Resistance Training and White Matter Lesion Progression in Older Women: Exploratory Analysis of a 12-Month Randomized Controlled Trial

Niousha Bolandzadeh, PhD,[abcde] Roger Tam, PhD,[f] Todd C. Handy, PhD,[g] Lindsay S. Nagamatsu, PhD,[h] Chun Liang Hsu, MSc,[acde] Jennifer C. Davis, PhD,[aeij] Elizabeth Dao, MSc,[acde] B. Lynn Beattie, MD,[ek] and Teresa Liu-Ambrose, PhD, PT[abcde]

OBJECTIVES: To assess whether resistance training (RT) slows the progression of white matter lesions (WMLs) in older women.

DESIGN: Secondary analysis of a 52-week randomized controlled trial of RT, the Brain Power Study.

SETTING: Community center and research center.

PARTICIPANTS: Of 155 community-dwelling women aged 65 to 75 enrolled in the Brain Power Study, 54 who had evidence of WMLs on magnetic resonance imaging (MRI) at baseline were included in this secondary analysis.

INTERVENTION: Participants were randomized to once-weekly RT (1× RT), twice-weekly RT (2× RT), or twice-weekly balance and tone (BAT). Assessors were blinded to participant assignments.

MEASUREMENTS: WML volume was measured using MRI at baseline and trial completion.

RESULTS: At trial completion, the 2× RT group had significantly lower WML volume than the BAT group ($P = .03$). There was no significant difference between the BAT group and the 1× RT group at trial completion ($P = .77$). Among participants in the two RT groups, reduced WML progression over 12 months was significantly associated with maintenance of gait speed (correlation coefficient (r) = −0.31, $P = .049$) but not with executive functions ($r = 0.30$; $P = .06$).

CONCLUSION: Engaging in progressive RT may reduce WML progression. **J Am Geriatr Soc 63:2052–2060, 2015.**

Key words: resistance training; white matter lesions; magnetic resonance imaging

From the [a]Aging, Mobility and Cognitive Neuroscience Laboratory; [b]Experimental Medicine Program; [c]Djavad Mowafaghian Centre for Brain Health; [d]Centre for Hip Health and Mobility; [e]Vancouver Coastal Health Research Institute; [f]Department of Radiology; [g]Department of Psychology, University of British Columbia, Vancouver, British Columbia, Canada; [h]Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, Illinois; [i]School of Population and Public Health, University of British Columbia; [j]Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Research Institute; and [k]Division of Geriatric Medicine, Faculty of Medicine, University of British Columbia, Vancouver, Canada.

Address correspondence to Dr. Teresa Liu-Ambrose, Djavad Mowafaghian Centre for Brain Health, c/o Liu-Ambrose Lab, 2215 Wesbrook Mall, Vancouver, BC, V6T 2B5 Canada. E-mail: teresa.ambrose@ubc.ca

DOI: 10.1111/jgs.13644

Cognitive impairment and falls significantly increase morbidity and mortality in older adults.[1,2] Both geriatric syndromes are associated with white matter lesions (WMLs),[3,4] which appear as hyperintensities on T2-weighted magnetic resonance imaging (MRI) and are markers of (but not specific to) cerebral small-vessel disease.[5] These covert lesions are highly prevalent in older adults,[6] with epidemiological studies reporting a prevalence of 85% or greater.[7–9] Thus, interventions that prevent or slow the progression of WMLs may be of great societal value by preserving cognitive function and mobility in older adults.[10]

Recognized metabolic and vascular risk factors for WMLs include type 2 diabetes mellitus, dyslipidemia, and hypertension.[6] Thus, interventions that reduce metabolic and vascular risk factors may prevent or slow the progression of WMLs. In this regard, physical activity is a promising strategy. It reduces metabolic and vascular risk factors, as well as overall morbidity and mortality.[11,12] A 5-year prospective cohort study showed that higher levels of physical activity were associated with reduced WML progression in older adults without dementia.[13] Moreover, a recent cross-sectional study of 88 older adults found that moderate to vigorous physical activity, measured using accelerometry, was significantly associated with lower volume of WMLs.[14]

Broadly, there are two distinct forms of physical activity: aerobic exercise (e.g., running) and resistance training (RT; e.g., lifting weights). Aerobic training is well known for its potent ability to reduce vascular risk factors,[11,12]

0002-8614/15/$15.00

and thus, it is a focus in research on cerebral small-vessel disease research.[15] However, RT also has significant cardiometabolic benefits.[16,17] Specifically, a meta-analysis of randomized controlled trials[16] concluded that RT should be recommended in the management of type 2 diabetes mellitus and metabolic disorders. Another meta-analysis of randomized controlled trials[17] suggested that moderate-intensity RT is an effective intervention strategy to reduce and prevent high blood pressure. A 6-month randomized trial of RT[18] showed that RT positively impacted arterial size, function, and wall thickness, which could lead to lower cardiovascular risk. RT may also promote cerebrovascular function; a small cross-sectional study demonstrated that regular RT was associated with greater cerebral perfusion in otherwise healthy older women.[19] As such, RT may reduce metabolic and vascular risk factors and modulate the progression of WMLs. Moreover, recent studies have shown the beneficial effect of RT on cognitive function and mobility.[20] Thus, reduced progression of WMHs might be one mechanism through which RT preserves cognitive function and mobility.

To the knowledge of the authors of this study, no randomized controlled trial has examined the effect of exercise (RT or aerobic training) on WML progression in older adults. Thus, using neuroimaging data from a 12-month single-blind randomized controlled trial (clinicaltrials.gov Identifier: NCT00426881) of exercise,[21] this was a planned exploratory analysis to assess: 1) the effect of RT on the progression of WMLs in community-dwelling older women; and 2) the association between WML progression and changes in executive functions (measured using the Stroop Color Word Test) and mobility (measured by physiological falls risk and gait speed).

METHODS

Study Design

This was a randomized, controlled 52-week prospective study of RT (Brain Power Study[21]). The research team trained assessors were blinded to group allocation of participants. MRI data were acquired at baseline and trial completion in a subset of eligible participants.

Participants

The sample consisted only of women because cognitive response to exercise differs between sexes.[20] Participants were recruited using print advertisements and a television interview about the study. Individuals were screened in a standardized telephone interview. Briefly, women who lived in metro Vancouver, Canada, were eligible for study entry if they were aged 65 to 75, were living independently in their own home, scored 24 or higher on the Mini-Mental State Examination (MMSE), and had visual acuity of at least 20/40, with or without corrective lenses. Those who had a current medical condition for which exercise is contraindicated, had participated in RT (using free weights, weight machines, or resistance bands) one or more times per week on a regular basis in the 6 months before study entry, had a neurodegenerative disease or stroke, had depression, did not speak and understand English fluently, were taking cholinesterase inhibitors, or were undergoing estrogen replacement or testosterone therapy were excluded.

The Consolidated Standards of Reporting Trial flowchart shows the number and distribution of participants included in this secondary analysis (Figure 1). Only women with WMLs on their baseline MRI were included in this secondary analysis. Ethical approval was obtained from the Vancouver Coastal Health Research Institute and the University of British Columbia (UBC) Clinical Research Ethics Board. All participants provided written informed consent.

Descriptive Variables

At baseline, participants underwent a physician assessment to confirm current health status and eligibility for the study. Information was collected on age, years of education, height, weight, MMSE score, Montreal Cognitive Assessment (MoCA) score, blood pressure, and waist-to-hip ratio. Comorbidities, such as type 2 diabetes mellitus, hypertension, and dyslipidemia, were assessed using the Functional Comorbidity Index (FCI).[22] The Geriatric Depression Scale (GDS)[23] was used to screen for depression. Current level of physical activity was determined using the Physical Activities Scale for the Elderly (PASE) self-report questionnaire.[24] In addition, isotonic quadriceps strength (one-repetition maximum) and peak muscle power were assessed using an air-pressure digital resistance leg press machine (Keiser Sports Health Equipment, Fresno, CA).

Dependent Variable: WMLs

Structural MRI Data Acquisition

Structural MRI data were acquired on a research-dedicated MRI scanner (3T Achieva; Philips Medical Systems, Best, the Netherlands) at the UBC MRI Research Centre. A T2-weighted scan and a proton-density-weighted (PD-weighted) scan were acquired for each subject. For the T2-weighted images, the repetition time (TR) was 5,431 ms and the echo time (TE) was 90 ms. For the PD-weighted images, the TR was 2,000 ms and the TE was 8 ms. T2- and PD-weighted scans had dimensions of $256 \times 256 \times 60$ voxels and a voxel size of $0.937 \times 0.937 \times 3.000$ mm.

Structural Data Processing and Analysis

MRI preprocessing was performed with publicly available tools that are widely used for neuroimaging studies. Each MRI image underwent the following preprocessing steps before lesion identification and segmentation were performed. MRI intensity inhomogeneity was corrected using a multiscale version of the nonparametric nonuniform intensity normalization method (N3),[25] a structure-preserving noise-removal filter (SUSAN) was applied,[26] and all nonbrain tissue was removed using the brain extraction tool (BET).[27]

A radiologist with extensive experience in WML identification identified and digitally marked the WMLs following a set of guidelines[28] that is minimalistic and allows

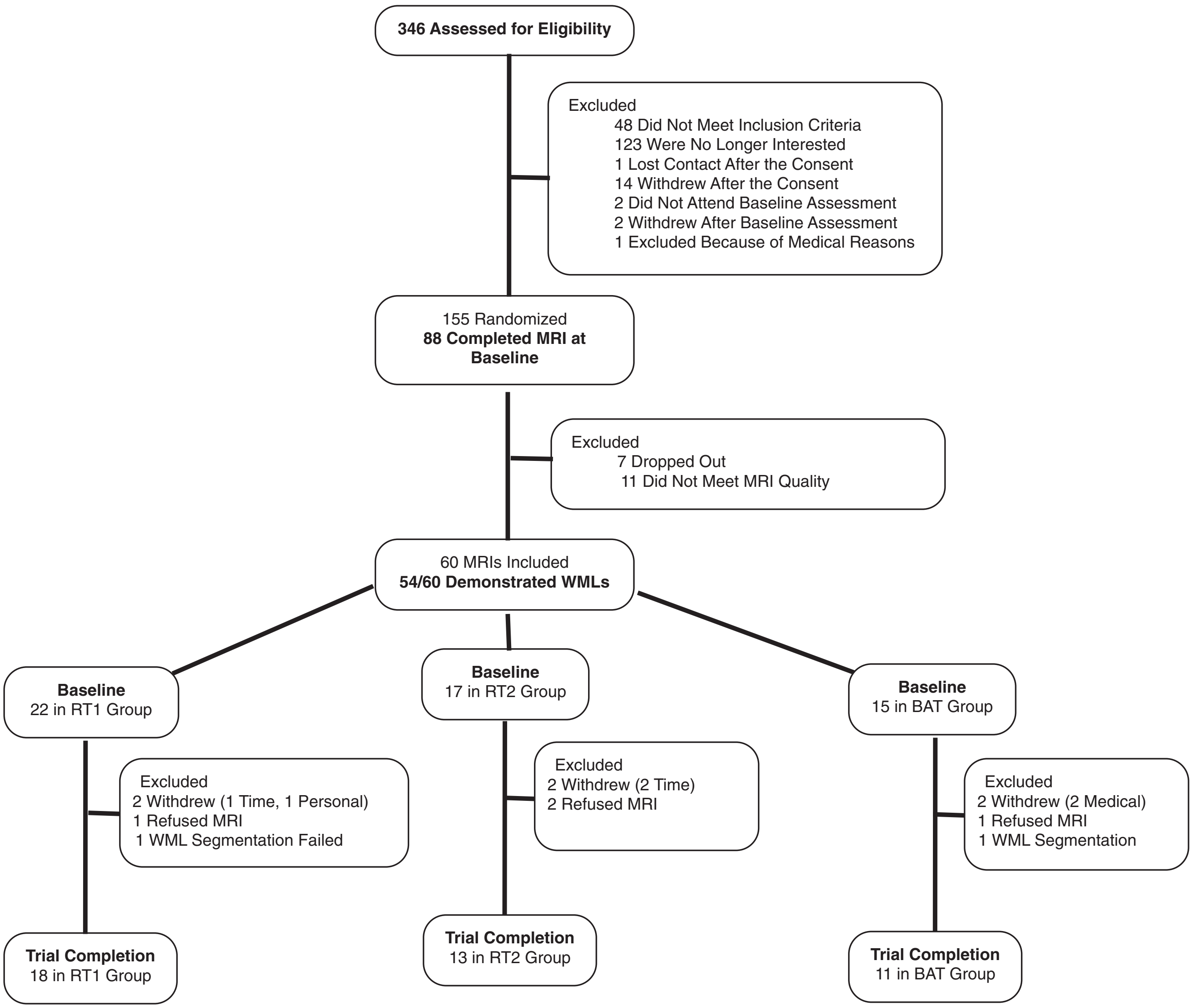

Figure 1. Consolidated Standards of Reporting Trial flowchart of participants. MRI = magnetic resonance imaging; RT1 = once-weekly resistance training; RT2 = twice-weekly resistance training; BAT = balance and tone; WML = white matter lesion.

the seeding procedure to be efficient and intuitive. Specifically, the radiologist marked all distinct WMLs regardless of their size, placed more than one point on a lesion if the additional points would help define the extent of the lesion, and placed at least one point near the center of each lesion.

The WMLs were then segmented using a method that automatically computed the extent of each marked lesion.[28] Full details on the point placement procedure and subsequent automatic segmentation have been previously described,[28] but briefly, the seed points were processed using a customized Parzen windows classifier[29] to estimate the intensity distribution of the lesions. The algorithm included heuristics to optimize the accuracy of the estimated distributions by dynamically adjusting the position and the number of seed points used for the Parzen window computation, as well as a spatial method that approximated visual shape partitioning to identify areas that were likely to be false positives. The segmentation method was previously validated extensively on large data sets with a large range of lesion loads and was found to be highly accurate when compared with expert segmentations and robust to variations in the placement of the seed points.[28] The lesion masks were then used to quantify WML volumes in mm^3 at baseline and trial completion. Appendix S1 represents baseline and trial completion lesion masks overlaid on T2 images from one participant. The seeds that the radiologist marked are shown as red dots.

Executive Functions

White matter lesions are associated with impaired cognitive function and, in particular, executive functions.[4] The primary outcome for the Brain Power Study was the Stroop Color Word Test, a measure of specific cognitive processes of selective attention and conflict resolution.[21] There were three conditions for the Stroop Color Word Test. Participants were required to read out words printed in black ink (e.g., "blue") read out the color of colored "X's", and name the ink color in which color words were printed (e.g., the word "blue" printed in red ink) while ignoring the word itself. There were 80 trials for each condition and the time to complete each condition was recorded. The ability to attend selectively and control response output was calculated as the time difference between the third condition and the second condition (Stroop color-words condition minus Stroop colored-X's condition); smaller time differences indicate better selective attention and conflict resolution.

Physiological Falls Risk and Gait Speed

Numerous studies have highlighted the association between WMLs and impaired mobility;[10,30] falls are significant consequences of impaired mobility. Physiological falls risk was assessed using the short form of the valid and reliable Physiological Profile Assessment (PPA),[31] and gait speed was assessed by asking participants to walk at their usual pace along a 4-m path. Gait speed was calculated in m/s from the mean of two trials.

Randomization

The randomization sequence was generated using www.randomization.com and was concealed until interventions were assigned. The research coordinator held this sequence independently and remotely. The research coordinator enrolled participants and randomized them to one of three groups: once-weekly RT (1× RT), twice-weekly RT (2× RT), or twice-weekly balance and tone (BAT).

Sample Size

This exploratory analysis was planned before the study was initiated, as indicated by the inclusion of the structural MRI sequences necessary for WML quantification. The required sample size for this study's primary research question[21] was calculated based on previous[32] predictions of 12-month changes in the Stroop Color Word Test. Specifically, based on previous work[32] that demonstrated that a home-based program of strength and balance training exercises significantly improved Stroop Color Word Test performance, 6% improvement was predicted for the 1× RT and 12% improvement for the 2× RT, and 10% deterioration in the BAT group (control group) was estimated. Assuming a 20% attrition rate, using an alpha level of < .05 and a common standard deviation of 25 seconds, 52 participants per group ensured a power of 0.80.

Exercise Intervention and Compliance

The exercise classes began 1 month after the baseline assessments were completed. A detailed description of these classes has been previously published.[21] The classes were 60 minutes long, with 10 minutes of warm-up, 40 minutes of core content, and 10 minutes of cool-down. Certified fitness instructors who received additional training and education from the study investigators led all classes. Adherence was calculated based on the percentage of total classes attended.

Resistance Training

Both RT programs were progressive. A combination of a system of pressurized air machines (Keiser) and free weights was used to provide the training stimulus. The machine-based exercises consisted of biceps curls, triceps extensions, seated rows, latissimus dorsi pull-downs, leg presses, hamstring curls, and calf raises. The intensity of the training stimulus was at a work range of six to eight repetitions (two sets), and the training stimulus was increased using the seven-repetition maximum method. Mini-squats, mini-lunges, and lunge walks were also included in the RT programs. The number of sets completed and the load lifted for each exercise was recorded for each participant at every class.

BAT Training

The BAT program consisted of stretching, range of motion, basic core strength including Kegel exercises (exercises to strengthen the pelvic for floor muscles), balance (tai chi–based forms, tandem stand, tandem walking, single-leg stance), and relaxation exercises. Other than body weight, no additional loading (hand weights, resistance bands) was used in any of the exercises. Participants assigned to the BAT group served as controls to avoid the confounding effect of social interaction and changes in lifestyle secondary to study population.

Adverse Effects

Participants were questioned about the presence of any adverse effects, such as musculoskeletal pain or discomfort, at each exercise session. All instructors also monitored participants for symptoms of angina pectoris and shortness of breath during the exercise classes.

Statistical Analysis

All analyses were full analysis set[33] (defined as the analysis set that is as complete and as close as possible to the intention-to-treat ideal of including all randomized participants). Statistical analyses were performed using SPSS version 20.0 (SPSS Statistics for Mac; IBM Corp., Armonk, NY). Because WMLs were distributed nonnormally, they were log-transformed, their normality was checked for after the log transformation, and they were used as continuous log-transformed variables in the analyses. The overall alpha was set at $P \leq .05$.

Effect of RT on WML volumes

Between-group differences in log-transformed WML volumes at trial completion were compared using multiple linear regression analysis. Baseline WML volume, experimental group, baseline waist-to-hip ratio, and baseline FCI were included as covariates in the models based on biological relevance and their association to metabolic and cardiovascular risk.[6] Two planned simple contrasts

Table 1. Baseline Characteristics of the 54 Participants with White Matter Lesions (WMLs)

Characteristic	Once-Weekly RT, n = 22	Twice-Weekly RT, n = 17	Balance and Tone, n = 15
Age, mean ± SD	69.6 ± 2.6	69.2 ± 3.1	69.3 ± 2.8
Education, n (%)			
<High school	0 (0)	1 (5.9)	0 (0)
Some high school	2 (9.1)	0 (0)	2 (13.3)
High school graduate	2 (9.1)	5 (29.4)	3 (20)
Trade or professional certificate	4 (18.2)	2 (11.8)	2 (13.3)
University certificate	5 (22.7)	1 (5.9)	1 (6.7)
University degree	9 (40.9)	8 (47.1)	7 (46.7)
Height, cm, mean ± SD	160.7 ± 6.4	161.3 ± 7.4	162.9 ± 5.8
Weight, kg, mean ± SD	68.2 ± 14.6	68.1 ± 12.5	69.5 ± 9.4
Diastolic Blood Pressure, mmHg, mean ± SD	84.5 ± 13.8	80.1 ± 10.9	89.1 ± 24.0
Systolic Blood Pressure, mmHg, mean ± SD	150.9 ± 18.1	135.6 ± 25.7	142.4 ± 20.6
Waist-to-Hip Ratio, mean ± SD	0.83 ± 0.07	0.83 ± 0.06	0.84 ± 0.05
Geriatric Depression Scale score, mean ± SD	0.04 ± 0.21	0.64 ± 1.36	0.60 ± 2.06
Functional Comorbidity Index, mean ± SD	1.82 ± 1.86	2.41 ± 1.97	1.93 ± 1.43
Mini-Mental State Examination score, mean ± SD	28.9 ± 1.0	28.8 ± 1.1	28.7 ± 1.3
Montreal Cognitive Assessment score, mean ± SD	25.8 ± 2.9	25.6 ± 2.9	24.4 ± 3.5
Stroop color-words condition —Stroop colored-X's condition, seconds, mean ± SD	46.7 ± 18.2	48.3 ± 16.4	46.9 ± 17.9
Physiological Profile Assessment score, mean ± SD	0.12 ± 1.02	0.29 ± 1.11	0.29 ± 1.08
Gait speed, m/s, mean ± SD	1.14 ± 0.21	1.17 ± 0.19	1.20 ± 0.17
Physical Activity Scale for the Elderly score, mean ± SD	125.0 ± 80.1	135.1 ± 61.9	118.2 ± 43.8
One-repetition maximum, N, mean ± SD	321.1 ± 81.5	306.1 ± 47.6	345.2 ± 72.5
Peak Muscle Power, W, mean ± SD	704.4 ± 205.5	565.5 ± 204.9	635.0 ± 192.1
WMLs, mm^3, mean ± SD	1,507.2 ± 1,903.0	1,470.9 ± 2,225.2	2,306.2 ± 4,508.4

RT = resistance training; SD = standard deviation.

were performed to assess differences between the 1× RT group and the BAT group and between the 2× RT group and the BAT group.

Correlations Between Change in WML Volume and Change in Stroop Color Word Test Performance, PPA, and Gait Speed

In the two RT groups, one-tailed Pearson correlations were calculated to determine whether WML progression over the 12-month randomized controlled trial was associated with Stroop Color Word Test performance, PPA, and gait speed. Change in WMLs was calculated as the difference between the log-transformed baseline and trial completion values. Changes in Stroop Color Word Test performance, PPA, and gait speed were also calculated as the difference between baseline and trial completion values. Thus, a positive change in WML volume, Stroop Color Word Test performance, and PPA would indicate improvement. Conversely, a negative change in gait speed would indicate improvement. All correlations were adjusted for waist-to-hip ratio and MoCA scores.

RESULTS

Participants

Eighty-eight of the 155 participants who consented and were randomized in the Brain Power Study underwent MRI scanning at baseline, 54 of whom demonstrated evidence of WMLs. Of these 54 participants, 42 completed MRI at trial completion (Figure 1). Of these 42 participants, 18 were assigned to 1× RT, 13 to 2× RT, and 11 to BAT programs.

Baseline characteristics of the 54 participants with evidence of WMLs at baseline are reported in Table 1; they do not significantly differ from the original 155 participants.[21] Their mean age ± standard deviation was 69.4 ± 2.8, similar to the mean age of the entire cohort (69.6 ± 2.9).[21] The three groups were not significantly different at baseline. The 2× RT group significantly improved mean peak quadriceps muscle power at trial completion compared with the BAT group (P = .008).

Adherence and Adverse Effects

Exercise adherence over 1 year for the primary study was 67.9% and was not significantly different between the three groups (1× RT, 71.0%; 2× RT group, 70.3%; BAT group, 62.0%). Regarding adverse events, 29.8% of the 1× RT group, 10.9% of the 2× RT group, and 9.5% of the BAT group had musculoskeletal complaints (e.g., knee joint discomfort, bursa irritation in the lateral hip), all of which resolved or diminished within 4 weeks of onset. One participant in the BAT group experienced one fall during the exercise class, which did not result in injury.

Effect of Exercise on WML Volumes

Table 2 provides the baseline and trial completion WML volume data for the 42 participants who completed the trial and both MRI sessions, including raw and log-transformed values. At trial completion, the 2× RT group had significantly lower WML volume than the BAT group ($P = .03$; Figure 2). There was no significant difference between the BAT group and the 1× RT group at trial completion ($P = .77$).

Correlations Between Change in WML Volume and Change in Stroop Color Word Test Performance, PPA, and Gait Speed

Reduced WML progression over the 12-month trial was significantly associated with maintenance of gait speed in the two RT intervention groups ($r = -0.31$, $P = .049$) (Figure 3). Change in WML volume was not significantly associated with change in Stroop Color Word Test performance ($r = 0.30$, $P = .06$) or with PPA ($r = 0.13$, $P = .25$).

Table 2. Descriptive Values of Raw and Log-Transformed White Matter Lesion (WML) Measures at Baseline and Trial Completion (N = 42)

WMLs	Baseline	Trial Completion
Once-weekly RT group, n	18	18
Raw (mm³), mean ± SD	1,774.52 ± 2,007.44	1,920.26 ± 2,127.23
Log-transformed, mean ± SD	2.81 ± 0.75	2.85 ± 0.74
Twice-weekly RT group, n	13	13
Raw (mm³), mean ± SD	1,805.03 ± 2,456.57	1,903.50 ± 2,684.03[a]
Log-transformed, mean ± SD	2.82 ± 0.73	2.80 ± 0.79
BAT group, n	11	11
Raw (mm³), mean ± SD	810.52 ± 1,082.03	952.51 ± 1,310.84
Log-transformed, mean ± SD	2.52 ± 0.75	2.58 ± 0.73

[a] Significantly different from the balance and tone (BAT) group at $P < .05$.
RT = resistance training; SD = standard deviation.

DISCUSSION

These novel proof-of-concept findings suggest that in community-dwelling women aged 65 to 75, 12 months of twice-weekly progressive RT reduces WML progression. Furthermore, reduced WML progression during the 12-month trial was associated with maintained gait speed.

White matter lesions are known risk factors for mobility and cognitive decline.[4,6,30,34] Moreover, they are highly prevalent in otherwise healthy older adults, and their progression over time has significant clinical consequences, which increase the risk of disability and reduce quality of life in older adults.[7] Therefore, strategies to prevent or reduce the progression of WMLs are of great importance. To the knowledge of the authors, this is the first study to demonstrate that engaging in progressive RT can significantly reduce WML progression in community-dwelling older women.

Resistance training provides a broad range of systemic benefits,[35,36] including moderating the development of sarcopenia, or age-related loss in skeletal muscle mass. The multifactorial deleterious sequelae of sarcopenia include falls, fractures, and physical disability.[35] Of particular relevance to WML progression, sarcopenia is an emerging risk factor for metabolic disorders. This may not be surprising given that skeletal muscle is the primary tissue for glucose and triglyceride metabolism.[37] Specifically, the Korea National Health and Nutrition Examination Survey showed that sarcopenia was associated with insulin resistance, diabetes mellitus, and metabolic syndrome in nonobese adults aged 20 and older.[38] Moreover, the Third

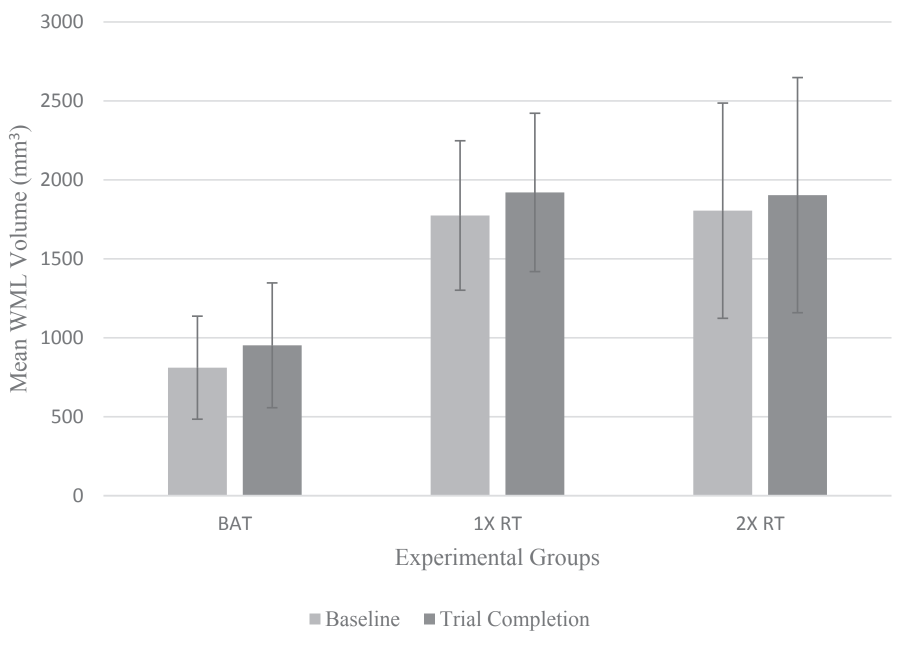

Figure 2. Change in white matter lesion (WML) volume from baseline to trial completion. *At trial completion, the twice-weekly resistance training (2× RT) group had significantly lower WML volume than the balance and tone (BAT) group. 1× RT = once-weekly resistance training.

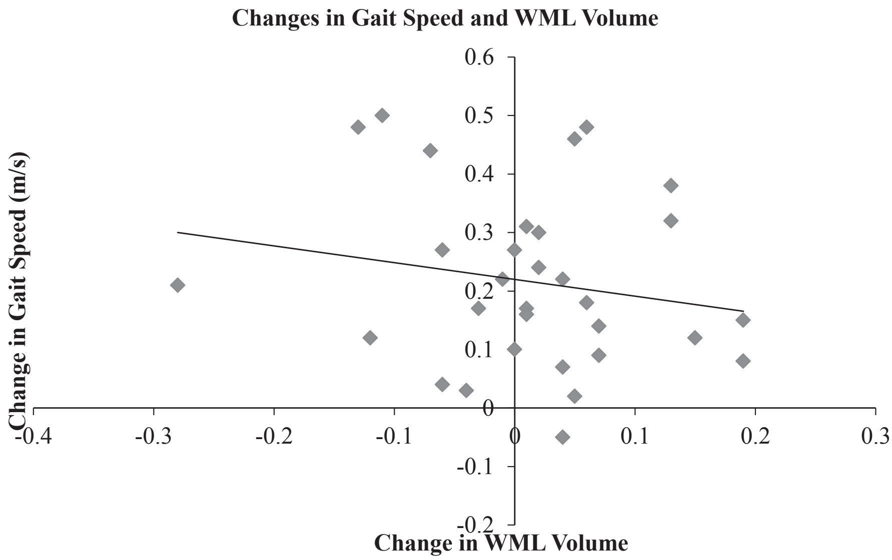

Figure 3. Scatterplot presents the association between change in white matter lesion (WML) volume and change in gait speed from baseline to trial completion, in the 1× RT and 2× RT groups (N = 31). Change in WML volume was calculated as baseline log-transformed WML value – trial completion log-transformed WML value. (Transformed data are not in its original units of measurement, such as mm^3.) Thus, a positive change score in WML volume would indicate reduced WML progression over the 6-month intervention period, and a negative change score would indicate increased WML volume progression. Change in gait speed was also calculated as baseline gait speed – trial completion gait speed. Hence, a negative change score would indicate improvement, and a positive change score would indicate decline in gait speed.

National Health and Nutrition Examination Study found that sarcopenia, independent of obesity, was associated with adverse glucose metabolism.[39] Thus, RT may reduce WML progression by reducing cardiometabolic risk factors. Previous randomized controlled trials that showed that RT improves insulin resistance and glycemic control support this hypothesis.[40] Furthermore, a 2011 review concluded that the metabolic and cardiovascular benefits of RT include better body composition, less abdominal fat mass, lower resting blood pressure, better lipoprotein-lipid profiles, and better glycemic control.[41]

Resistance training also has cardiovascular and cerebrovascular benefits. A 6-month randomized longitudinal trial of exercise demonstrated that RT increased the diameter and improved the function of the brachial artery and decreased carotid arterial wall thickness.[18] More specifically, greater intima-media thickness (IMT) of the carotid artery is closely related to the severity of atherosclerotic changes associated with cardiovascular disease. Previous research has reported mixed results regarding the ability of aerobic exercise to attenuate age-related increases in IMT.[42] This may be due to the significant shear stress created on the endothelial cell layer of arteries secondary to sustained increases in blood flow during aerobic exercise.[42,43] In contrast, RT results in periodic increases in blood flow, creating an alternative type of stress on the endothelial cells.[42] Thus, RT might be one possible modality to enhance arterial endothelial function and decrease cardiovascular risk. In addition, higher levels of endothelial dysfunction have been found to be associated with lower cerebrovascular perfusion.[44] Of particular relevance to the current results, a previous study showed that older women who engaged in RT at least once a week had significantly greater cerebrovascular perfusion than women who did not.[19]

The current results also suggest that participants who participated in RT more often (2× RT) received greater benefit with regard to WML progression than those who participated less often (1× RT), indicating a dose-response effect. The previous observation that 2× RT resulted in significant functional plasticity in two regions of the cortex associated with response inhibition and conflict resolution, whereas 1× RT did not, supports this,[45] although because of the smaller sample, additional investigations are needed to examine whether there is a dose-response effect of RT on WML progression.

In addition, it was demonstrated that reduced WML progression was associated with maintenance of gait speed, which concurs with and extends previous cross-sectional studies demonstrating a significant association between WML and gait speed.[30,46] The current results suggest that strategies that reduce the progression of WMLs may contribute directly to the maintenance of gait speed in older adults. Specifically, a 12-week randomized controlled trial of gait rehabilitation[47] demonstrated that baseline WML severity moderated the beneficial effect of exercise training on gait speed. The current findings suggest that, in addition to its severity, WML progression rate may be an important factor in changes in gait speed. Given that recent evidence suggests that the association between WMLs and mobility is independent of executive functions,[48] strategies that reduce the progression of WMLs may contribute directly to improved gait speed in older adults.

This study has limitations. First, the study sample of older women limits the generalizability of the results to older men. Second, the small number of participants included in this exploratory analysis increased the possibility of Type II error and imbalance in baseline characteristics.[49] Thus, future studies with larger sample sizes are needed to confirm the current findings and to extend understanding of the role of RT on WML progression. Specifically, based on the log-transformed WML volume data (Table 2), the overall effect size was 0.60 (expressed as a standardized difference, Cohen d). Based on this effect size, assuming an alpha of 0.05 (two-tailed) and a beta of 0.20, future studies should include a minimum of 45 participants per group to provide a power of 0.80 (G*Power 3.1).[50] Future studies should also aim to determine the mechanisms by which RT reduces WML progression in older adults. Finally, the study investigated the volume of WMLs in the whole brain. Further research on WMLs in specific regions of the brain would advance understanding of the effect of exercise on lesion progression in different brain regions and, ultimately, on cognitive function and mobility.

CONCLUSION

This randomized controlled trial provided novel proof-of-concept evidence that pragmatic RT may reduce WML progression in community-dwelling older women. Furthermore, reduced WML progression was associated with maintenance of gait speed. The potential clinical implications of these results are significant because WMLs are prevalent in older adults[6] and have negative consequences for mobility and cognitive function.

ACKNOWLEDGMENTS

We would like to thank our radiologist, Dr. Alex Mazur, who performed the lesion marking on the MRI dataset. We thank the Brain Power Study participants for their time and commitment.

This work was supported by operating grants from the Vancouver Foundation (BCM06–0035, Teresa Liu-Ambrose), an Establishment Grant from the Michael Smith Foundation for Health Research (MSFHR; CI-SCH-063 [05–0035], Teresa Liu-Ambrose), and the Jack Brown and Family Alzheimer Research Foundation Society. Teresa Liu-Ambrose is a Canada Research Chair in Physical Activity, Mobility and Cognitive Neuroscience. Niousha Bolandzadeh is a Heart and Stroke Foundation of Canada Doctoral trainee. Lindsay S. Nagamatsu is a Canadian Institutes of Health Research (CIHR) postdoctoral fellow. Chun Liang Hsu is an Alzheimer's Society Research Programme doctoral trainee. Jennifer C. Davis is an MSFHR and a CIHR postdoctoral fellow. Elizabeth Dao is a CIHR doctoral trainee.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author Contributions: Study concept and design: Liu-Ambrose, Tam, Handy, Beattie. Acquisition of data: Nagamatsu, Hsu, Liu-Ambrose. Analysis and interpretation: All authors. Critical revision of the manuscript for important intellectual content: All authors. Study supervision: Liu-Ambrose.

Sponsor's Role: None.

REFERENCES

1. Delbaere K, Van den Noortgate N, Bourgois J et al. The Physical Performance Test as a predictor of frequent fallers: A prospective community-based cohort study. Clin Rehabil 2006;20:83–90.
2. Morley JE. The top 10 hot topics in aging. J Gerontol A Biol Sci Med Sci 2004;59A:24–33.
3. Srikanth V, Beare R, Blizzard L et al. Cerebral white matter lesions, gait, and the risk of incident falls: A prospective population-based study. Stroke 2009;40:175–180.
4. Bolandzadeh N, Davis JC, Tam R et al. The association between cognitive function and white matter lesion location in older adults: A systematic review. BMC Neurol 2012;12:126.
5. Huijts M, Duits A, van Oostenbrugge RJ et al. Accumulation of MRI markers of cerebral small vessel disease is associated with decreased cognitive function. A study in first-ever lacunar stroke and hypertensive patients. Front Aging Neurosci 2013;5:72.
6. Kuo HK, Lipsitz LA. Cerebral white matter changes and geriatric syndromes: Is there a link? J Gerontol A Biol Sci Med Sci 2004;59A:818–826.
7. de Leeuw FE, de Groot JC, Achten E et al. Prevalence of cerebral white matter lesions in elderly people: A population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001;70:9–14.
8. Longstreth WT Jr, Manolio TA, Arnold A et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke 1996;27:1274–1282.
9. Liao D, Cooper L, Cai J et al. Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control. The ARIC Study. Atherosclerosis Risk in Communities Study. Stroke 1996;27:2262–2270.
10. Zheng JJ, Delbaere K, Close JC et al. White matter hyperintensities are an independent predictor of physical decline in community-dwelling older people. Gerontology 2012;58:398–406.
11. Dishman RK, Berthoud HR, Booth FW et al. Neurobiology of exercise. Obesity (Silver Spring) 2006;14:345–356.
12. Cotman CW, Berchtold NC. Exercise: A behavioral intervention to enhance brain health and plasticity. Trends Neurosci 2002;25:295–301.
13. Podewils LJ, Guallar E, Beauchamp N et al. Physical activity and white matter lesion progression: Assessment using MRI. Neurology 2007;68:1223–1226.
14. Burzynska AZ, Chaddock-Heyman L, Voss MW et al. Physical activity and cardiorespiratory fitness are beneficial for white matter in low-fit older adults. PLoS ONE 2014;9:e107413.
15. Middleton LE, Corbett D, Brooks D et al. Physical activity in the prevention of ischemic stroke and improvement of outcomes: A narrative review. Neurosci Biobehav Rev 2013;37:133–137.
16. Strasser B, Siebert U, Schobersberger W. Resistance training in the treatment of the metabolic syndrome: A systematic review and meta-analysis of the effect of resistance training on metabolic clustering in patients with abnormal glucose metabolism. Sports Med 2010;40:397–415.
17. Cornelissen VA, Fagard RH. Effect of resistance training on resting blood pressure: A meta-analysis of randomized controlled trials. J Hypertens 2005;23:251–259.
18. Spence AL, Carter HH, Naylor LH et al. A prospective randomized longitudinal study involving 6 months of endurance or resistance exercise. Conduit artery adaptation in humans. J Physiol 2013;591:1265–1275.
19. Xu X, Jerskey BA, Cote DM et al. Cerebrovascular perfusion among older adults is moderated by strength training and gender. Neurosc Lett 2014;560:26–30.
20. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: A meta-analytic study. Psycholl Sci 2003;14:125–130.
21. Liu-Ambrose T, Nagamatsu LS, Graf P et al. Resistance training and executive functions: A 12-month randomized controlled trial. Arch Intern Med 2010;170:170–178.
22. Groll DL, To T, Bombardier C et al. The development of a comorbidity index with physical function as the outcome. J Clin Epidemiol 2005;58:595–602.
23. Yesavage JA. Geriatric depression scale. Psychopharmacol Bull 1988;24:709–711.
24. Washburn RA, McAuley E, Katula J et al. The Physical Activity Scale for the Elderly (PASE): Evidence for validity. J Clin Epidemiol 1999;52:643–651.
25. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans Med Imaging 1998;17:87–97.
26. Smith SM, Brady JM. SUSAN—a new approach to low level image processing. Int J Comput Vis 1997;23:45–78.

27. Smith SM. Fast robust automated brain extraction. Hum Brain Mapp 2002;17:143–155.
28. McAusland J, Tam R, Wong E et al. Optimizing the use of radiologist seed points for improved multiple sclerosis lesion segmentation. IEEE Trans Biomed Eng 2010;57:2689–2698.
29. Parzen E. On estimation of a probability density function and mode. Ann Mathematical Stat 1962;33:1065–1076.
30. Bolandzadeh N, Liu-Ambrose T, Aizenstein H et al. Pathways linking regional hyperintensities in the brain and slower gait. NeuroImage 2014;99:7–13.
31. Lord SR, Menz HB, Tiedemann A. A physiological profile approach to falls risk assessment and prevention. Phys Ther 2003;83:237–252.
32. Liu-Ambrose T, Donaldson MG, Ahamed Y et al. Otago home-based strength and balance retraining improves executive functioning in older fallers: A randomized controlled trial. J Am Geriatr Soc 2008;56:1821–1830.
33. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. Stat Med 1999;18:1905–1942.
34. Rosano C, Kuller LH, Chung H et al. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. J Am Geriatr Soc 2005;53:649–654.
35. Borst SE. Interventions for sarcopenia and muscle weakness in older people. Age Ageing 2004;33:548–555.
36. Layne JE, Nelson ME. The effects of progressive resistance training on bone density: A review. Med Sci Sports Exerc 1999;31:25–30.
37. Stump CS, Henriksen EJ, Wei Y et al. The metabolic syndrome: Role of skeletal muscle metabolism. Ann Med 2006;38:389–402.
38. Moon SS. Low skeletal muscle mass is associated with insulin resistance, diabetes, and metabolic syndrome in the Korean population: The Korea National Health and Nutrition Examination Survey (KNHANES) 2009–2010. Endocr J 2014;61:61–70.
39. Srikanthan P, Hevener AL, Karlamangla AS. Sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia: Findings from the National Health and Nutrition Examination Survey III. PLoS ONE 2010;5:e10805.
40. Castaneda C, Layne JE, Munoz-Orians L et al. A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. Diabetes Care 2002;25:2335–2341.
41. Strasser B, Schobersberger W. Evidence for resistance training as a treatment therapy in obesity. J Obes 2011;2011: doi: 10.1155/2011/482564.
42. Olson TP, Dengel DR, Leon AS et al. Moderate resistance training and vascular health in overweight women. Med Sci Sports Exerc 2006;38: 1558–1564.
43. Niebauer J, Cooke JP. Cardiovascular effects of exercise: Role of endothelial shear stress. J Am Coll Cardiol 1996;28:1652–1660.
44. Sabayan B, Westendorp RG, Grond J et al. Markers of endothelial dysfunction and cerebral blood flow in older adults. Neurobiol Aging 2014;35:373–377.
45. Liu-Ambrose T, Nagamatsu LS, Voss MW et al. Resistance training and functional plasticity of the aging brain: A 12-month randomized controlled trial. Neurobiol Aging 2012;33:1690–1698.
46. Zheng JJ, Delbaere K, Close JC et al. Impact of white matter lesions on physical functioning and fall risk in older people: A systematic review. Stroke 2011;42:2086–2090.
47. Nadkarni NK, Studenski SA, Perera S et al. White matter hyperintensities, exercise, and improvement in gait speed: Does type of gait rehabilitation matter? J Am Geriatr Soc 2013;61:686–693.
48. Zheng JJ, Lord SR, Close JC et al. Brain white matter hyperintensities, executive dysfunction, instability, and falls in older people: A prospective cohort study. J Gerontol A Biol Sci Med Sci 2012;67A:1085–1091.
49. Portney LG, Watkins MP. Foundations of Clinical Research: Applications to Practice. Norwalk, CT: Appleton & Lange, 1993.
50. Faul F, Erdfelder E, Lang AG et al. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175–191.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Baseline and trial completion lesion masks overlaid on T2 images. The seeds that the radiologist marked are shown as red dots.

Please note: Wiley-Blackwell is not responsible for the content, accuracy, errors, or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.