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RESEARCH ARTICLE

Resistance training and subcortical vascular cognitive impairment: A 12-month randomized trial

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Abstract

INTRODUCTION: It is unknown whether progressive resistance training (PRT) improves cognitive function in adults with cerebral small vessel disease and mild cognitive impairment (i.e., subcortical vascular cognitive impairment [SVCI]).

METHODS: We conducted a 12-month randomized trial comparing PRT versus balance and tone exercises (BAT) on the Alzheimer's Disease Assessment Scale Cognitive Plus (ADAS-Cog-Plus).

RESULTS: Ninety-one participants were randomized (PRT = 45; BAT = 46); 76 completed the trial. Adherence was not different between groups ($p = 0.18$). At 12 months, PRT significantly improved ADAS-Cog-Plus scores (estimated mean difference: −0.18; 95% confidence interval [CI: −0.35, −0.01]; $p = 0.04$). Planned contrasts stratified by

sex showed a significant PRT effect on ADAS-Cog-Plus scores for females (mean difference: −0.27; 95% CI: [−0.49, −0.05]; $p = 0.02$), but not for males. PRT also significantly reduced C-reactive protein (estimated mean difference: −2.93; 95% CI: [−5.36, −0.49]; $p = 0.02$). No significant differences were observed for other secondary outcomes.
DISCUSSION: PRT may have a small beneficial effect on cognitive function in SVCI.
CLINICAL TRIAL REGISTRATION: This trial was registered with ClinicalTrials.gov (NCT02669394).

KEYWORDS
mild cognitive impairment, progressive resistance training, randomized controlled trial, vascular cognitive impairment

Highlights

- Exercise is effective in preventing or reducing key risk factors for subcortical vascular cognitive impairment (SVCI), but only one trial of aerobic exercise has been conducted in SVCI. No trial has examined the effect of progressive resistance training in adults with SVCI.
- Compared with an active control group, progressive resistance training significantly improved cognitive function in adults with SVCI, and females benefitted more than males.
- Resistance training also significantly reduced C-reactive protein, a biomarker of systemic inflammation that is associated with SVCI.

1 | BACKGROUND

Cerebrovascular disease is the second most common cause of dementia, accounting for up to 38% of all dementia cases.[1] Vascular cognitive impairment (VCI) encompasses all levels of cognitive decline, from mild cognitive deficits to dementia, due to overt or covert cerebrovascular disease.[2] The most common cause of VCI is cerebral small vessel disease, in which covert ischemic damage to the brain leads to the development of subcortical vascular cognitive impairment (SVCI).[3,4] In SVCI, cerebrovascular damage predominantly manifests as white matter hyperintensities (WMHs) of presumed vascular origin and lacunes.[5] Impaired mobility and falls are also common among those with SVCI.[6]

Fortunately, SVCI may be the most preventable form of cognitive dysfunction in older adults because its key risk factors, which include hypertension, type 2 diabetes mellitus, and hypercholesterolemia, are modifiable. Cohort studies show physical activity reduces the risk of SVCI and vascular dementia.[7,8] A 2023 systematic review and meta-analysis of nine observational prospective studies concluded that while physical activity may reduce the risk of vascular dementia, randomized clinical trials are needed.[8] Notably, in a 2025 systematic review of randomized trials of exercise in persons with VCI (i.e., post-stroke cognitive impairment and SVCI) that included 14 trials, only 1 randomized trial (of aerobic training) was in SVCI.[9]

The best type of exercise intervention for persons with SVCI is unknown. Broadly, the two most common forms of exercise training are: (1) aerobic training and (2) resistance training. Current clinical research efforts in SVCI and exercise focus solely on aerobic training[9–11] despite evidence which suggests resistance training has important benefits for cognitive function.[12–15] Moreover, resistance training can significantly reduce C-reactive protein (CRP),[16] a biomarker of systemic inflammation that is associated with cerebral small vessel disease[17] and cognitive impairment in cerebral small vessel disease.[18] Resistance training can also significantly reduce hemoglobin A1c (HbA1c),[19] a measure of long-term blood glucose control that is associated with cerebral small vessel disease, lower hippocampal volume, and cognitive decline.[20] Notably, there is evidence to suggest that resistance training is more effective than aerobic exercise in reducing HbA1c levels in adults with type 2 diabetes mellitus.[21] Resistance training may also reduce arterial stiffness,[22] which is associated with cerebral small vessel disease[23] and cognitive decline.[24] However, whether resistance training reduces arterial stiffness in older adults remains underexamined.[25]

This 12-month, single-blind, proof-of-concept randomized clinical trial assessed whether progressive resistance training improves cognitive function in community-dwelling adults with cerebral small vessel disease and mild cognitive impairment (i.e., SVCI).

2 | METHODS

2.1 | Study design and setting

This was a two-arm parallel, single-blind, proof-of-concept randomized clinical trial conducted in a research center (Vancouver, British Columbia, Canada). This trial included a 12-month intervention (Figure 1). Ethical approval was provided by the University of British Columbia (UBC) Clinical Research Ethics Board (H15-00972) and the Vancouver Coastal Health Research Institute (V15-00972). All participants provided informed consent. The trial protocol has been published.[26]

2.2 | Recruitment

We recruited through community-based advertisements and specialized medical clinics in Metro Vancouver. To increase diversity of participants, we advertised on various bus routes and provided reimbursement for transportation. Enrollment and randomization occurred from May 26, 2016 to March 17, 2021. The COVID-19 pandemic halted recruitment from March 2020 to October 2020.

2.3 | Inclusion and exclusion criteria

Eligible participants were community-dwelling adults who met study criteria for SVCI, defined as the presence of both cerebral small vessel disease and mild cognitive impairment.[27] Cerebral small vessel disease was defined as the presence of WMHs and/or lacunes on magnetic resonance imaging (MRI). Mild cognitive impairment was defined by a Montreal Cognitive Assessment (MoCA) score $< 26/30$,[28] no prior diagnosis of dementia, and preserved functional independence determined by interview.[29]

Additional inclusion criteria were: (1) aged ≥ 55 years; (2) a Mini-Mental State Examination (MMSE)[30] score $\geq 20/30$; (3) English speaking; (4) able to comply with scheduled visits, treatment plan, and other trial procedures; (5) not expected to start or already on a stable fixed dose of cognitive medications during the 12-month study period; (6) able to walk independently with or without assistive devices; (7) not engaged in progressive resistance training over the last 6 months; and (8) ability to provide informed consent.

Exclusion criteria were: (1) a clinical diagnosis of neurodegenerative disease (e.g., Parkinson's disease), dementia, or genetic cause of SVCI; (2) at high risk for cardiac complications during exercise; (3) taking medications that may negatively affect cognitive function as determined by study physician; (4) planning to participate, or already enrolled, in a clinical drug trial or exercise trial concurrent to this trial; or (5) are unable to meet MRI scanning requirements, as specified by the UBC 3T MRI Research Centre. All participants provided written informed consent.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using traditional (e.g., PubMed) sources. Exercise is effective in preventing or reducing key risk factors for subcortical vascular cognitive impairment (SVCI). A systematic review of 14 randomized trials of exercise in adults with post-stroke cognitive impairment or SVCI; only 1 trial (of aerobic training) was in SVCI. No trial has examined the effect of progressive resistance training on cognitive function in adults with SVCI.
2. **Interpretation**: Our findings suggests that progressive resistance training may promote cognitive function in SVCI, and females may benefit more than males.
3. **Future directions**: To increase the precision by which we can recommend exercise to adults with SVCI to promote their cognitive health, future studies need to: (a) explore the effects of different types of exercise training, (b) identify moderators of exercise efficacy (e.g., biological sex), and (c) examine the distinct mechanisms by which each exercise modality may exert its benefits.

2.4 | Randomization and blinding

The randomization scheme was generated with permuted blocks on May 26, 2016 and stored by randomization.com (http://www.randomization.com). The sequence was held independently and remotely by an investigator not involved in the trial on a day-to-day basis. Participants were enrolled and randomized (1:1) to either a 12-month, twice-weekly progressive resistance training (PRT) program or a 12-month, twice-weekly balance and tone (BAT; active control) program. Allocation was concealed.

Assessors were blinded to participant allocation by not being involved in trial coordination or the delivery of exercise classes. Participants were also asked to refrain from discussing their study involvement or experience during assessments with assessors. Participants and those who delivered the interventions were not blinded. The success of blinding was not formally assessed.

2.5 | Experimental groups

Each treatment arm included twice-weekly supervised classes of 60 minutes for 12 months as described previously.[26] All instructors were trained by the research team and delivered the interventions based on protocols. Due to public health mandates and spread of COVID-19, in-person training was not offered from March 19, 2020 to August 6, 2020, November 26, 2020 to December 8, 2020, and April 20 to April 29, 2021. Instead, participants were asked to train at home. For

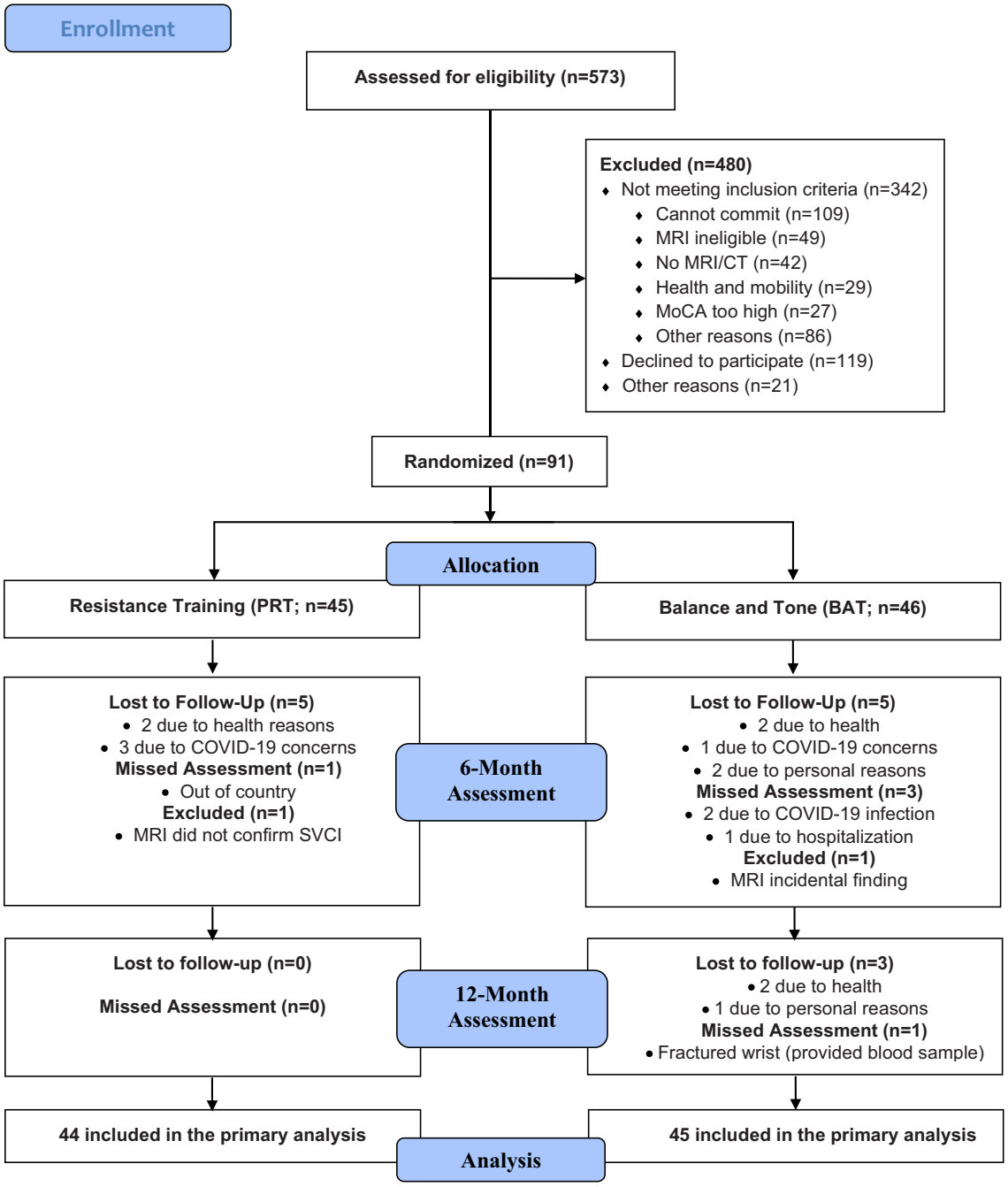

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) flowchart of participants. BAT, balance and tone; CT, computed tomography; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; PRT, progressive resistance training; SVCI, subcortical vascular cognitive impairment.

at-home training, participants were provided the necessary equipment and provided access to instructional videos either by YouTube or DVD, and were called on a weekly basis to monitor progress, adherence, and adverse events.

2.5.1 | Progressive resistance training

The PRT program consisted of exercises using a Keiser pressurized air system and free weights. The pressurized air system exercises included leg press, seated hamstring curls, latissimus dorsi pull downs, and seated rows. Exercises using free weights included wall squats, lunges, prone stability ball hamstring curls, standing calf raises, bicep curls, triceps extensions, various core exercises, and balance exercises. The first 4 weeks of the program were focused on orienting participants with the exercises and familiarizing them with proper technique. The intensity of training began at a load at which participants could complete two sets of 10 to 12 repetitions with proper form. At week 4, training intensity progressed to 70% to 85% of predicted one repetition maximum (RM) using the 8RM method. Every 4 weeks the 8RM test

was repeated. The number of sets completed and the load lifted was recorded for each participant at each class.

For at-home training due to the COVID-19 pandemic, PRT participants were provided with resistance bands of various weights that can be anchored and exercise diaries to document each training session.

2.5.2 | Balance and tone training

The BAT program consisted of stretching, various core exercises, simple balance exercises (e.g., tandem standing, single leg stand), functional movements (e.g., sit-to-stand), deep breathing, and relaxation techniques. Other than body weight, no additional loading was applied to the exercises. Notably, none of the BAT exercises were progressive in nature, either in loading or difficulty. The BAT program has been used in prior trials of exercise[13,31] and serves as a control for confounding variables such as physical activity associated with traveling to classes, social interaction, and changes in lifestyle secondary to study participation. For at-home training due to the COVID-19 pandemic, BAT participants were provided with a Pilates ball and exercise diaries to document each training session.

2.6 | Measures

Measures were acquired at baseline, 6 months (i.e., midpoint), and 12 months (i.e., end of intervention) by blinded assessors.

2.6.1 | Descriptors

Biological sex, education level, smoking status, and current medication use were recorded. Global cognitive function was assessed by the MMSE[30] and the MoCA.[28] The Functional Comorbidity Index[32] measured the number of comorbid conditions. The Center for Epidemiologic Studies Depression Scale assessed depression.[33] The Framingham Risk Score was calculated to estimate each participant's 10-year cardiovascular disease risk.[34] Brachial pulse pressure (i.e., the difference between systolic blood pressure and diastolic pressure) was measured in the supine position; it is significantly associated with WMHs, stroke risk, cognitive impairment, and dementia.[35] Magnetic resonance images were visually assessed and the severity of WMHs was visually quantified using the Fazekas Scale.[36] We tracked which participants' training or assessments were impacted by the COVID-19 pandemic and who contracted COVID-19 via self-report.

2.6.2 | Outcomes

The Alzheimer's Disease Assessment Scale Cognitive Plus (ADAS-Cog-Plus) was the primary cognitive outcome of this trial. The ADAS-Cog-Plus uses a multidimensional item response theory model and the *mirt* package in R[37] to generate a global cognitive score and the standard error of measurement from the 13-item ADAS-Cog (ADAS-Cog-13) and additional standard cognitive assessments.[38] For the current trial, we used the ADAS-Cog-13,[39] Trail Making Test Parts A and B,[40] Digit Span Forward and Backward,[41] Digit Symbol Substitution Test,[42] and category fluency (i.e., animal and vegetables)[40] as the input variables into the scoring algorithm. Scores were calculated using parameters from a calibration based on Alzheimer's Disease Neuroimaging Initiative 1 data.[38] Lower ADAS-Cog-Plus scores represent better cognitive performance; scores of ≈ -1.0 indicate healthy cognitive functioning, of 0.0 indicate mild cognitive impairment, and of 1.0 indicate dementia.[38] For more information regarding the development and scoring of the ADAS-Cog-Plus, please refer to its technical summary.[38]

The ADAS-Cog-Plus was selected as the primary outcome because evidence suggests it is more sensitive to subtle cognitive changes than the original ADAS-Cog-13 or 11-item ADAS-Cog (ADAS-Cog-11).[43] Notably, the version of the ADAS-Cog-Plus (i.e., ADAS-Cog-13 plus Trail Making Test Parts A and B, Digit Span Forward and Backward, Digit Symbol Substitution Test, and category fluency) used in this trial includes all the components of the Vascular Dementia Assessment Scale,[44] which can differentiate persons with different WMH ratings (i.e., mild, moderate, or severe). The Vascular Dementia Assessment Scale is the ADAS-Cog-13 with Digit Span Backward, Digit Symbol Substitution Test, and categorical fluency.[44] A minimally important difference has yet to be established for the ADAS-Cog-Plus.

The ADAS-Cog-13 was a secondary cognitive outcome.[39] Scores range from 0 to 85, with higher scores indicating greater cognitive impairment; a change of 3.0 points is a minimally important difference.[45]

Additional pre-specified secondary outcomes included the Short Physical Performance Battery (SPPB),[46] the Timed Up and Go (TUG),[47] the dual TUG,[48] the Six-Minute Walk Test (6MWT),[49] Physiological Profile Assessment (PPA),[50] dominant isometric quadriceps strength using a strain gauge to the nearest 0.5 kg, and arterial stiffness measured using carotid–femoral pulse-wave velocity (Complior; Alam Medical). Current physical activity was assessed using the Physical Activity Scale for the Elderly (PASE).[51] In a subset of consenting participants, HbA1c and CRP levels were determined from fasting blood samples collected in the morning by standard venipuncture and analyzed by the Provincial Health Services Authority blood laboratory services.

2.7 | Adverse events and fidelity

During the 12-month intervention period, participants were instructed to report any adverse events to research staff. Three independent investigators reviewed all adverse events and classified them based on the definitions provided by the National Institute on Aging Adverse Event and Serious Adverse Event Guidelines. Adherence was determined from: (1) in-person class attendance recorded by the instructors and (2) number of at-home training sessions completed recorded by participants in exercise diaries provided by the research team. Adherence was calculated as: {(total session completed/total session

expected) x 100}; total session expected was the same regardless of attrition status. To assess whether loading progressed in the PRT group, we estimated 1RM using the 8RM method on the Keiser leg press and latissimus dorsi pull-down machines at baseline, 6 months, and 12 months among PRT participants.

2.8 | Statistical analyses

All analyses were conducted in R version 4.3.2. This trial allows the evaluation of statistical significance of the treatment effect between groups on the ADAS-Cog-Plus at the end of the 12-month intervention.[26] A prior 6-month randomized clinical trial of aerobic exercise on cognitive function, as measured by the ADAS-Cog-11, in adults with SVCI observed an effect size of 0.89 (Cohen *d*) in the complete case analysis.[11] Assuming a more conservative effect size of 0.60, an alpha of 0.05 (two tailed), and a beta of 0.20, 35 participants per group would provide a power of 0.80. We aimed to recruit a total of 88 participants with SVCI (i.e., 44 participants per group) to accommodate a 20% attrition rate.

Treatment effects for the primary outcome, ADAS-Cog-Plus, were evaluated using linear mixed models with full information maximum likelihood estimation. The model included random intercepts and fixed effects of time (i.e., 6 months and 12 months), experimental group, and the time by group interaction. Time was specified as a categorical variable, allowing for the examination of treatment differences at 6 and 12 months (i.e., primary endpoint). Unequal variance was allowed across time and group. Baseline ADAS-Cog-Plus score, MoCA score, biological sex, education, PASE, functional mobility, cardiovascular risk, Fazekas Scale score, and COVID-19 infection (i.e., yes/no) were included as fixed-effect covariates. A similar linear mixed model with full information maximum likelihood estimation was conducted for the secondary cognitive outcome of ADAS-Cog-13.

Additional linear mixed models with full information maximum likelihood estimation were conducted for the secondary outcome measures of: (1) SPPB, (2) TUG and dual TUG, (3) 6MWT, (4) PPA, (5) dominant isometric quadriceps strength, (6) carotid–femoral pulse-wave velocity, (7) PASE, and (8) blood biomarkers. Baseline value of outcome, MoCA score, biological sex, education, cardiovascular risk, Fazekas Scale score, and COVID-19 infection (i.e., yes/no) were included as fixed-effect covariates.

All participants with available data at baseline were included in the model. With the exception of blood-based outcomes (PRT = 40; BAT = 43), all participants provided data for primary and secondary outcomes at baseline (PRT = 44; BAT = 45). Table S1 in supporting information shows the number of participants who provided data at each time point for all outcomes. All linear mixed models used full-estimation maximum likelihood to estimate model parameters,[52] which uses all available observed data points for each participant to estimate model parameters under the assumption that data are missing at random. Estimated marginal means, within-group differences from baseline, and between-group differences for planned contrasts at 6 and 12 months were calculated for all models. The overall alpha was set at 0.05 (two sided). Given that this was a proof-of-concept trial, we did not account for multiple comparisons.

There are sex differences in the effect of exercise on cognitive outcomes.[53] Thus, we explored whether biological sex moderated the effects of the intervention on cognitive outcomes (i.e., ADAS-Cog-Plus and ADAS-Cog-13). Linear mixed models using full information maximum likelihood estimation were conducted. The models included random intercepts and fixed effects of time (i.e., 6 months and 12 months), experimental group, biological sex, and the time by group by sex interaction. The same fixed-effect covariates as the primary analysis were used. Simple planned contrasts were then conducted to explore between-group differences in cognitive outcomes at 6 and 12 months, stratified by biological sex. In the event of significant effects, we conducted post hoc contrasts comparing the estimated between-group differences (i.e., PRT – BAT) in cognitive outcomes for males versus females.

To examine whether progressive loading occurred in the PRT program, using paired *t* tests, we examined whether PRT participants significantly increased their estimated 1RM on the Keiser leg press and latissimus dorsi pull-down exercises from baseline to 6 months, and from baseline to 12 months.

3 | RESULTS

3.1 | Participant characteristics

Ninety-one participants were enrolled and randomized. The final assessment was made on June 2, 2022. After randomization, two participants were deemed ineligible. One participant's MRI scan showed a significant brain tumor (incidental finding) and one participant's MRI scan did not show WMHs on visual examination. Both participants were excluded from all analyses (Figure 1). Table 1 provides the baseline descriptive characteristics of the 89 participants (65.17% female) with a mean age of 75 years (standard deviation [SD] = 6). Of the 89 participants, 83 consented to providing blood samples at baseline. The median Fazekas Scale score was 1, indicating mild white matter damage among study participants.[36] The mean baseline MMSE (mean = 27.31; SD = 1.92), MoCA (mean = 21.20; SD = 3.33), and ADAS-Cog-Plus scores (mean = –0.14; SD = 0.71) indicate participants had mild cognitive impairment.[28,38] More BAT participants contracted COVID-19 versus PRT participants.

3.2 | Impact of the COVID-19 pandemic

This trial was impacted by the COVID-19 pandemic. Specifically, the intervention of 21 participants (10 PRT participants; 11 BAT participants) were modified; they were asked to complete at-home training versus in-person training. The 12-month assessment for five participants (three PRT participants; two BAT participants) was delayed by 12 weeks because of the pandemic. During this time, participants continued with at-home training.

TABLE 1 Baseline characteristics by group ($N = 89$).

Variable[a]	PRT ($n = 44$)	BAT ($n = 45$)
Age (years)	74 (6)	75 (6)
Males *n*, %	14, 31.82%	17, 37.78%
Body Mass Index (kg/m^2)	27.11 (5.66)	27.76 (5.28)
Education *n*, %		
High School or Less	5, 11.36%	8, 17.78%
Trade School or Some College	15, 34.09%	10, 22.22%
University Degree or Higher	24, 54.55%	27, 60.00%
Smoking Status *n*, %		
Non-Smoker	25, 56.82%	31, 68.89%
Past Smoker	18, 40.91%	14, 31.11%
Current Smoker	1, 2.27%	0, 0.00%
Number of Prescription Medications	3.43 (2.66)	2.38 (1.91)
Falls in the Last 12 Months	1.73 (0.79)	1.36 (0.67)
Mini-Mental State Examination (/30 pts)	27.50 (1.94)	27.13 (1.91)
Montreal Cognitive Assessment (/30 pts)	21.52 (3.25)	20.89 (3.43)
Functional Comorbidity Index	3.63 (1.43)	3.67 (2.07)
CESD	7.02 (5.83)	7.66 (5.93)
Framingham Risk Score (%)	18.02% (9.79%)	18.15% (11.49%)
Supine Systolic Blood Pressure (mmHg)	132.14 (17.79)	131.73 (19.23)
Supine Diastolic Blood Pressure (mmHg)	78.44 (9.75)	77.22 (10.92)
Supine Brachial Pulse Pressure (mmHg)	53.80 (14.29)	54.53 (17.38)
Fazekas Score		
1	22, 50.00%	25, 55.56%
2	16, 36.36%	11, 24.44%
3	6, 13.64%	9, 20.00%
COVID-19 Infection (yes/no)[b]	1, 2.27%	3, 6.67%
ADAS-Cog-Plus	−0.18 (0.65)	−0.10 (0.77)
ADAS-Cog-13 (/85 pts)	13.44 (4.92)	13.98 (5.85)
Short Physical Performance battery (/12 pts)	10.27 (1.48)	10.29 (1.60)
Timed Up and Go (s)	9.47 (2.35)	9.68 (2.76)
Dual Timed Up and Go (s)	12.31 (3.34)	13.17 (7.21)
Six-Minute Walk Test (m)	469.12 (82.10)	474.58 (90.42)
Physiological Profile Assessment	1.81 (1.10)	1.63 (0.99)
Dominant Quadriceps Strength (kg)	27.73 (13.36)	30.78 (12.48)
Pulse-Wave Velocity (m/s)	10.88 (4.41)	9.89 (3.98)
Physical Activity Scale for the Elderly	101.04 (38.25)	112.89 (57.10)
C-Reactive Protein (mg/L)	4.26 (11.88)	2.54 (3.27)
Hemoglobin A1c (%)	6.17 (1.07)	5.89 (0.52)

Abbreviations: ADAS-Cog-13, 13-item Alzheimer's Diseases Assessment Scale Cognitive subscale; ADAS-Cog-Plus, Alzheimer's Disease Assessment Scale Cognitive Subscale Plus; BAT, balance and tone; CESD, Center for Epidemiological Studies Depression scale; PRT, progressive resistance training.

[a] $n = 83$ for blood biomarkers.

[b] Self-report of having contracted COVID-19 during the 12-month trial.

3.3 | Outcomes

Table 2 describes the results of the intention-to-treat analysis. Table 3 provides within-group change from baseline to 6 months, and from baseline to 12 months. At 12 months, participants in the PRT group had significantly better ADAS-Cog-Plus performance compared with the BAT group (estimated mean difference: −0.18; 95% confidence interval [CI: −0.35, −0.01]; $p = 0.04$). A post hoc calculation indicated that this effect was small (Cohen $d = 0.18$). However, the effect of the PRT intervention on ADAS-Cog-13 performance was not statistically different from BAT (estimated mean difference: −1.31; 95% CI: [−2.91, 0.29]; $p = 0.11$). At 6 months, participants in the PRT group had significantly better TUG performance compared with the BAT group (estimated mean difference: −0.56 seconds; 95% CI: [−1.11, −0.01]; $p = 0.04$). At 12 months, participants of the PRT group had significantly lower CRP compared with the BAT group (estimated mean difference: −2.93 mg/L; 95% CI: [−5.36, −0.49]; $p = 0.02$). There were no between-group differences in the additional pre-specified secondary outcome measures at either 6 or 12 months (Table 2).

Table 4 describes sex differences in the effect of the intervention on cognitive outcomes. The time by group by sex interaction was not significant at 6 and 12 months for all outcomes ($ps > 0.05$). At 12 months, simple planned contrasts conducted separately within each biological sex showed a significant effect of the PRT intervention versus BAT on ADAS-Cog-Plus performance (estimated mean difference: −0.27; 95% CI: [−0.49, −0.05]; $p = 0.02$) for females, but not for males. Post hoc contrasts comparing the estimated between-group differences (i.e., PRT − BAT) in ADAS-Cog-Plus performance for males versus females were not significant at 12 months (estimated mean difference: −0.23; 95% [CI: −0.58, 0.12]; $p = 0.20$).

At 12 months, simple planned contrasts, stratified by biological sex, showed no significant effect of the PRT intervention versus BAT on ADAS-Cog-13 performance for males (estimated mean difference: −1.38; 95% CI: −4.06, 1.31; $p = 0.31$) or females (estimated mean difference −1.31; 95% CI: −3.34, 0.73; $p = 0.21$).

3.4 | Adverse events

No serious adverse events were reported and no adverse events resulted in study withdrawal or permanent discontinuation of PRT or

TABLE 2 Estimated mean differences in outcome variables at 6 months and 12 months for intention-to-treat analysis ($N = 89$).

Outcome[a]	PRT – BAT at 6 months (95% CI)	*p*	PRT – BAT at 12 months (95% CI)	*p*
ADAS-Cog-Plus	−0.02 (−0.19, 0.15)	0.83	−0.18 (−0.35, −0.01)	0.04
ADAS-Cog13 (/85 pts)	−0.96 (−2.55, 0.62)	0.23	−1.31 (−2.91, 0.29)	0.11
Short Physical Performance Battery (/12 pts)	0.02 (−0.54, 0.58)	0.95	−0.07 (−0.63, 0.49)	0.81
Timed Up and Go (s)	−0.56 (−1.11, −0.01)	0.04	−0.17 (−0.72, 0.38)	0.54
Dual Timed Up and Go (s)	−0.51 (−1.87, 0.86)	0.46	−0.41 (−1.77, 0.96)	0.56
Six-Minute Walk Test (m)	4.88 (−17.80, 27.60)	0.67	−7.58 (−30.30, 15.10)	0.51
Physiological Profile Assessment	0.22 (−0.29, 0.72)	0.40	−0.04 (−0.55, 0.48)	0.89
Dominant Quadriceps Strength (kg)	0.75 (−2.79, 4.29)	0.68	2.45 (−1.21, 6.10)	0.19
Pulse-Wave Velocity (m/s)	0.19 (−1.04, 1.43)	0.76	0.43 (−0.85, 1.70)	0.51
Physical Activity Scale for the Elderly	−4.34 (−28.80, 20.12)	0.73	−13.33 (−36.40, 9.69)	0.25
C-Reactive Protein (mg/L)	0.48 (−1.90, 2.85)	0.69	−2.93 (−5.36, −0.49)	0.02
Hemoglobin A1c (%)	0.13 (−0.09, 0.34)	0.24	0.13 (−0.09, 0.35)	0.24

Abbreviations: ADAS-Cog-13, 13-item Alzheimer's Diseases Assessment Scale Cognitive subscale; ADAS-Cog-Plus, Alzheimer's Disease Assessment Scale Cognitive Subscale Plus; BAT, balance and tone; CI, confidence interval; PRT, progressive resistance training.
[a]$n = 83$ for blood biomarkers.

TABLE 3 Estimated mean change in outcome variables from baseline for intention-to-treat analysis ($N = 89$).

	Adjusted within-group change baseline – 6 months (95% CI)		Adjusted within-group change baseline – 12 months (95% CI)	
Outcome[a]	PRT ($n = 44$)	BAT ($n = 45$)	PRT ($n = 44$)	BAT ($n = 45$)
ADAS-Cog-Plus	0.09 (−0.20, 0.38)	0.15 (−0.14, 0.45)	0.20 (−0.08, 49)	0.11 (−0.19, 0.40)
ADAS-Cog-13 (/85 pts)	1.59 (−0.81, 3.98)	1.16 (−1.35, 3.68)	2.13 (−0.27, 4.52)	1.36 (−1.16, 3.87)
Short Physical Performance Battery (/12 pts)	−0.77 (−1.62, 0.08)	−0.73 (−1.59, 0.12)	−0.85 (−1.70, −0.01)	−0.87 (−1.73, −0.02)
Timed Up and Go (s)	0.81 (−3.85, 5.47)	0.46 (−4.99, 5.92)	0.87 (−3.79, 5.53)	0.91 (−4.55, 6.36)
Dual Timed Up and Go (s)	2.46 (−6.23, 11.15)	2.82 (−11.42, 17.05)	3.12 (−5.57, 11.81)	3.57 (−10.66, 17.81)
Six-Minute Walk Test (m)	−17.21 (−55.73, 21.32)	−6.86 (46.00, 32.28)	−3.00 (−42.80, 36.81)	−5.12 (−44.23, 33.99)
Physiological Profile Assessment	0.25 (−0.46, 0.96)	0.28 (−0.39, 0.96)	0.31 (−0.41, 1.02)	0.09 (−0.58, 0.77)
Dominant Quadriceps Strength (kg)	−2.79 (−8.44, 2.87)	1.02 (−4.14, 6.45)	−2.02 (−7.71, 3.67)	3.47 (−2.03, 8.98)
Pulse-Wave Velocity (m/s)	1.04 (−0.97, 3.05)	0.24 (−1.65, 2.14)	0.71 (−1.33, 2.76)	0.15 (−1.76, 2.06)
Physical Activity Scale for the Elderly	−4.90 (−35.50, 25.69)	2.61 (−29.52, 34.74)	−2.08 (−32.48, 28.32)	−3.56 (−32.26, 28.13)
C-Reactive Prrotein (mg/L)	0.91 (−3.85, 5.66)	−0.33 (−3.31, 2.64)	2.04 (−2.75, 6.82)	−2.61 (−5.60, 0.38)
Hemoglobin A1c (%)	−0.04 (−0.48, 0.39)	−0.19 (−0.50, 0.12)	0.03 (−0.42, 0.46)	−0.12 (−0.43, 0.19)

Abbreviations: ADAS-Cog-13, 13-item Alzheimer's Diseases Assessment Scale Cognitive subscale; ADAS-Cog-Plus, Alzheimer's Disease Assessment Scale Cognitive Subscale Plus; BAT, balance and tone; CI, confidence interval; PRT, progressive resistance training.
[a]$n = 83$ for blood biomarkers.

BAT. A total of 113 non-serious adverse events were reported, 63 in the PRT group and 50 in the BAT group. Seventy-four events were deemed to be not related or most likely not related to the trial. Of the remaining 39 possibly, most-likely, or definitely related non-serious adverse events, 25 were in the PRT group and 14 were in the BAT group.

For the PRT group, 13 of the 25 non-serious adverse events were reported by five PRT participants. Thus, the total number of PRT participants who experienced ≥ 1 non-serious adverse event(s) was 12. Twenty-three events were related to musculoskeletal discomfort that resolved with time (i.e., mild discomfort) or managed with stretches or exercise modifications (i.e., moderate discomfort), one participant fainted during class, and one participant experienced dizziness during class. For the one participant who fainted, they were taken to the emergency department. Treatment provided was a reduction in blood pressure medication dose. For the one participant who experienced dizziness, they were advised to see their family physician who referred them to a cardiologist.

TABLE 4 Sex differences in estimated mean change in outcome variables from baseline ($N = 89$).

	Males				Females			
	Adjusted within-group change (95% CI)		Adjusted between-group differences (95% CI)		Adjusted within-group change (95% CI)		Adjusted between-group differences (95% CI)	
Outcome	PRT ($n = 14$)	BAT ($n = 17$)	PRT – BAT	p	PRT ($n = 31$)	BAT ($n = 29$)	PRT – BAT	p
Change from baseline to 6 months (midpoint)								
ADAS-Cog-Plus	0.36 (−0.06, 0.77)	0.35 (−0.09, 0.79)	0.09 (−0.20, 0.38)	0.55	−0.10 (−0.42, 0.23)	−0.04 (−0.41, 0.34)	−0.07 (−0.29, 0.14)	0.51
ADAS-Cog-13 (/85 pts)	3.77 (0.30, 7.24)	2.62 (−0.92, 6.16)	−0.95 (−3.67, 1.78)	0.49	0.28 (−2.50, 3.07)	0.08 (−3.00, 3.17)	−0.94 (−2.94, 1.06)	0.35
Change from baseline to 12 months (trial completion)								
ADAS-Cog-Plus	0.50 (0.09, 0.91)	0.37 (−0.06, 0.81)	−0.04 (−0.32, 0.25)	0.80	0.00 (−0.32, 0.33)	−0.14 (−0.51, 0.24)	−0.27 (−0.49, −0.05)	0.02
ADAS-Cog-13 (/85 pts)	4.57 (1.11, 8.03)	2.99 (−0.54, 6.53)	−1.38 (−4.06, 1.31)	0.31	0.71 (−2.07, 3.50)	0.15 (−2.97, 3.26)	−1.31 (−3.34, 0.73)	0.21

Abbreviations: ADAS-Cog-13, 13-item Alzheimer's Diseases Assessment Scale Cognitive subscale; ADAS-Cog-Plus, Alzheimer's Disease Assessment Scale Cognitive Subscale Plus; BAT, balance and tone; CI, confidence interval; PRT, progressive resistance training.

For the BAT group, two of the non-serious events were reported by one participant. Thus, the total number of BAT participants who experienced ≥ 1 non-serious adverse event(s) was 12. Four BAT participants each experienced a fall; three occurred while performing BAT exercises, and one occurred while a participant was biking to class and fell without sustaining injuries. Of the three falls that occurred while performing BAT exercises, one occurred at home and resulted in a 2-inch laceration to their forehead and a visit to the emergency department. Neuroimaging was unremarkable and the laceration was stitched. Study personnel reviewed falls prevention tips with this participant (e.g., not being distracted while doing exercises, reduce clutter on the floor, etc.). Two participants experienced dizziness during class that resolved with eating a snack. Two participants rolled off their stability ball during class but sustained no injuries. The remaining six participants experienced musculoskeletal discomfort that resolved with time (i.e., mild discomfort) or managed with stretches or exercise modifications (i.e., moderate discomfort).

The incidence proportion (i.e., number of participants who experienced ≥ 1 adverse event in group/number of participants in group)[54] was similar between PRT and BAT. The incidence proportion for the PRT group was 0.273 (i.e., 12/44) or 27.3%. The incidence proportion for the BAT group was 0.266 (i.e., 12/45) or 26.6%.

3.5 | Fidelity

Adherence was not significantly different between PRT and BAT ($p = 0.18$). Mean adherence was 75.06% for the PRT group and 70.68% for the BAT group. The attrition total rate was 14.61% (i.e., 13 of 89); five from the PRT group and eight from the BAT group.

Table 5 provides the estimated 1RM on the Keiser leg press and latissimus dorsi pull-down exercises for the PRT participants. The data suggest progressive loading occurred in the PRT program. From baseline, PRT participants significantly increased in estimated 1RM on the leg press at 6 months (estimated difference from baseline: −213.04 N; 95% CI: [−375.19, −50.89]; $p = 0.01$) and at 12 months (estimated difference from baseline: −512.55 N; 95% CI: [−750.57, −274.53]; $p < 0.001$). Similarly, PRT participants significantly increased in estimated 1RM for the latissimus dorsi pull-down at 6 months (estimated difference from baseline: −47.21 N; 95% CI: [−75.86, −18.56; $p = 0.002$) and at 12 months (estimated difference from baseline: −71.24 N; 95% CI: [−104.63, −37.85]; $p < 0.001$).

4 | DISCUSSION

This proof-of-concept randomized trial suggests engaging in PRT may benefit cognitive function in community-dwelling adults with cerebral small vessel disease confirmed by MRI and mild cognitive impairment (i.e., SVCI), a population at risk for dementia and functional decline. We found a small, significant improvement in cognitive function, as measured by the ADAS-Cog-Plus at the end of the 12-month PRT intervention, relative to the active control (i.e., BAT) group. The results also

TABLE 5 Estimated 1RM at baseline, 6 months, and 12 months for PRT group ($n = 39$).

	Baseline (SD)	6 months (SD)	12 months (SD)	Baseline – 6 months (95% CI)	*p*	Baseline – 12 months (95% CI)	*p*
Leg press (N)	1110.67 (313.47)	1323.71 (428.11)	1623.22 (628.23)	−213.04 (−375.19, −50.89)	0.01	−512.55 (−750.57, −274.53)	<0.01
Lat. pull-down (N)	219.17 (57.22)	266.38 (72.88)	290.41 (84.24)	−47.21 (−75.86, −18.56)	<0.01	−71.24 (−104.63, −37.85)	<0.01

Abbreviations: CI, confidence interval; PRT, progressive resistance training; SD, standard deviation.

suggest that there may be sex differences in the effect of PRT on cognitive function in adults with SVCI. Progressive resistance training also significantly reduced CRP levels after 12 months.

Only one prior published trial has examined the effect of exercise on cognitive outcomes in community-dwelling adults with SVCI.[9,11] The trial by Liu-Ambrose et al.[11] focused on moderate-intensity aerobic training and found a small, significant improvement in ADAS-Cog performance after 6 months. The current results concur and contrast with this prior finding; PRT significantly improved ADAS-Cog-Plus performance but did not significantly improve ADAS-Cog performance. The ADAS-Cog-Plus, developed by the Alzheimer's Disease Neuroimaging Initiative investigators, is more responsive to subtle cognitive changes in mild cognitive impairment than the original ADAS-Cog-13, without impairing validity.[43] The sample size estimation for this trial was based on the ADAS-Cog-Plus. Thus, it is reasonable that we observed an effect for the ADAS-Cog-Plus and not for the ADAS-Cog-13. Nevertheless, it is noteworthy that the between-group difference of 1.31 points on the ADAS-Cog-13 observed in this trial is within the range observed in prior pharmaceutical trials among persons with SVCI (i.e., 1–2 points).[55–57] Given that a minimally important difference for the ADAS-Cog-Plus has not been established and longitudinal trajectories of cognitive change in SVCI remain poorly defined, the clinical interpretation of the observed PRT-related cognitive effect is uncertain.

Impaired mobility and falls are common among persons with SVCI.[58] Progressive resistance training improves gait and balance in older adults[59] and is a central component of evidence-based exercise programs to prevent falls.[60] In this trial, PRT provided minimal benefit to physical function, including physiological falls risk, compared with the BAT group. PRT significantly improved functional mobility at 6 months but not at 12 months. The lack of between-group differences in physical function at 12 months may be because the BAT group included balance exercises and functional movements (e.g., sit-to-stand). Notably, the COVID-19 pandemic may have magnified the potential benefit of the BAT group; physical activity levels significantly decreased and sedentary behavior significantly increased among older adults during the quarantine period of COVID-19 worldwide.[61,62] Conversely, because PRT exercises require more expertise to deliver per protocol (e.g., progression based on 8RM) versus BAT exercises, the potential benefit of PRT on physical outcomes may have been attenuated by COVID-19 modifications.

PRT did not have a significant effect on carotid–femoral pulse-wave velocity. This finding is consistent with the conclusions of a systematic review and meta-analysis of 10 randomized controlled trials in healthy young adults (310 participants; mean age = 29).[63] A systematic review and meta-analysis of 24 randomized controlled trials of exercise in older adults found aerobic exercise training and combined exercise training (i.e., aerobic exercise and resistance training) were effective in reducing pulse-wave velocity, but not resistance training.[25] However, this conclusion was based on one study, highlighting the dearth of randomized controlled trials of resistance training in older adults with pulse-wave velocity as an outcome of interest. Current guidelines recommend a carotid–femoral pulse-wave velocity exceeding 10

m/s threshold to detect hypertension mediated organ damage;[64] study participants had a baseline mean carotid–femoral pulse-wave velocity of 10.37 m/s (SD = 4.20). The PRT participants showed a decrease of 1.04 m/s and 0.71 m/s in in carotid–femoral pulse-wave velocity at 6 and 12 months, respectively, while the BAT participants showed a decrease of 0.24 m/s and 0.15 m/s. An increase of 1 m/s in carotid-femoral pulse-wave velocity at 12 months translates to a 7% increased risk of a cardiovascular event.[65] Thus, despite the lack of statistical significance, the degree of reduction in pulse-wave velocity observed in the PRT participants may be of clinical significance.

Twelve months of PRT significantly reduced CRP levels compared with BAT. This aligns with prior research.[16,66] CRP is a biomarker of systemic inflammation that is associated with cerebral small vessel disease[17] and cognitive impairment in cerebral small vessel disease.[18] A normal CRP level is 3.0 mg/L (or 0.3 mg/dL), mild elevation is 3.1 mg/L to 10 mg/L, moderate elevation is 10.1 mg/L to 100 mg/L, and marked elevation is > 100 mg/L.[67] The mean baseline CRP values indicate normal to mild elevation among the majority of the study participants. Thus, the biological relevance of the observed CRP reduction with PRT in this trial appears limited. Nevertheless, minor CRP elevations are common in the general population and are associated with poorer prognoses across a range of conditions, and are predictive of mortality.[68] PRT may lower CRP levels through biological pathways involving the release of myokines, which play a role in regulating systemic inflammation.[69] Myokines are cytokines or peptides that are produced and released by muscle fibers, especially during muscle contractions.[69] A narrative review concluded that resistance training can induce the production of different myokines, including interleukin-6, meteorin-like hormone, irisin, and brain-derived neurotrophic factor.[70] Further research is needed to explore these potential mechanisms, as they were beyond the scope of this trial.

Existing meta-analytic evidence demonstrates that resistance training can significantly reduce HbA1c levels among older adults with type 2 diabetes mellitus.[19] The mean baseline HbA1c values indicate prediabetes (i.e., 5.7%–6.4%) among the majority of study participants.[71] Thus, the absence of a significant effect of PRT on HbA1c may be attributed to the fact that participants did not have type 2 diabetes mellitus.

The biological sex-stratified exploratory analysis showed evidence of sex differences in the effect of PRT on cognitive function. Specifically, PRT females showed improved performance on the ADAS-Cog-Plus compared with BAT females. This finding aligns with a systematic review and meta-analysis that reported a larger effect of resistance training on executive function in studies with a higher proportion of female participants.[53] However, because sex did not significantly moderate the effect of PRT on cognitive function, this exploratory finding should be interpreted as hypothesis generating. Moreover, the overall evidence on sex differences in the cognitive benefits of exercise remains inconclusive.[72] Thus, more research designed specifically to assess sex differences in the effect of exercise on cognitive function and the underlying mechanisms is needed.

There are limitations. Notably, the COVID-19 pandemic impacted this trial's recruitment, data collection, and the delivery of both PRT and BAT. In the effort to sustain the trial throughout the quarantine period of COVID-19, protocol deviations occurred. Specifically, both PRT and BAT became home-based programs during the shutdown of the university and its research facilities. Thus, progression of PRT exercises based on 8RM (per protocol) was not possible and this may have attenuated the effect of PRT on outcomes. Even after re-opening of facilities, the home-based programs were offered as an option to existing participants who were reluctant to attend in-person classes. Assessments were delayed because of the inability to conduct in-person testing; however, for these individuals, they were offered to continue to train at home. All these deviations may have biased the results. Beyond protocol deviations, it is well recognized that COVID-19 infections are associated with a range of symptoms, including reduced cognitive function, poor mental health, and increased cardiovascular risk.[73] Even without infection, evidence shows the COVID-19 pandemic resulted in significant reductions in cognitive performance among older adults.[74] Reductions in cognitive performance were associated with reduced physical activity, increased alcohol use, and loneliness.[74] This trial tracked physical activity using the PASE but did not track alcohol use or feelings of loneliness. Given these significant confounds, future research is needed to confirm current findings. While this trial applied well-defined clinical criteria for SVCI, including neuroimaging,[75] participants may still present with mixed pathology, such as concomitant Alzheimer's disease. While there was a significant effect of PRT on ADAS-Cog-Plus, the effect was small and likely not of clinical importance. The majority of the study participants had a Fazekas Scale score of 1. Thus, our current results may not apply to those with more significant cerebral small vessel disease. This trial lacks race and ethnicity data, which limits our ability to examine potential disparities or differential effects among racialized individuals. Gender identity was not collected in this study and thus, gender-based analysis was not performed. We did not account for multiple comparisons and thus, the risk of Type 1 error is inflated. Because the trial was not powered for secondary outcomes or sex differences, any observed or not observed effects should be considered hypothesis generating and require confirmation in future trials.

Despite these limitations, our proof-of-concept trial provides preliminary evidence that a 12-month program of twice-weekly PRT promotes cognitive function in adults with cerebral small vessel disease confirmed by MRI and mild cognitive impairment. Future studies are needed to confirm current findings, explore the effects of different types of exercise training on outcomes in individuals with SVCI, identify moderators of exercise efficacy (e.g., biological sex), and examine the distinct mechanisms by which each exercise modality may exert its benefits.

AUTHOR CONTRIBUTIONS

T.L.-A. (principal investigator) wrote the grant application which was funded by Heart and Stroke Foundation of Canada and wrote the initial draft of the manuscript. T.L.A., C.K.B., G.-Y.R.H., K.M.M., and R.C.T. contributed to study conception and design. T.L.A., R.S.F., E.D., R.A.C., C.K.B., W.A.A., J.R.B., G.-Y.R.H., T.S.F., K.M.M., J.C.D., and L.F.T.B. contributed to acquisition of data. T.L.A., R.S.F., E.D., R.A.C., C.K.B.,

N.C.B.S.S., W.A.A., J.R.B., J.C.D., and R.C.T. contributed to the analysis and interpretation of data. All authors contributed to drafting or revising the manuscript critically. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

T.S.F. declares the following: (1) advisory board participation: AstraZeneca, Bayer, HLS Therapeutics, and Novartis; (2) speaker's bureau: AstraZeneca; expert witness testimony, CMPA, and plaintiff; and (3) board member: DESTINE Health and VGH/UBC Hospital Foundation. All other authors have no disclosures to declare. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants provided informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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