







# Program of Rehabilitative Exercise and Education to Avert Vascular Events After Non-Disabling Stroke or Transient Ischemic Attack (PREVENT Trial): A Randomized Controlled Trial

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## Abstract

**Background:** Non-disabling stroke (NDS) and transient ischemic attack (TIA) herald the possibility of future, more debilitating vascular events. Evidence is conflicting about potency of exercise and education in reducing risk factors for second stroke.

**Methods:** Three-site, single-blinded, randomized controlled trial with 184 participants <3 months of NDS or TIA (mean age, 65 years; 66% male) randomized to usual care (UC) or UC + 12-week program of exercise and education (PREVENT). Primary (resting systolic blood pressure) and secondary outcomes (diastolic blood pressure [DBPrest], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], total cholesterol [TC], TC/HDL, triglycerides, fasting glucose, and body mass index) were assessed at baseline, post-intervention, and 6- and 12-month follow-up. Peak oxygen consumption ( $VO_{2peak}$ ) was measured at baseline, post-intervention, 12-month assessments.

**Results:** Significant between-group differences at post-intervention favored PREVENT group over UC: DBPrest (mean difference [MD]:  $-3.2$  mmHg, 95% confidence interval [CI]:  $-6.3, -.2$ ,  $P = .04$ ) and LDL-C (MD:  $-.31$  mmol/L, 95% CI:  $-.42, -.20$ ,  $P = .02$ ). Trends of improvement in PREVENT group were noted in several variables between baseline and 6-month follow-up but not sustained at 12-month follow-up. Of note,  $VO_{2peak}$  did not change over time in either group.

**Conclusion:** Impact of PREVENT on vascular risk factor reduction was more modest than anticipated, possibly because several outcome variables approximated normative values at baseline and training intensity may have been sub-optimal. Further investigation is warranted to determine when exercise and education programs are viable adjuncts to pharmaceutical management for reduction of risk factors for second stroke.

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## Keywords

Stroke, secondary prevention, exercise, education, heart disease risk factors

## Introduction

Non-disabling stroke (NDS) and transient ischemic attack (TIA) have long been regarded as relatively benign conditions due to lack of overt impairments and long-term consequences.<sup>1</sup> The reality is that NDS and TIA are harbingers of further, more debilitating vascular events or death.<sup>2</sup> The probability of a second stroke or death within the first 2 years following NDS and TIA is not trivial—from 10% in low-risk groups to up to 31% in high-risk groups.<sup>3</sup> Although the highest probability of second stroke is during the acute period, the risk persists long term and is independent of the severity of the index stroke.<sup>4</sup> Recurrent strokes are associated with greater physical disability, more institutionalization, and higher fatality rates,<sup>5</sup> and have been referred to as the most potentially modifiable outcome of stroke or TIA.<sup>6</sup> Thus, a multi-faceted secondary stroke reduction program represents a significant opportunity to lower the total stroke burden, even for patients with minor presenting events.

Most individuals presenting with TIA or NDS have significant atherosclerotic lesions throughout their vascular system and manifest, or are at increased risk of, co-morbid cardiovascular disease.<sup>7</sup> A host of factors interact synergistically to accelerate the progression of atherosclerosis, thereby increasing the risk of further cerebrovascular disease. Because many risk factors are modifiable, they are obvious targets of secondary prevention. However, control of vascular risk factors after TIA or stroke remains unacceptably poor;<sup>8</sup> a secondary analysis of two large data sets reported achieving control in only 10.6% of people with a history of stroke.<sup>9</sup> Particularly concerning is the lack of control of resting systolic and diastolic blood pressure (SBPrest and DBPrest), considering that hypertension accounts for a significant proportion of the aftermath of stroke and is, therefore, the most important risk factor to target for secondary prevention.<sup>10</sup>

Clinical guidelines for secondary stroke prevention recommend a combination of pharmacological therapy and non-pharmacological interventions, including education, exercise, and lifestyle counselling.<sup>11-13</sup> Lack of patient awareness and knowledge of cardiovascular risks is a known barrier to averting further events.<sup>14,15</sup> Positive effects of exercise on cardiovascular risk factors,<sup>16,17</sup> exercise capacity,<sup>16</sup> and mental wellbeing<sup>18</sup> in the general population are broadly recognized. Despite the suggestion from a modelling study that non-pharmacological strategies after stroke could result in at least 80% reduction in further vascular events,<sup>19</sup> evidence of effectiveness of such strategies remains equivocal. Six

systematic reviews of randomized controlled trials (RCTs) on non-pharmacological interventions for vascular risk factor reduction post-stroke offer conflicting results—reduction in SBPrest and DBPrest;<sup>20</sup> improvement in SBPrest, high-density lipoprotein cholesterol (HDL-C), and fasting glucose;<sup>21</sup> decrease in SBPrest, DBPrest, and total cholesterol;<sup>22</sup> and no effects.<sup>23-25</sup> These divergent findings are due, in part, to heterogeneity in terms of populations (e.g., stroke severity and time post-onset), experimental interventions (exercise, education, and/or lifestyle counselling), and comparison interventions (e.g., usual care [UC] and no intervention). The relative effectiveness of non-pharmacological interventions has not been systematically studied; however, Wang and colleagues<sup>22</sup> reported greater reductions in SBPrest with exercise and education compared to exercise alone. Further evidence of sustainability of results is lacking; only three RCTs included in the above reviews included follow-up greater than 6 months.<sup>26-28</sup>

We undertook this study to investigate short and long-term effects of a community-based program of rehabilitative exercise and education as an adjunct to pharmacological management to reduce vascular risk factors in people after NDS/TIA. SBPrest, the most robust predictor of secondary vascular events,<sup>29</sup> was selected as the primary outcome measure, and NDS or TIA as the population of interest to enhance homogeneity of stroke severity and ability to engage in exercise. The primary hypothesis was that the Program of Rehabilitative Exercise and Education to Avert Vascular Events after Non-disabling Stroke or Transient Ischemic Attack (PREVENT) program would be more effective than UC in reducing SBPrest at post-intervention. The secondary hypothesis was that improvements in SBPrest would be maintained at 6- and 12-month follow-ups. We also investigated the short and long-term effects of the PREVENT program vs UC on other modifiable vascular risk factors (i.e., DBPrest, lipids, fasting glucose, body mass index, and waist girth), cardiorespiratory fitness, depression, and fatigue.

## Methods

### Design

The study was a single-blind, parallel two-group RCT conducted at one urban and two rural community facilities (NCT00885456). Participants were randomly assigned to one of 2 groups (PREVENT +UC or UC alone), using the Stroke Prognosis Instrument II (SPI-II) for stratification. The SPI-II is a tool designed to stratify patients following TIA or NDS

by prognosis for stroke or death in 2 years: 1. SPI-II Level 1 (0-3 points, low-risk) 2. Level 2 (4-7 points, moderate-risk) or Level 3 (8-15 points, high-risk).<sup>3</sup> Allocation concealment was assured through use of sequentially numbered, opaque, sealed envelopes containing group assignment, which were prepared by an individual not involved in the study and opened after completion of the baseline assessment. Each site's ethics review board approved the study protocol, and all participants provided written informed consent.

**Participants.** We enrolled men and women over 17 years of age within 3 months of first probable or definite TIA (symptom resolution in  $\leq 24$  h) or NDS (National Institutes of Health Stroke Scale [NIHSS]  $< 6$ ).<sup>30</sup> Potential participants were excluded if they had contraindications to maximal exercise stress testing,<sup>31</sup> musculoskeletal or cognitive limitations that could preclude participation in the program, or involvement in other pharmacological or physical intervention studies. Family physicians of the participants were informed of intent to participate.

Calculation of sample size was based on the primary outcome, resting SBP, using estimates obtained from a previous study that examined the effects of aerobic exercise on resting SBP post-stroke.<sup>32</sup> A sample size of 89 in each group would have 80% power to detect a difference in means of 6.5 mmHg, assuming a common standard deviation of 15.4 and a type 1 error rate of 5% (two-sided). In anticipation of 10% attrition increased the target sample size was increased to 98 per group (196 in total).

### Intervention Protocols

**Usual Care.** Following acute management, all participants in the PREVENT and UC groups attended an outpatient neurovascular clinic for: (i) a neurological assessment, (ii) counseling regarding stroke/TIA and diagnostic test results, and (iii) assessment, modification and education of secondary prevention factors (i.e., dietary intake, lipid profile, adherence to medication regime, physical activity, smoking, alcohol intake, self-referral to weight loss, and smoking cessation programs). Required therapeutic interventions (e.g., medications, diagnostic/laboratory tests) were initiated or adjusted, and referrals were sent to appropriate team members or clinics (e.g., social work, physiotherapy, occupational therapy, dietitian, speech language pathologist, diabetes center, hypertension clinic, anticoagulation clinic, and smoking cessation). Follow-up care was provided by 1-3 return clinic visits after which patients were referred to their primary care physician.

### PREVENT Intervention

Participants randomized to the PREVENT group engaged in a multi-modal, case-managed program of exercise and education. Because the intervention was behavior-focused,

strategies known to facilitate and sustain behavior change were incorporated<sup>33-35</sup>: (i) meetings of participants and program providers to identify personal health goals, and related barriers and facilitators, (ii) exercise sessions supervised by health professionals, (iii) user-friendly health passports to record exercise schedule, medication regimen, and vascular risk factors, (iv) positive reinforcement, and (v) adult learning strategies (interactive educational sessions with participant involvement in content selection). Based on our previous exercise trials, we set a priori targets for adherence in attending exercise and education sessions: attending at least 75% of the total number of exercise sessions and at least 75% of the total number of education sessions.

**Group exercise component** 60-minute, group-based (4-6 PREVENT participants) exercise sessions were held twice weekly for 12 weeks in community centers and led by trained physiotherapists or kinesiologists. Substitute sessions for missed appointments were provided. The standardized program involved: (i) 10-minute warm-up, (ii) 10-15 minutes of progressive strengthening training of major muscle groups at 60-70% of one-repetition maximum, (iii) 30 minutes of aerobic training with three 10-minute stations of treadmill walking, stationary cycling, and stepping at a prescribed intensity (heart rate recorded during the baseline exercise test at 60-80% of  $VO_{2peak}$ <sup>31</sup>), and (iv) 5-10 minute cool-down. Heart rate and RPE were monitored intermittently, and blood pressure and blood sugars (when indicated) were measured before and after exercise. Aerobic training and strengthening exercises were prescribed and progressed according to ACSM guidelines (individualized and gradual increase in duration/repetitions and intensity/resistance as tolerated by the participant).<sup>31</sup> During the exercise sessions the therapists stressed the importance of continuing physical activity after completion of the program for 30 minutes per day, 5 days per week at a rating of perceived exertion (RPE) of "somewhat hard" to "hard."<sup>36</sup>

**Education component** Once weekly a multi-disciplinary team conducted an interactive 60-minute group session for participants, family members, and or caregivers. Discussion topics were: 1. Heart healthy eating: the basics, 2. Goal setting, 3. Exercise: The Basics, 4. Cardiovascular risk factors and BP self-monitoring, 5. Nutrition: building on the basics, 6. Exercise: Building on the basics, 7. Cardiovascular medications, 8. Healthy weight, 9. Smoking cessation, 10. Stress and coping, 11. Fine-tuning healthy eating, and 12. Wrap-up. The same slide decks were used across sites to ensure consistency of content.

### Assessment Protocols

Participant characteristics (i.e., age, sex, employment status, time post-onset and side of lesion, stroke severity [NIHSS],<sup>37</sup> cognitive status [Montreal Cognitive Assessment<sup>38</sup>], comorbidities, and medications) were collected at enrollment. All assessments for each participant were conducted at

baseline (pre-randomization), post-intervention, 6- and 12-months at a consistent time of day and by the same trained independent assessor blinded to the hypotheses and group assignment. Participants (necessarily unblinded) were instructed not to divulge their group assignment to the assessor. To determine the effectiveness of blinding, the assessor was asked to indicate on each assessment form their “guess” of the group assignment of each participant.

Given the diversity of potential health benefits of exercise, several vascular risk factors and physical and psychosocial variables were measured, based on the secondary stroke prevention literature, clinical relevance, psychometric qualities, and feasibility. Resting SBP was selected as the primary variable, measured in accordance with published guidelines.<sup>39</sup> Secondary outcomes included other markers of cardiovascular risk: DBPrest, 12-h fasting lipid profile (low-density lipoprotein cholesterol [LDL-C], HDL-C, high-density lipoprotein cholesterol [HDL-C], total cholesterol, triglycerides, ratio of total cholesterol to HDL-C), and 12-h fasting glucose.

Peak oxygen consumption ( $VO_{2peak}$ ), the gold standard for assessment of exercise capacity, was measured *via* open-circuit spirometry during a symptom-limited, graded, treadmill test (GXT) using an incremental ramp protocol (slow, regular, fast ramp) with a 2-min warm-up and cool-down, 1-min stages of exercise, continuous monitoring of electrocardiographic activity, and periodic recording of BP and RPE.<sup>40</sup> Selection of ramp protocol was based on comfortable overground speed, with the slow protocol for speeds < .9 m per second (mps); regular, .9-1.2 mps; and fast > 1.2 mps. Participants unfamiliar with treadmill walking received a brief orientation prior to the GXT. Testing was conducted by a trained physiotherapist, electrocardiogram activity was monitored by a technician, and test termination followed ACSM criteria.<sup>31</sup>

Standardized questionnaires were used to assess tertiary outcomes—*anxiety and depression* (Hospital Anxiety and Depression Scale, HADS-A and HADS-D, each subscale consisting of seven items with higher scores indicating more severe symptoms<sup>41</sup>) and *general fatigue* (Fatigue Assessment Scale, FAS, ten items with higher scores indicating more severe symptoms<sup>42</sup>).

**Data Analysis.** Before analysis, data were inspected to identify and remove outliers. Descriptive statistics were used to summarize demographic and clinical characteristics on admission. Between-group baseline differences were assessed with independent *t*-tests (continuous data), Pearson chi-squared tests (nominal data), and when assumptions of normality were violated (Kolmogorov-Smirnov test), non-parametric methods. Short-term effects on outcome variables were assessed by comparing pre-post change scores between groups using two-tailed independent *t*-tests. To examine treatment effects over time a mixed model analysis of variance (ANOVA) with repeated measures was used, with one

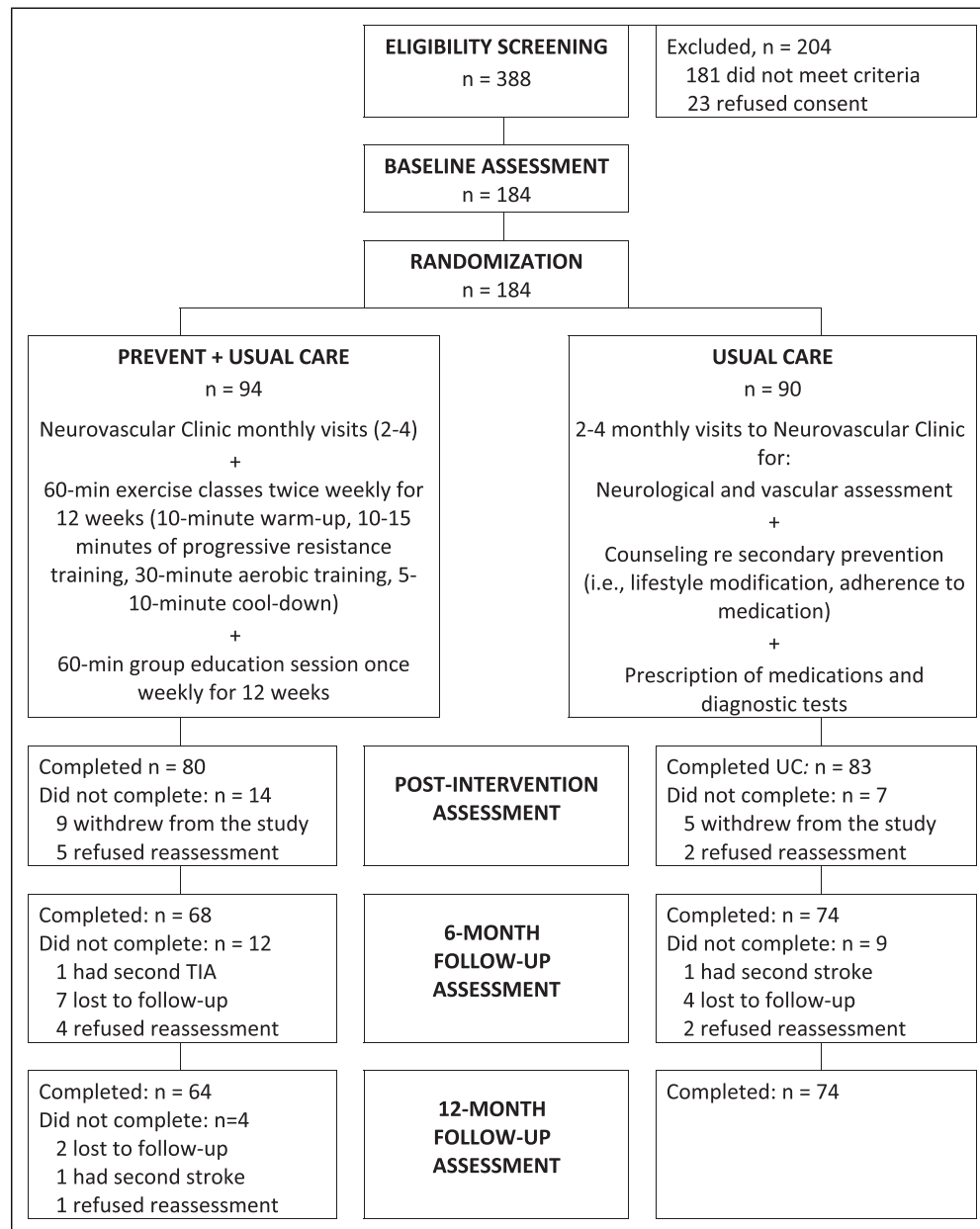
between-subject factor at 2 levels (2 groups: PREVENT, UC) and one within-subject factor at 4 levels (time: baseline, post-program, 6-month follow-up, and 12-month follow-up). To control for baseline differences between groups, we planned to include variables that were significantly different at baseline as covariates in the analyses. Subgroup analysis was also conducted to compare outcomes of participants who had adhered to the PREVENT program (>75% attendance) to the UC group. Two-sample tests for proportions were performed to determine whether the blinded assessor’s guesses of group assignment at post-testing and 6- and 12-month evaluations were better than chance. Analyses were conducted using both intention-to-treat (last observation carried forward) and per protocol. Alpha level was set at < .05.

## Results

### Participants

Of 388 people screened, 184 (47%) were randomized into the PREVENT group ( $n = 94$ ) and UC group ( $n = 90$ ) (Figure 1). Enrollment was terminated before reaching our target sample of 196 participants because of premature closure at one site due to slow recruitment and protracted recruitment at the remaining two sites. No significant differences were found in baseline characteristics between groups (Table 1). The majority were over 60 years of age, male, overweight, and on antithrombotic, antilipidemic, and antihypertensive agents. During the intervention period no changes in prescription medications were made in the PREVENT group and two changes were made in the UC group (an antidepressant and an antilipidemic were discontinued in two cases due to side effects). In the post-intervention period, 11 modifications were made in the PREVENT group (an antithrombotic and an antidepressant were discontinued in two cases; antilipidemics were discontinued in two cases and dose of antilipidemics was increased in two cases; dose of antihypertensive was increased in two cases and reduced in one case; and an antihyperglycemic and bronchodilator were added in two cases), and in the UC group, eight adjustments were made (an antithrombotic was added in one case and discontinued in another; dose of antihypertensive was increased in one case and reduced in one case, and type of antihypertensive was changed in another case; an antihyperglycemic was added in one case and the dose was increased in another; and an anxiolytic was added in one case).

The assessment protocol required an average of 2.25 h including rest intervals and was well tolerated. The blinded assessor’s guesses of group assignment were no better than chance, with the correct guess made 58% at the post-test ( $P = .29$ ), 54% cases at the 6-month follow-up ( $P = .64$ ), and 55% of cases at the 12-month follow-up ( $P = .54$ ). No adverse events occurred during or following the cardiopulmonary stress tests. The regular ramp protocol was used in 65% of stress tests, slow ramp in 19% and fast ramp in 16%. All



**Figure 1.** CONSORT flow diagram of subject progress through the phases of the trial.

participants reached volitional exhaustion during GXTs, attaining an average of 93.5% (SD = 9.8) of age-predicted maximum heart rate and a peak respiratory exchange ratio of 1.18 (SD = .11). Target heart rates of 60–80% of baseline  $VO_{2peak}$  were achieved during the majority of the exercise sessions, with the percentage of age-predicted maximal heart rate progressing over time—from a mean of 72% (SD = 9.8) in Week 1 to 75% (SD = 13.1) in Week 2, and 79% (SD = 11.0) in Week 11. However, the duration over which the target intensities was sustained during each exercise session was not documented.

Fourteen (7.6%) participants (9 PREVENT and 5 UC) withdrew from the trial during the intervention period.

Among those who completed the PREVENT program, 77 (96%) attended >75% of the sessions. Five PREVENT and 2 UC participants did not return for the post-intervention assessment. Total attrition over the course of the study was 25%, exceeding our anticipated attrition (10%) and that of another trial with a similar design (15%).<sup>26</sup> Participants cited excessive time commitments as the main reason for terminating participation. There were no reports of adverse events (e.g., falls or other injuries, chest pain or other cardiac related symptoms, and intolerance to the training) during the intervention period. In the follow-up period one PREVENT group participant had a second TIA and another had a second stroke, and one UC group participant had a second stroke.

**Table 1.** Baseline Characteristics.

Characteristic <sup>a</sup>	PREVENT Group (n = 94)	UC Group (n = 90)	P Value
Age years	64.3 ± 10.2 (38-89)	65.9 ± 9.9 (43-84)	.27
Men	59 (63)	62 (69)	.38
Time post-TIA or NDS months	2.3 ± 0.6	2.4 ± 0.7	.30
Side of lesion left	46 (53)	33 (40)	.07
NIHSS 0-42	.58 ± .89	.49 ± .83	.32
0	54 (57)	60 (67)	
1	25 (27)	15 (17)	
2-5	10 (11)	12 (13)	
Missing	5 (5)	3 (3)	
Montreal Cognitive Assessment 0-30	26.7 ± 2.3	26.5 ± 2.8	.37
Employment			.79
Employed	29 (30)	23 (26)	
Unemployed/Retired	65 (70)	67 (74)	
Living alone	25 (27)	22 (24)	.92
Smoking history			.45
Current/Former/Never	6 (6)/61 (65)/27 (29)	10 (11)/53 (59)/27 (30)	
Body mass index kg/m <sup>2</sup>	30.8 ± 6.7	29.5 ± 5.9	.17
Overweight BMI >25-<30	33 (35)	32 (36)	
Obese BMI ≥30	34 (36)	31 (34)	
Cardiovascular history			
Hypertension <sup>b</sup>	67 (71)	68 (76)	.51
Diabetes mellitus	23 (24)	17 (19)	.45
Coronary artery disease	13 (14)	12 (13)	.63
Atrial fibrillation	8 (9)	10 (11)	.37
CAD risk score	6.1±3.3	6.3±3.0	.59
Arthritis	38 (40)	36 (40)	.41
Medications			
Antithrombotics	86 (92)	78 (90)	.51
Antilipidemics	81 (87)	73 (84)	.54
Antihypertensives	66 (71)	60 (69)	.77
Antihyperglycemics	28 (30)	20 (23)	.28
Antidepressants	10 (11)	7 (8)	.53

<sup>a</sup>Values are mean ± standard deviation (range) or n (%).

<sup>b</sup>Hypertension defined as >140/90 or using antihypertensive medication.

TIA, transient ischemic attack; NDS, non-disabling stroke; NIHSS, National Institutes of Health Stroke Scale; CAD, coronary artery disease.

## Outcome Assessment

Results of the intention-to-treat analyses are reported. No differences in the results were found using per protocol analyses. As well, planned subgroup analyses comparing outcomes of adherers vs non-adherers in the PREVENT group did not reveal any differences (data not shown).

**Primary Outcome: Systolic Blood Pressure.** Pre-post intervention decreases in SBPrest were not statistically different between groups. ANOVA revealed significant main effects of time for SBPrest ( $P = .002$ ) but no significant group-by-time interactions (Table 2). Mean SBPrest values for the PREVENT group improved compared to baseline values at post-intervention and 6-month follow-up. By the 12-month follow-up, SBPrest of the PREVENT group approximated baseline values.

**Secondary Variables: Other Vascular Risk Factors.** Baseline values for total cholesterol (PREVENT,  $4.0 \pm .9$ ; UC:  $4.0 \pm 1.1$ ,  $P = .73$ ) and total cholesterol: HDL (PREVENT,  $3.5 \pm 1.0$ , UC;  $3.7 \pm 1.3$ ,  $P = .23$ ) were within the normative range in both groups and did not change over the course of the study (data not shown). Pre-post differences in DBPrest and LDL of the PREVENT group were significantly greater compared to the UC group ( $P = .04$ , see Table 2). ANOVA revealed no significant group-by-time interactions but significant main effects of time for DBPrest ( $P = .001$ ), HDL ( $P = .006$ ), and LDL ( $P = .34$ ). With the exception of BMI, waist girth, and, notably VO<sub>2</sub>peak, there were trends of improvement in vascular risk factors from baseline to 6-month follow-up for both groups.

**Tertiary Outcomes: Patient-Reported Psychosocial Variables.** No significant pre-post, between-group differences, or group-by-

**Table 2.** Cardiovascular Risk Factors at Baseline, Post-Training, 6-Month and 12-Month Follow-up.

Variable	Group	Baseline	Post-treatment	Pre-post between-group $\Delta$ (95% CI)	6-month follow-up	12-month follow-up	Main effect of time <i>P</i>	Group-by-time interaction
Resting SBP mmHg	PREVENT	131.8±15.7	125.9±16.7		126.8±15.1	130.6±17.5	.002	.379
	UC	131.7±18.4	129.3±18.1		128.2±16.8	128.9±18.3		
$\Delta$ from baseline (95% CI)	PREVENT		-5.9 (-10.8, -1.0)	-3.5 (-8.8, 1.8)	-5.0 (-9.2, -.1)	-1.2 (-6.2, .2)		
	UC		-2.4 (-7.9, 3.1)		-3.5 (-1.0, 10.1)	-2.8 (-7.8, 2.1)		
Resting DBP mmHg	PREVENT	76.6±11.1	72.2±12.0		71.8±8.1	73.0±9.7	.001	.206
	UC	74.9±9.8	73.7±14.6		73.8±9.0	72.5±9.9		
$\Delta$ from baseline (95% CI)	PREVENT		-4.4 (-7.9, -.9)	-3.2 (-6.3, -.2) <sup>b</sup>	-4.8 (-7.8, -1.8)	-3.6 (-7.0, .0)		
	UC		-1.2 (-4.9, 2.5)		-1.1 (-1.8, 4.0)	-2.4 (-5.7, .8)		
LDL-C Mmol	PREVENT	2.24±0.8	1.94±0.8		1.96±0.6	2.01±0.5	.034	.299
	UC	2.24±0.9	2.23±0.8		2.21±0.8	2.10±0.7		
$\Delta$ from baseline (95% CI)	PREVENT		-.30 (.06, .54)	-.31 (-.42, -.20) <sup>b</sup>	-.28 (-.51, -.05)	-.23 (-.46, .01)		
	UC		.01 (-.26, .27)		-.03 (-.27, .21)	-.14 (-.35, .07)		
HDL-C Mmol/L	PREVENT	1.16±0.4	1.24±0.4		1.28±0.5	1.27±0.6	.006	.242
	UC	1.15±0.3	1.17±0.3		1.19±0.3	1.22±0.3		
$\Delta$ from baseline (95% CI)	PREVENT		.08 (.01, .15)	.06 (.00, .12)	.12 (.06, .34)	.11 (.03, .18)		
	UC		.02 (-.03, .09)		.04 (-.05, .13)	.07 (.00, .15)		
Triglycerides Mmol/L	PREVENT	1.40±0.8	1.22±0.7		1.23±0.6	1.21±0.6	.096	.244
	UC	1.41±0.8	1.38±0.7		1.29±0.7	1.22±0.6		
$\Delta$ from baseline (95% CI)	PREVENT		-.18 (-.41, .05)	-.15 (-.83, .38)	-.17 (-.40, .06)	-.19 (-.42, .04)		
	UC		-.03 (-.26, .20)		-.21 (-.35, .11)	-.19 (-.41, .03)		
Fasting Glucose Mmol/L	PREVENT	6.2±1.8	5.9±1.1		5.9±1.5	5.9±1.5	.278	.372
	UC	6.0±1.7	6.0±2.1		6.1±2.3	5.9±1.4		
$\Delta$ from baseline (95% CI)	PREVENT		-.3 (-.75, .15)	-.3 (-.79, .19)	-.3 (-.83, .03)	-.3 (-.83, .23)		
	UC		.0 (-.57, .57)		.1 (-.72, .52)	-.1 (-.59, .39)		
BMI kg/m <sup>2</sup>	PREVENT	30.8±6.7	30.5±7.3		30.2±6.5	30.8±8.0	.447	.921
	UC	29.5±5.9	29.6±8.4		30.0±7.3	30.2±6.8		
$\Delta$ from baseline (95% CI)	PREVENT		-.3 (-2.0, 1.4)	.4 (-1.3, 2.1)	-.6 (-2.7, 1.5)	-.0 (-1.9, 1.8)		
	UC		.1 (-1.5, 1.7)		.5 (-2.5, 1.5)	.7 (-1.1, 2.5)		
Waist girth cm	PREVENT	103.6±15.7	104.8±17.8		102.5±15.8	103.2±16.2	.330	.827
	UC	102.1±15.2	103.2±16.7		103.4±15.0	104.5±15.2		
$\Delta$ from baseline (95% CI)	PREVENT		1.2 (-1.7, 3.2)	.9 (-.1, 1.2)	-1.1 (-6.0, 3.8)	-4 (-5.5, 4.7)		
	UC		1.7 (-.7, 4.0)		1.3 (-6.0, 3.4)	2.4 (-2.3, 7.1)		
VO <sub>2</sub> peak ml/kg/min <sup>a</sup>	PREVENT	18.9±5.8	19.7±5.2			20.0±5.8	.001	.072
	UC	19.5±5.7	19.4±5.8			20.1±6.5		
$\Delta$ from baseline (95% CI)	PREVENT		.8 (-.8, 2.5)	.9 (-2.6, .8)		1.1 (-.6, 2.8)		
	UC		-.1 (-1.8, 1.6)			.6 (-3.3, 4.5)		

Values are mean ±SD. Abbreviations: CI, confidence interval;  $\Delta$ , change; SBPrest, resting systolic blood pressure; DBPrest, resting diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index; VO<sub>2</sub>peak, peak oxygen consumption.

<sup>a</sup>Data not collected at 6-month follow-up.

<sup>b</sup><.05 pre-post between-group comparison.

**Table 3.** Tertiary, patient-reported outcomes at baseline, post-training, 6-month and 12-month follow-up.

Variable	Group	Baseline	Post-Treatment	Pre-post Between-Group $\Delta$ (95% CI)	6-Month follow-up	12-Month follow-up	P, Main Effect of Time	P, Group-By-Time Interaction
FAS 10-50	PREVENT	20.4 $\pm$ 5.9	19.8 $\pm$ 5.3		17.1 $\pm$ 4.8	17.5 $\pm$ 5.6	.000	.205
	UC	19.8 $\pm$ 6.0	19.7 $\pm$ 5.8		19.6 $\pm$ 7.7	18.8 $\pm$ 5.9		
$\Delta$ from baseline (95% CI)	PREVENT		-.6 (-2.2, 1.0)	-.7 (-2.4, 1.0)	-3.3 (-5.0, -1.6)	-2.9 (-4.7, -1.2)		
	UC		.1 (-1.4, 1.6)		-.2 (-2.3, 1.9)	-1.0 (-2.6, .7)		
HADS-A 0-21	PREVENT	5.2 $\pm$ 4.1	5.1 $\pm$ 4.1		4.6 $\pm$ 3.8	3.9 $\pm$ 3.8	.002	.083
	UC	5.5 $\pm$ 4.0	4.4 $\pm$ 3.8		4.5 $\pm$ 3.9	4.4 $\pm$ 3.6		
$\Delta$ from baseline (95% CI)	PREVENT		-.1 (-1.0, .7)	-.9 (-2.1, 0.3)	-.6 (-1.9, .6)	-1.3 (-2.2, .3)		
	UC		-1.0 (-1.8, -.2)		-1.0 (-2.2, .2)	-1.1 (-2.3, .0)		
HADS-D 0-21	PREVENT	3.4 $\pm$ 2.8	3.1 $\pm$ 2.9		2.9 $\pm$ 2.6	2.3 $\pm$ 2.2	.004	.603
	UC	3.5 $\pm$ 3.2	3.4 $\pm$ 3.1		3.3 $\pm$ 2.9	3.0 $\pm$ 2.6		
$\Delta$ from baseline (95% CI)	PREVENT		-.3 (-1.0, .4)	-.2 (-1.1, .7)	-.5 (-1.4, .4)	-1.1 (-1.8, -.3)		
	UC		-.1 (-.8, .6)		-.2 (-1.2, .8)	-.5 (-1.3, .2)		

Values are mean  $\pm$  SD. Abbreviations: CI, confidence interval;  $\Delta$ , change; FAS, Fatigue Assessment Scale; HADS, Hospital Anxiety and Depression Scale.

time interactions over the course of the study were detected in any patient-reported variable (Table 3). However, significant main effects of time were found for all variables with trends of improvement in FAS at 6- and 12-month follow-up and HADS-A and HADS-D at 12-month follow-up for the PREVENT group and in HADS-A at post-intervention and 12-month follow-up for the UC group.

## Discussion

The primary hypothesis of superiority of the PREVENT intervention of exercise and education over UC for short-term improvement of SBPrest post NDS/TIA was not supported. This finding is counter to meta-analytic evidence of significant decrease in SBPrest following stroke or TIA following structured exercise programs, with greater reduction when exercise was supplemented with behavioral interventions such as education.<sup>21,22</sup> A previous trial with a multi-component approach that was initiated 2 weeks post-onset of TIA or NDS and involved participants similar in profile to the PREVENT participants reported an almost 3-fold greater reduction in mean SBPrest compared to our study (mean difference [MD]: -9.8 mmHg; 95% CI = -17.1, 2.53 vs -3.5 mmHg; 95% CI = -8.8, 1.8).<sup>43</sup> Later initiation of the PREVENT program (mean of 2.3 months vs 2 weeks post-onset of TIA or NDS<sup>43</sup>) may partially account for our more modest response, given that time interval between stroke onset and therapy is predictive of the impact of exercise after stroke.<sup>44</sup> In fact, Faulkner and colleagues<sup>43</sup> postulated that a critical window might exist for an effective training response early post-stroke.

Another factor that likely contributed to the disparity between our results and those of Faulkner and colleagues<sup>43</sup> was better control of SBPrest in the PREVENT participants at baseline (131.8  $\pm$  15.7 vs 140.0  $\pm$  14.3 mmHg). Although aerobic training has been shown to reduce SBPrest in both normotensive and hypertensive individuals, the magnitude of effect is greater with higher baseline values.<sup>45</sup> Further investigation is necessary to determine if UC alone is adequate for patients after TIA or NDS who have reasonable control of SBPrest and other risk factors.

Reduction in DBPrest following non-cardioembolic stroke is associated with a significantly lower risk of recurrent stroke and other major vascular events.<sup>46</sup> Thus, despite mean DBPrest at baseline in the normative range for both groups,<sup>46</sup> the finding of a significant pre-post, between-group difference in DBPrest in favor of the PREVENT group (MD: 3.2 mmHg; 95% CI -6.3, -2.0) may be of clinical significance for secondary stroke prevention. As with SBPrest, evidence is contradictory regarding the effect of exercise on DBPrest post-stroke—the conclusion of one meta-analysis reflected our finding (MD: -2.6 mmHg; 95% CI -4.7, -.5)<sup>22</sup> whereas another did not (MD: -2.3 mmHg; 95% CI -4.7, .2).<sup>21</sup>

Although lowering LDL-C is another recognized strategy for mitigating the risk of recurrent stroke, only one previous exercise trial reported a significant reduction in LDL.<sup>12</sup> The significant pre-post between-group difference found in LDL-C in our study (MD: -.31 mmol/L; 95% CI -.42, -.20) exceeded that reported in the meta-analysis by D'Isabella and colleagues<sup>21</sup> (MD: -.19 mmol/L; 95% CI -.88, .50). Although there is uncertainty about clinical benefit of the magnitude of change in LDL-



C in our trial, a reduction of 1 mmol/L has been associated with as much as a 20% decrease in 5-year risk of major vascular events, including ischemic stroke.<sup>47</sup> Further, LDL-C therapeutic targets for secondary stroke risk reduction have not been established definitively;<sup>21</sup> in one exercise trial involving people after recent mild stroke, the goal of attaining LDL-C values <2.59 mmol/L exceeded mean baseline LDL-C values in our study.<sup>28</sup>

HDL-C has been regarded as the lipid most improved through exercise,<sup>48</sup> but increases tend to be modest (mean net change of .07 mmol/L).<sup>49</sup> The pre-post difference within the PREVENT group had a similar magnitude of change (.08 mmol/L) but the mean between-group difference did not reach statistical significance. This neutral finding is supported by one stroke-specific meta-analysis<sup>22</sup> but not another.<sup>21</sup> Various factors influence the extent HDL-C improvements with exercise. In the systematic review by Kodama et al.<sup>49</sup> significant increases in HDL-C were associated with exercise duration of  $\geq 120$  min per week, baseline total cholesterol level  $\geq 5.7$  mmol/L, and BMI <28.<sup>49</sup> Only the first condition was met in the PREVENT group—weekly duration of structured exercise was 120 min, whereas mean baseline total cholesterol was 4.0 mmol/L, and mean BMI exceeded 30.

The secondary hypothesis of superiority of the PREVENT intervention over UC in long-term retention of SBPrest post NDS/TIA was not supported. Both groups showed trends of improvement in SBPrest over baseline at 6-month follow-up, which dissipated by the 12-month follow-up. Similar patterns were observed for DBPrest, HDL-C, and HDL-C in the PREVENT group only. Exercise adherence, which is regarded as an essential aspect of exercise-induced blood pressure management programs,<sup>50</sup> may help to explain the observed regression towards baseline values. Although participation was relatively high during delivery of the PREVENT program, the extent of adherence in the post-intervention period is unknown because long-term participation in exercise was not tracked. Whelton et al.<sup>50</sup> noted less marked reduction in blood pressure in studies with longer follow-up periods, probably because commitment to exercise tends to wane over time.

Lack of change in other vascular risk factors (total cholesterol, ratio of total cholesterol to HDL-C, triglycerides, 12-h fasting glucose, BMI, and waist girth) in both PREVENT and UC groups over the course of the study is in keeping with findings of most exercise trials involving people post-stroke or TIA.<sup>21,22</sup> Exceptions include a decrease in total cholesterol following an 8-week exercise and education program after mild stroke or TIA,<sup>43</sup> and exercise-related reductions in BMI post-TIA between post-intervention and 12-month follow-up.<sup>26</sup>

Surprisingly, only one previous exercise trial on secondary stroke prevention after mild stroke and TIA<sup>28</sup> was cited that assessed VO<sub>2</sub>peak—the definitive index of exercise capacity for deconditioned or elderly individuals.<sup>51</sup> Our finding of a lack of a significant gain in post-intervention VO<sub>2</sub>peak in the PREVENT group vs UC group (overall gains of 4.2% vs  $-.5\%$ , respectively) aligns with the results of the other study.<sup>28</sup>

The finding is difficult to explain—in numerous stroke trials we and others have demonstrated robust exercise-elicited changes in VO<sub>2</sub>peak using similar training protocols.<sup>23</sup> One factor that might have contributed was the high proportion (70%) of PREVENT participants who were overweight or obese; non-stroke participants in a previous aerobic exercise trial with a range of BMI of 28–40 kg/m<sup>2</sup> experienced very modest improvements in VO<sub>2</sub>max (mean of 5.8%).<sup>52</sup>

Another factor may have played a role in the lack of significant improvement in VO<sub>2</sub>peak—the challenge in a group exercise format of ensuring that training is performed at the prescribed intensity consistently throughout the session. In both the PREVENT and the above-mentioned study by Boss et al.<sup>28</sup> the therapist-participant ratio was as high as 1:5. Although this ratio is within the standard for cardiac rehabilitation programs, it is conceivable that the participants' level of effort waned when not directly supervised. In a recent community-based exercise trial of ambulatory people post-stroke, participants struggled to achieve and sustain the prescribed dose of exercise.<sup>53</sup> Issues underlying this problem were not explored by the investigators but previously reported personal barriers to exercise post-stroke, including lack of motivation to exercise, health concerns (e.g., fatigue and depression), and motor impairments, may have been contributing factors.<sup>54</sup> The importance of exercise dose to exercise-related outcomes is well documented in older adults<sup>55</sup> (e.g., a robust dose-response relationship is often observed between intensity of aerobic exercise and HDL-C levels<sup>56</sup>). Yet the systematic reviews on the effects of exercise on cardiovascular risk factors after stroke did not take into account the exercise intensities used in the trials reviewed.<sup>20–22</sup> Underdosing during PREVENT exercise sessions may have contributed to lack of change in VO<sub>2</sub>peak as well as other neutral results of this trial.

Despite the lack of change in exercise capacity in our study, improvements were found in both DBPrest and LDL-C in the PREVENT group compared to the UC group at post-intervention, possibly because of the dual impact of exercise and education on these specific variables. Similarly, in the above-mentioned secondary stroke prevention study by Boss and colleagues,<sup>28</sup> in which there was not a significant improvement in VO<sub>2</sub>peak, significantly more participants in exercise group achieved the composite endpoint of optimal medical therapy (i.e., blood pressure of <140/90 mmHg) and LDL-c of <100 mg/dL).

In accordance with previous exercise trials post NDS and TIA,<sup>57,58</sup> we did not observe statistically significant between-groups differences in HAD-A and HAD-D. Baseline values for anxiety and depression as well as fatigue (FAS) were below established symptom thresholds for stroke population,<sup>59,60</sup> thus diminishing the potential for modification. As well, a meta-analysis showed that extent of exercise-induced change in depressive symptoms after stroke is related to the training intensity.<sup>61</sup> Encouraging, however, were trends of reductions in all three patient-reported outcomes in the PREVENT group over the course of the study, and the fact the mean reduction in the FAS score of the PREVENT group between baseline and 6-

and 12-month follow-ups exceeded the minimal clinically important difference of 1.7.<sup>62</sup>

Strengths of this trial include using rural and urban community settings for the exercise program to enhance “real-world” validity of the study; measuring, rather than estimating, VO<sub>2</sub> peak; and tracking progress for 12 months post-intervention. The study was not powered to detect change in hard clinical outcomes (i.e., recurrent TIA, stroke, cardiac events, and death) and the targeted sample size was not attained. Nonetheless, the study was the largest exercise trial to date on risk factor reduction for secondary stroke prevention. Other limitations included unequal exposure to intervention of experimental and control groups, lack of use of participant logs to record daily physical activity during and after intervention, absence of structured participant feedback regarding the exercise and education programs, and lack of follow-up in the post-intervention period to monitor adherence to physical activity. Further, since the PREVENT trial involved a combined therapeutic approach, it was not possible to establish whether observed changes were attributable to exercise or education or both.

## Conclusion

The impact of this largely neutral trial on exercise-induced vascular risk factor reduction for secondary stroke prevention was more modest than we had anticipated, given the known potency of exercise as a physiological stimulus. The significant between-group differences found in DBPrest and LDL-C at post-intervention, in favor of the PREVENT group, were not sustained at follow-up. The PREVENT group more often demonstrated trends of improvement in SBPrest, HDL-C and FAS than controls. Several risk factors approximated normative values at baseline, thus limiting the potential for impact. Also, a blunted fitness training effect suggests that the exercise intensity may have been sub-optimal. Further study is warranted that incorporates selection of participants within the first month after TIA or NSD who have baseline vascular risk factors outside the normative range, baseline assessment of personal barriers to exercise, participant-specific targets for risk factor improvement, and close monitoring of exercise intensity to determine if a program of exercise and education is a viable adjunct to pharmaceutical management of cardiovascular risk factors after TIA or NSD.

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## References

1. Rothwell PM, Buchan A, Johnston SC. Recent advances in management of transient ischaemic attacks and minor ischaemic strokes. *Lancet Neurol.* 2006;5:323-331. doi:10.1016/S1474-4422(06)70408-2.
2. Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack—proposal for a new definition. *N Engl J Med* 2002;347:1713-1716. doi:10.1056/NEJMs020987.
3. Kernan WN, Viscoli CM, Brass LM, et al. The stroke prognosis instrument II (SPI-II): A clinical prediction instrument for patients with transient ischemic attack and nondisabling stroke. *Stroke.* 2000;31:456-462. doi:10.1161/01.str.31.2.456.
4. Lioutas VA, Ivan CS, Himali JJ, et al. Incidence of transient ischemic attack and association with long-term risk of stroke. *J Am Med Assoc.* 2021;325(4):373-381. doi:10.1001/jama.2020.25071.
5. Hankey G. Secondary stroke prevention. *Lancet Neurol.* 2014;13(2):178-194. doi:10.1016/S1474-4422(13)70255-2.
6. Edwards JD, Kapral MK, Fang J, Swartz RH. Long-term morbidity and mortality in patients without early complications after stroke or transient ischemic attack. *Can Med Assoc J.* 2017;189:E954-E961. doi:10.1503/cmaj.161142.
7. Roth E. Heart disease in patients with stroke. Part 1: Classification and prevalence. *Arch Phys Med Rehabil.* 1993;74:752-760. doi:10.1016/0003-9993(93)90038-c.
8. Brenner DA, Zweifler RM, Gomez CR, et al. Awareness, treatment, and control of vascular risk factors among stroke survivors. *J Stroke Cerebrovasc Dis.* 2010;19(4):311-320. doi:10.1016/j.jstrokecerebrovasdis.2009.07.001.
9. Muntner P, DeSalvo KB, Wildman RP, Raggi P, He J, Whelton P. Trends in the prevalence, awareness, treatment, and control of cardiovascular disease risk factors among noninstitutionalized patients with a history of myocardial infarction and stroke. *Am J Epidemiol.* 2006;163:913-920. doi:10.1093/aje/kwj124.
10. Whitworth JA, World Health Organization International Society of Hypertension Writing Group. World health organization (WHO)/international society of hypertension (ISH) statement on management of hypertension. *J Hypertens.* 2003;21(11):1983-1992. doi:10.1097/00004872-200311000-00002.
11. Gladstone D, Lindsay MP, Douketis J, et al. Canadian stroke best practice recommendations: Secondary prevention of stroke update 2020. *Can J Neurol Sci* 2021;Jun 18:1-23. doi:10.1017/cjn.2021.127.
12. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: A guideline for healthcare professionals from the

- American heart association/American stroke association. *Stroke* 2014;45:2160-2236. doi:10.1161/STR.0000000000000024.
13. Intercollegiate Stroke Working Party. *National Clinical Guideline for Stroke*. 5 ed. London, UK: Royal College of Physicians; 2016.
  14. Koenig KL, Whyte EM, Munin MC, et al. Stroke-related knowledge and health behaviors among poststroke patients in inpatient rehabilitation. *Arch Phys Med Rehabil* 2007;88:1214-1216. doi:10.1016/j.apmr.2007.05.024.
  15. Croquelois A, Bogousslavsky J. Risk awareness and knowledge of patients with stroke: Results of a questionnaire survey 3 months after stroke. *J Neurol Neurosurg Psychiatr*. 2006;77:726-728. doi:10.1136/jnnp.2005.078618.
  16. Lin X, Zhang X, Guo J, et al. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: A systematic review and meta-analysis of randomized controlled trials. *J Am Med Assoc* 2015;4(7):e002014. doi:10.1161/JAHA.115.002014.
  17. Hagberg JM, Park J-J, Brown MD. The role of exercise training in the treatment of hypertension an update. *Sports Med*. 2000;30(3):193-206. doi:10.2165/00007256-200030030-00004.
  18. Dale H, Brassington L, King K. The impact of healthy lifestyle interventions on mental health and wellbeing: A systematic review. *Ment Health Rev J*. 2014;19(1):1-26. doi:10.1108/MHRJ-05-2013-0016.
  19. Hackam DG, Spence JD. Combining multiple approaches for the secondary prevention of vascular events after stroke: A quantitative modeling study. *Stroke*. 2007;38(6):1881-1885. doi:10.1161/strokeaha.106.475525.
  20. Lawrence M, Pringle J, Kerr S, Booth J, Govan L, Roberts NJ. Multimodal secondary prevention behavioral interventions for TIA and stroke: A systematic review and meta-analysis. *PLoS One*. 2015;10(3):e0120902. doi:10.1371/journal.pone.0120902.
  21. D'Isabella NT, Shkredova DA, Richardson JA, Tang A. Effects of exercise on cardiovascular risk factors following stroke or transient ischemic attack: A systematic review and meta-analysis. *Clin Rehabil*. 2017;31(12):1561-1572. doi:10.1177/0269215517709051.
  22. Wang C, Redgrave J, Shafizadeh M, Majid A, Kilner K, Ali A. Aerobic exercise interventions reduce blood pressure in patients after stroke or transient ischaemic attack: A systematic review and meta-analysis. *Br J Sports Med*. 2019;53(24):1515-1525. doi:10.1136/bjsports-2017-098903.
  23. Saunders DH, Sanderson M, Hayes S, et al. Physical fitness training for stroke patients. *Cochrane Database Syst Rev* 2020;3(3):CD003316. doi:10.1002/14651858.CD003316.pub7.
  24. Bridgwood B, Lager KE, Mistri AK, Khunti K, Wilson AD, Modi P. Interventions for improving modifiable risk factor control in the secondary prevention of stroke. *Cochrane Database Syst Rev*. 2018;5(5):CD009103. doi:10.1002/14651858.CD009103.pub3.
  25. Heron N, Kee F, Cardwell C, Tully MA, Donnelly M, Cupples ME. Secondary prevention lifestyle interventions initiated within 90 days after TIA or 'minor' stroke: A systematic review and meta-analysis of rehabilitation programmes. *Br J Gen Pract*. 2017;67(654):e57-e66. doi:10.3399/bjgp16X688369.
  26. Faulkner J, Lambrick D, Woolley B, Stoner L, Wong L, McGonigal G. The long-term effect of exercise on vascular risk factors and aerobic fitness in those with transient ischaemic attack: a randomized controlled trial. *J Hypertens*. 2014;32(10):2064-2070. doi:10.1097/HJH.0000000000000283.
  27. Kono Y, Yamada S, Yamaguchi J, et al. Secondary prevention of new vascular events with lifestyle intervention in patients with noncardioembolic mild ischemic stroke: A single-center randomized controlled trial. *Cerebrovasc Dis* 2013;36(2):88-97. doi:10.1159/000352052.
  28. Boss HM, Van Schaik SM, Deijle IA, et al. Safety and feasibility of post-stroke care and exercise after minor ischemic stroke or transient ischemic attack: MotiveS & MoveIT. *Neuro-Rehabilitation* 2014;34(3):401-407. doi:10.3233/NRE-141049.
  29. Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet* 2005;366:29-36. doi:10.1016/S0140-6736(05)66702-5.
  30. Brott T, Adams HP, Olinger CP. Measurements of acute cerebral infarction: A clinical examination scale. *Stroke*. 1989;20:864-870. doi:10.1161/01.str.20.7.864.
  31. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 10th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2017.
  32. Rimmer JH, Rauworth AE, Wang EC, Nicola TL, Hill B. A preliminary study to examine the effects of aerobic and therapeutic (nonaerobic) exercise on cardiorespiratory fitness and coronary risk reduction in stroke survivors. *Arch Phys Med Rehabil*. 2009;90(3):407-412. doi:10.1016/j.apmr.2008.07.032.
  33. Barnett E, Anderson T, Blosnich J, Halverson J, Novak J. Promoting cardiovascular health from individual goals to social environmental change. *Am J Prev Med*. 2005;29:107-112. doi:10.1016/j.amepre.2005.07.036.
  34. Baranowski T, Anderson C, Carmack C. Mediating variable framework in physical activity interventions. How are we doing? How might we do better? *Am J Prev Med*. 1998;15:266-297. doi:10.1016/s0749-3797(98)00080-4.
  35. Sammut M, Fini N, Haracz K, Nilsson M, English C, and Janssen H. Increasing time spent engaging in moderate-to-vigorous physical activity by community-dwelling adults following a transient ischemic attack or non-disabling stroke: A systematic review. *Disabil Rehabil* 2020;June 1:1-16. doi:10.1080/09638288.2020.1768599.
  36. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14:377-381.
  37. National Institute of Neurological Disorders and Stroke (US). *NIH Stroke Scale of Neurological Disorders and Stroke*. Bethesda, MD: National Institute Dept. of Health and Human Services; 2011.
  38. Nasreddine ZS, Phillips NA, Bedirian V, Whitehead V. The montreal cognitive assessment (MoCA): A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53:695-699. doi:10.1111/j.1532-5415.2005.53221.x.

39. Nerenberg K, Zarnke K, Leung AAK, et al. Hypertension Canada's 2018 guidelines for diagnosis, risk assessment, prevention, and treatment of hypertension in adults and children. *Can J Cardiol* 2018;34:506-525.
40. Myers J, Bellin D. Ramp exercise protocols for clinical and cardiopulmonary exercise testing. *Sports Med*. 2000;30(1): 23-29. doi:10.2165/00007256-200030010-00003.
41. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67:361-370. doi:10.1111/j.1600-0447.
42. Michielson HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The fatigue assessment scale. *J Psychosom Res*. 2003;54:345-353. doi:10.1016/s0022-3999(02)00392-6.
43. Faulkner J, Lambrick D, Woolley B, Stoner L, Wong LK, McGonigal G. Effects of early exercise engagement on vascular risk in patients with transient ischemic attack and nondisabling stroke. *J Stroke Cerebrovasc Dis*. 2013;22:e388-e396. doi:10.1016/j.jstrokecerebrovasdis.2013.04.014.
44. Lam JM, Globas C, Cerny J, et al. Predictors of response to treadmill exercise in stroke survivors. *Neurorehabil Neural Repair* 2010;24(6):567-574. doi:10.1177/1545968310364059.
45. Kelley GA, Kelley KA, Tran ZV. Aerobic exercise and resting blood pressure: A meta-analytic review of randomized, controlled trials. *Prev Cardiol*. 2001;4(2):73-80. doi:10.1111/j.1520-037x.2001.00529.x.
46. Park J, Ovbiagele B. Post-stroke diastolic blood pressure and risk of recurrent vascular events. *Eur J Neurol*. 2017;24(11): 1416-1423. doi:10.1111/ene.13411.
47. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267-1278. doi:10.1016/S0140-6736(05)67394-1.
48. Wang Y, Xu D. Effects of aerobic exercise on lipids and lipoproteins. *Lipids Health Dis*. 2017;16:132. doi:10.1186/s12944-017-0515-5.
49. Kodama S, Tanaka S, Saito K, et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: A meta-analysis. *Arch Intern Med* 2007;167(10):999-1008. doi: 10.1001/archinte.167.10.999.
50. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: A meta-analysis of randomized, controlled trials. *Ann Intern Med*. 2002;136:493-503. doi:10.7326/0003-4819-136-7-200204020-00006.
51. Howley ET, Bassett DR, Welch HG. Criteria for maximal oxygen uptake: Review and commentary. *Med Sci Sports Exerc*. 1995;27:1292-1301.
52. Lunt H, Draper N, Marshall H, et al. High intensity interval training in a real world setting: A randomized controlled feasibility study in overweight inactive adults, measuring change in maximal oxygen uptake. *PLoS One* 2014;9(1):e83256.
53. Reynolds H, Steinfort S, Tillyard J, et al. Feasibility and adherence to moderate intensity cardiovascular fitness training following stroke: A pilot randomized controlled trial. *BMC Neurol* 2021;21(1):132. doi:10.1186/s12883-021-02052-8.
54. Nicholson S, Sniehotta FF, van Wijck F, et al. A systematic review of perceived barriers and motivators to physical activity after stroke. *Int J Stroke* 2013;8(5):357-364. doi:10.1111/j.1747-4949.2012.00880.x.
55. Huang G, Wang R, Chen P, Huang SC, Donnelly JE, Mehlferber JP. Dose-response relationship of cardiorespiratory fitness adaptation to controlled endurance training in sedentary older adults. *Eur J Prev Cardiol*. 2020;23(5):518-529. doi:10.1177/2047487315582322.
56. Mann S, Beedie C, Jimenez A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: Review, synthesis and recommendations. *Sports Med*. 2014;44:211-221. doi:10.1007/s40279-013-0110-5.
57. Kirk HJ, Kersten P, Crawford P, Keens A, Ashburn A, Conway J. The cardiac model of rehabilitation for reducing cardiovascular risk factors post transient ischemic attack and stroke: a randomized controlled clinical trial. *Clin Rehabil*. 2013;28(4):339-49. doi:10.1177/0269215513502211.
58. Faulkner J, McGonigal G, Woolley B, Stoner L, Wong L, Lambrick D. A randomized controlled trial to assess the psychosocial effects of early exercise engagement in patients diagnosed with transient ischaemic attack and mild, non-disabling stroke. *Clin Rehabil*. 2015;29(8):783-794. doi:10.1177/0269215514555729.
59. Rafsten L, Danielsson A, Sunnerhagen KS. Anxiety after stroke: Systematic review and meta-analysis. *J Rehabil Med*. 2018;50:769-778. doi:10.2340/16501977-2384.
60. Cumming TB, Mead G. Classifying post-stroke fatigue: Optimal cut-off on the fatigue assessment scale. *J Psychosom Res*. 2017;103:147-149. doi:10.1016/j.jpsychores.2017.10.016.
61. Eng JJ, Reime B. Exercise for depressive symptoms in stroke patients: A systematic review and meta-analysis. *Clin Rehabil*. 2014;28(8):731-739. doi:10.1177/0269215514523631.
62. Lemay K, Tulloch H, Pipe A, Reed J. Establishing the minimal clinically important difference for the hospital anxiety and depression scale in patients with cardiovascular disease. *J Cardiopulm Rehabil Prev*. 2019;39(6):E6-E11. doi:10.1097/HCR.0000000000000379.