change in
6 VO₂max at 24 weeks (1.93 ml/kg/min, 95% CI: 0.82 to 3.05, $p = 0.001$) and 52 weeks
7 (4.02 ml/kg/min, 95% CI: 2.71 to 5.32, $p = 0.001$) compared to baseline. Similarly, the
8 M2 group increased VO₂max at 24 weeks (2.28 ml/kg/min, 95% CI: 1.23 to 3.32, $p =$
9 0.000) and at 52 weeks (1.63 ml/kg/min, 95% CI: 0.43 to 2.83, $p = 0.008$) compared to
10 baseline.

11 The M2 group also decreased 24 h SBP at 24 weeks compared to baseline (-2.31
12 mmHg, 95% CI: -4.61 to -0.01, $p = 0.049$); while the M4 group did not present any
13 differences at any time points. On the other hand, the M4 group improved 24 h DBP
14 compared to baseline (-1.6 mmHg, 95% CI: -3.03 to -0.17, $p = 0.028$) at 52 weeks;
15 however, no changes were seen within the M2 group at any time points. Further, the M2
16 group showed increased Rec-FD at 24 weeks (0.48 score, 95% CI: 0.009 to 0.96, $p =$
17 0.46) whereas the M4 demonstrated similar results only at 52-weeks (0.71 score, 95%
18 CI: 0.14 to 1.28). Additionally, no significant changes within groups were observed over
19 time for CAC, IMT, Day SBP, Day DBP, Night SBP and Night DBP.

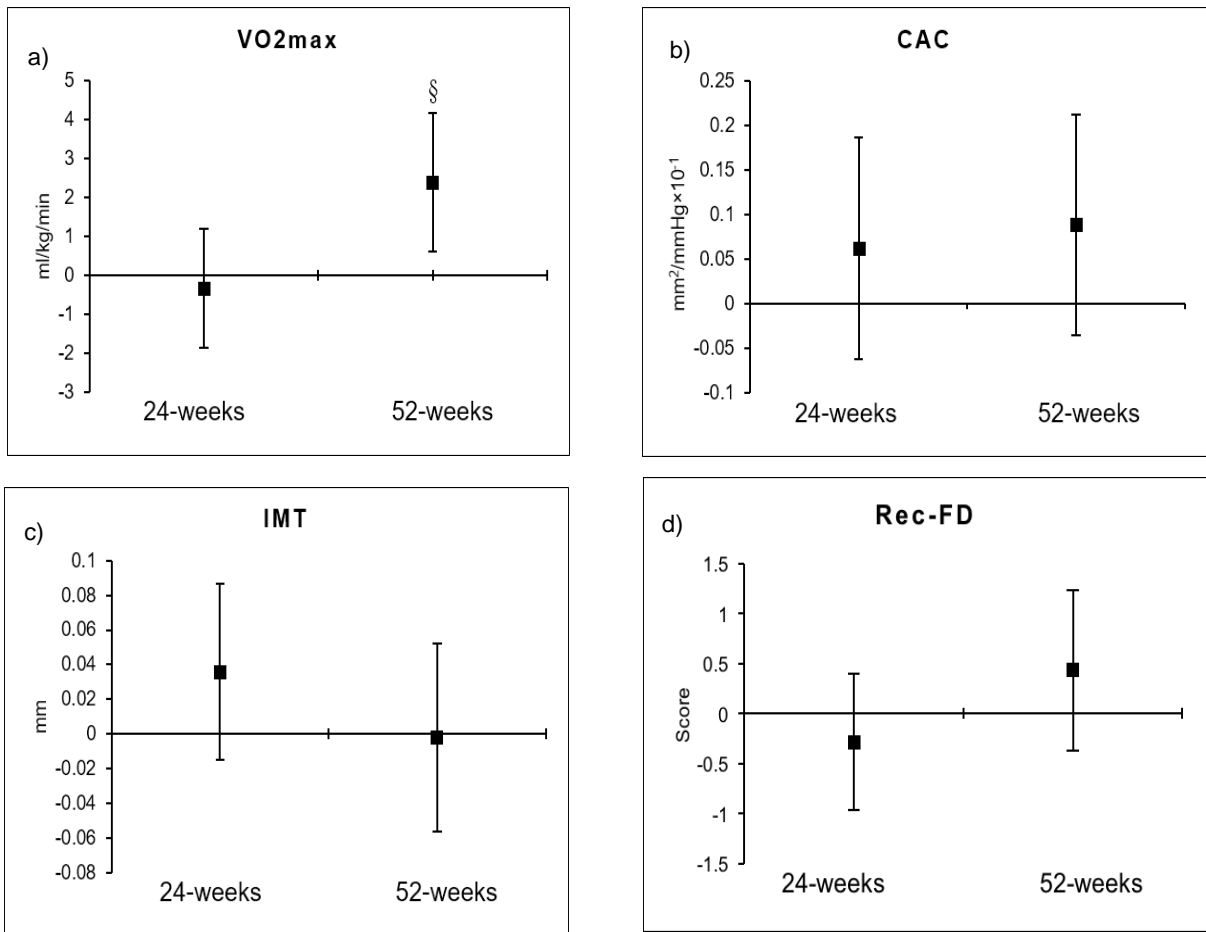


Figure 2. Difference between groups in mean change at 24 and 52 weeks using the M2 group as reference for: a) VO2max, b) CAC, c) IMT, and d) Rec-FD. Solid squares represent point estimates and bars represent associated 95% confidence intervals.

§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.

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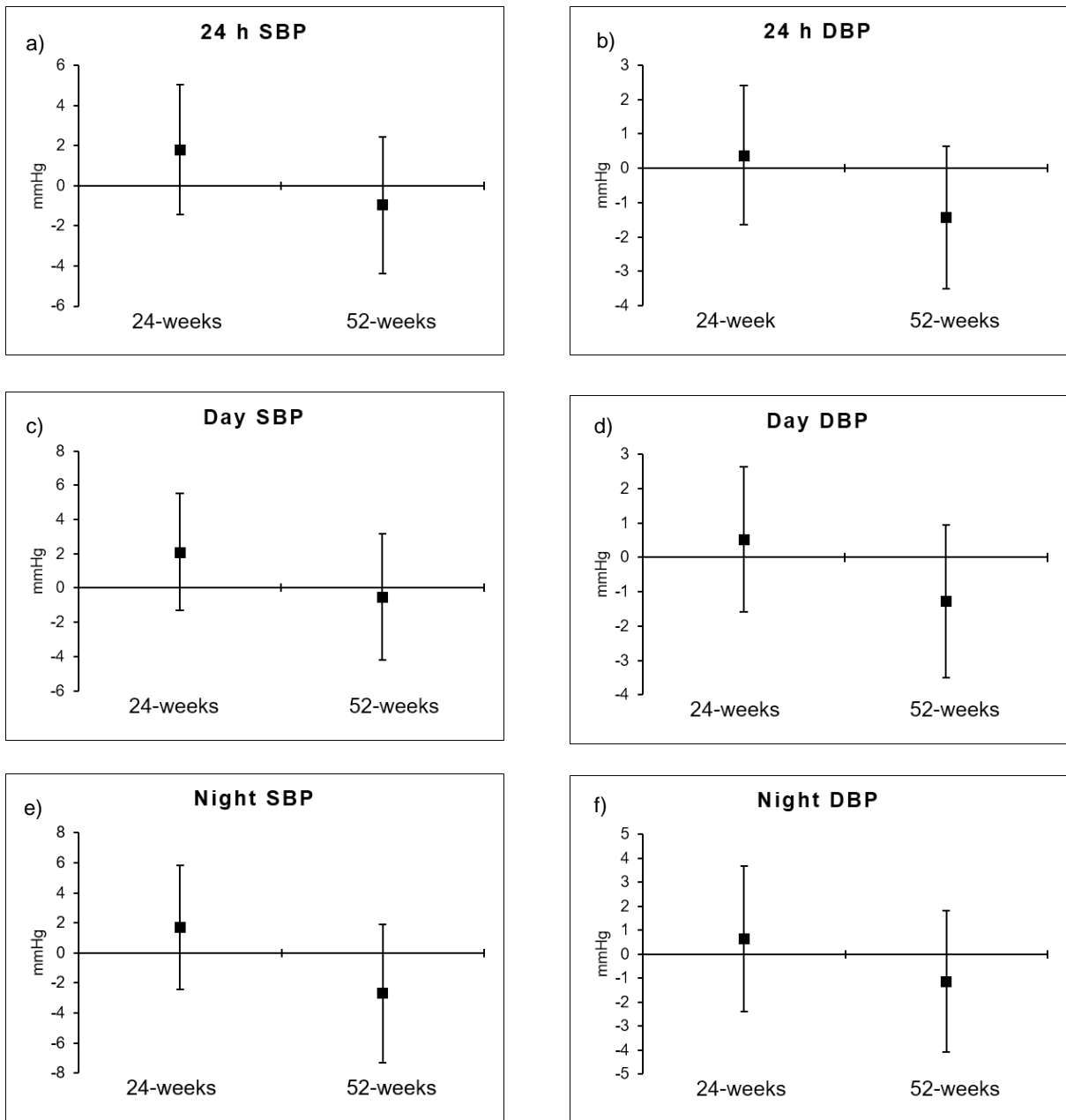


Figure 3. Difference between groups in mean change at 24 and 52 weeks using the M2 group as reference for: a) 24 h SBP, b) 24 h DBP, c) Day SBP, d) Day DBP, e) Night SBP, f) Night DBP. Solid squares represent point estimates and bars represent associated 95% confidence intervals.

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×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
VO ₂ max, 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.

1

2

1 **4. Discussion**

2 The objective of this study was to investigate the influence of multiple-modality
3 exercise combined with mind-motor training (M4), compared to multiple-modality
4 exercise alone (M4), on cardiovascular outcomes in a sample of community-dwelling
5 older adults with self-reported cognitive complaints. In this study, we found that
6 differences between groups were observed only at 52 weeks for VO₂max, where the M4
7 group showed a greater improvement compared to the M2 group. In within-group
8 analyses, both groups demonstrated positive changes from baseline in VO₂max (M4 =
9 7.14%, M2 = 8.5%) to 24 weeks; however, no differences between groups were seen.
10 Positive changes from baseline were also observed in the M2 group for 24 h SBP
11 (1.78%) at 24 weeks, accompanied by ~16.5% increase in Rec-FD; whereas, the M4
12 group demonstrated improvements at 52 weeks in 24 h DBP (-2.21%) from baseline with
13 a nearly 27% augmentation in Rec-FD. The changes observed in 24 h SBP and DBP did
14 not lead to significant differences between groups at either 24 or 52 weeks, similar to the
15 changes in Rec-FD.

16 Thus, the findings of the current study suggest that the addition of a mind-motor
17 component to the standardized multiple-modality exercise intervention does not seem to
18 promote any superior improvements in cardiovascular health fitness when compared to
19 multiple-modality exercise alone. Furthermore, multiple-modality exercise showed
20 positive changes in 24 h SBP and VO₂max in community-dwelling older adults. The
21 clinical and practical relevance of our findings are noteworthy, as increased VO₂max
22 (i.e., improved fitness) both groups and reduced systolic blood pressure in the M2 group
23 is directly associated with reduced risk for all-cause and cardiovascular disease mortality
24 in this population.(Ashor, Lara, Siervo, Celis-Morales, & Mathers, 2014; Blair et al.,
25 1989; G. Huang et al., 2015; Guoyuan Huang, Gibson, Tran, & Osness, 2005; Joyner,
26 2000; Vanhees, De Sutter, et al., 2012)

27 **4.1. Improvements in VO₂max**

28 The major finding of this study was the improvement in VO₂max after the 24-
29 week intervention period in both groups. Our results are in accordance with previous
30 studies with regards to the increase in VO₂max following an aerobic-based exercise

1 intervention.(G. Huang et al., 2015; Guoyuan Huang, Gibson, et al., 2005; Vanhees, De
2 Sutter, et al., 2012) In fact, a 16-week AE program (30 min/day at $\geq 60\%$ VO₂max, 3
3 days/week) has been shown to promote enhancement of aerobic capacity by 16-20%
4 (approximately 3.8 ml/kg/min) among healthy older subjects.(Chodzko-Zajko et al., 2009;
5 G. Huang et al., 2015; Guoyuan Huang, Gibson, et al., 2005; Guoyuan Huang, Shi,
6 Davis-Brezette, & Osness, 2005) Furthermore, the addition of a ST component may
7 have provided an additive benefit to VO₂max in both groups. Previous work reported
8 increased VO₂max after a period of ST in older adults. In a study by Lovell et al., lower
9 limb ST improved VO₂max in 8% in elderly men.(D. I. Lovell et al., 2009) In another
10 study, Hepple et al.(Hepple et al., 2015) reported an increase in VO₂max by 7.9% in
11 healthy older men who engaged in a 9-week ST program, followed by 9 weeks of AE
12 training on a cycle ergometer, compared to an 18-week AE program at the same
13 frequency and intensity. Likewise, two studies noticed a superior improvement in aerobic
14 capacity in older adults who underwent ST.(Brentano et al., 2008; Vincent et al., 2002)

15 A higher cardiac output, characterized by an augmentation in blood flow,
16 associated with increased capitalization and improvements in respiratory chain function,
17 are considered possible mechanisms by which AE training leads to improvement in
18 VO₂max.(Freudenberger et al., 2016)·(Bassett & Howley, 2000) Also, several
19 physiological adaptations to ST may be accounted for improvements in aerobic capacity
20 in older adults, such as augmentation of capillary density, myoglobin concentration,
21 mitochondria content and enzyme activity in the working muscle.(Brentano et al., 2008;
22 Cadore et al., 2010; Ozaki et al., 2013; Phillips et al., 2012) These physiological
23 adaptations may lead to increase in arterial-venous oxygen difference (a-vO₂), which
24 associated with elevated exercise-induced blood flow, are the key-factors that of ST-
25 induced improvements in VO₂max.(Brentano et al., 2008; D. Lovell, 2010; Ozaki et al.,
26 2013; Phillips et al., 2012)

27 Although aerobic- and resistance-based exercise interventions have been
28 associated with increase in VO₂max in older adults, the influence of multiple-modality
29 exercise training in cardiorespiratory fitness measured via VO₂max has not been largely
30 explored. Indeed, some studies have investigated impact of multiple-modality exercise

1 approach on cardiovascular fitness in the elderly(Capodaglio et al., 2005; Carvalho et
2 al., 2009; Gudlaugsson et al., 2012; Nelson et al., 2004; Ratel et al., 2012; Rubenstein &
3 et al., 2000; Sousa, Mendes, Abrantes, Sampaio, & Oliveira, 2013; F. Toraman & Şahin,
4 2004; N F Toraman & Ayceman, 2005; N Füsün Toraman, Erman, & Agyar, 2004);
5 however, only a few have used VO₂max as an outcome measure.(Ratel et al., 2012;
6 Villareal et al., 2011) For example, Villareal et al.(Villareal et al., 2011) investigated the
7 effects of a multicomponent exercise program (90 min/day, 3 days/week, for 12 weeks)
8 to improve physical function in frail obese older adults. After the intervention period, 15%
9 improvement in aerobic capacity (VO₂max) was seen in the intervention group
10 compared to the control group. In the same direction, Ratel and colleagues(Ratel et al.,
11 2012) noticed 13% improvement in older adults following a 16-week program of similar
12 characteristics. Regardless of the minor differences between the intervention
13 methodology applied in the current study and the work conducted by Villareal et
14 al.(Villareal et al., 2011) and Ratel et al.(Ratel et al., 2012), our results corroborate their
15 findings.

16 Besides the work conducted by Villareal and colleagues,(Villareal et al., 2011)
17 other studies investigating effects of multiple-modality exercise intervention in older
18 adults have used an alternative assessment of cardiovascular fitness and aerobic
19 capacity, i.e., the 6-min walking test (6MWT).(Capodaglio et al., 2005; Carvalho et al.,
20 2009; Gudlaugsson et al., 2012; Nelson et al., 2004; Rubenstein & et al., 2000; Sousa et
21 al., 2013; F. Toraman & Şahin, 2004; N F Toraman & Ayceman, 2005; N Füsün
22 Toraman et al., 2004) Rubenstein et al.(Rubenstein & et al., 2000) administered a
23 multiple-modality exercise intervention program in elderly men composed by ST, AE and
24 5 min of balance training once a week, for 12-weeks. Their findings indicated 10.42%
25 improvement in the 6MWT following the program. Likewise, a 9-week multicomponent
26 exercise training conducted by Toraman et al.(F. Toraman & Şahin, 2004; N F Toraman
27 & Ayceman, 2005) led to 17.48% and 10.43% improvement in the same test in older
28 adults aged at 67 and 80, respectively. The intervention program encompassed AE,
29 followed by ST and flexibility exercises.(F. Toraman & Şahin, 2004)

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

7 **4.2. Carotid Arterial Compliance and Blood Pressure**

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

12 Aerobic-based exercise interventions have successfully increased systemic and
13 local CAC,(Maeda et al., 2008, 2009; Miyaki et al., 2009; Moreau, Donato, Seals,
14 DeSouza, & Tanaka, 2003; Pescatello et al., 2004; Seals et al., 2008; Sugawara et al.,
15 2009, 2004, Tanaka et al., 2000, 1998) which reflects in improved arterial health and
16 reduced risk factors for cardiovascular diseases and all-cause mortality in older
17 adults.(Seals et al., 2008) Although in the current study participants exercised
18 aerobically at similar intensity (60-85% HR_{max}), exercise duration (20 min/day) and
19 frequency (3 days/week) were remarkably inferior to those reported in previous
20 studies.(Maeda et al., 2008, 2009; Miyaki et al., 2009; Seals et al., 2008; Sugawara et
21 al., 2004; Tanaka et al., 2000) These factors suggest that exercise volume (duration and
22 frequency), despite of intensity, might be a key-factor to improve arterial compliance in
23 older adults.(Sugawara et al., 2004) However, a recent systematic review and meta-
24 analysis(Ashor et al., 2014) indicated that AE intensity was rather more associated with
25 improved arterial stiffness than exercise duration and frequency. Furthermore, the
26 authors also noticed a tendency for a positive dose-response relationship between
27 exercise intensity and cardiovascular health, meaning that high-intensity physical activity
28 could benefit more cardiovascular health outcomes than low-intensity exercise.(Ashor et
29 al., 2014)

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

9 Aerobic exercise seems to attenuate age-related arterial stiffness and increase
10 arterial compliance through improvements in artery function and structure.(Maeda et al.,
11 2008, 2009; Sugawara et al., 2004) These improvements are understood as reduction of
12 endogenous endothelin-1 plasma concentration and angiotensin-2 (endothelium-derived
13 vasoconstrictors), and increased nitric oxide production (endothelium-derived
14 vasodilator).(Maeda et al., 2008, 2009; Sugawara et al., 2004) Animal models have also
15 demonstrated that the arteries of exercised animals had lower collagen and higher
16 elastin than non-exercised ones, representing improved distensibility capacity of the
17 vessel wall, leading to a better cardiovascular outcome.(Ashor et al., 2014)
18 Nonetheless, the mechanisms underlying reduction in CAC as a result of ST in older
19 adults remain unclear. Myichi and colleagues(Miyachi et al., 2004) proposed that ST-
20 induced arterial stiffening in young men might be a consequence of acute intermittent
21 elevations in arterial blood pressure during each exercise repetition, leading to changes
22 in the arterial structure and function (e.g., endothelium dysfunction).(Miyachi et al.,
23 2003, 2004) They also argue that, as ST is a strong stimulus to increase sympathetic
24 nervous system activity, CAC might be affected by chronic restraint on the arterial wall
25 via greater sympathetic adrenergic vasoconstrictor tone, hence, increasing arterial
26 stiffness.(Failla et al., 1999; Miyachi et al., 2003, 2004)

27 From this perspective, it is possible to assume that the multi-modal aspect of the
28 exercise training administered in our study (i.e., relatively low AE volume associated with
29 a ST component) may have restricted improvements in CAC immediately after the
30 training program in both groups. Our results are analogous to the findings described

1 previously in the study conducted by Cortez-Cooper and colleagues.(Cortez-Cooper et
2 al., 2008) Accordingly, in the systematic review and meta-analysis performed by Ashor
3 et al.,(Ashor et al., 2014) studies investigating the influence of combined exercise
4 interventions did not lead to any improvement in arterial stiffness.

5 Although in the current study only the M2 group demonstrated small reduction of
6 24 h SBP (2.31 mmHg) immediately after the exercise program, this finding is in
7 accordance with previous research.(Pescatello et al., 2004) Undeniably, aerobic- and
8 resistance-based exercise intervention reduces arterial blood pressure in normotensive
9 and those with hypertension in the general population.(Kelley & Kelley, 2000; Pescatello
10 et al., 2004) In older adults, however, there have been conflicting results from RTCs
11 regarding the effectiveness of exercise training in reducing blood pressure.(Pescatello et
12 al., 2004) In overall, AE interventions seem to be one of the most powerful non-
13 pharmacological strategies to attenuate arterial blood pressure and reduce
14 cardiovascular risk in this population.(Kelley & Kelley, 2000; Kelley & Sharpe Kelley,
15 2001) Although, our findings indicated modest reduction of approximately 1.8% in 24 h
16 SBP following the exercise program, the minimal decline in arterial blood pressure has
17 been associated with 5-14% reduced CVD incidence and 4% all-cause mortality.(Kelley
18 & Kelley, 2000; Kelley & Sharpe Kelley, 2001; Pescatello et al., 2004; Sakuragi &
19 Abhayaratna, 2010; Zieman et al., 2005)

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

28 **4.3. Follow-up Results**

29 It is remarkable that after the 28-week non-contact follow-up, the M4 group
30 demonstrated improvement VO₂max and reduced 24 h DBP. Firstly, this suggests that

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

20 **4.4. Study Limitations**

21 The absence of a non-intervention control group is a major limitation of this study,
22 as we could have seen significant difference in the remaining variables if the between-
23 group comparisons had included a group of participants who had not taken part in any of
24 the intervention programs. Another limitation relates to the CAC and IMT measurements;
25 although participants were provided with very specific instructions 24 hours prior to the
26 carotid arterial ultrasonography, compliance to these recommendations was not
27 monitored or enforced. There were also limitations regarding the power of our statistical
28 analyses, particularly due to the fact that our sample size was calculated based on an
29 effect size associated with a different outcome (i.e., global cognitive functioning)—this
30 could be the reason why in some instance, no differences between and within groups

1 were found in the remaining variables. Also, AE intensity was controlled based on target
2 HR defined prior to the intervention and participants were oriented to monitor their own
3 target HR; as such, the AE intensity relied on participants voluntarily and accurately
4 assessing their HR, which could have created room for underestimations. Finally, we
5 recruited high functioning, community-dwelling older adults with self-reported subjective
6 cognitive complaints, living in Woodstock, ON, Canada, predominantly Caucasian and
7 females. Thus, our findings may not be generalized to other populations, including older
8 adults with severe cognitive and/or mobility disorders, different ethnic and cultural
9 backgrounds, social and economic status.

10 **5. Conclusion**

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

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5 **Conflict of interest**

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

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 12 Community partners in Woodstock: South Gate Centre for Active Adults 50+ (Executive
 13 Director: Chris Cunningham); Woodstock Health & Fitness (President: Kapil Verma);
 14 Maranatha Christian Reformed Church; and Salvation Army Community Church.

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