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RESEARCH ARTICLE

Aerobic exercise in older people with subclinical sporadic cerebral small vessel disease: A randomized clinical trial

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Abstract

Introduction: The benefit and risk of aerobic exercise among older people harboring advanced cerebral small vessel disease (CSVD) upon cognition, mood, and motor functions are unknown.

Methods: This rater-blind randomized trial examined effects of a 24-week aerobic exercise training (60 min/session, twice/week) upon clinical (cognition, mood, motor functions) and hemodynamic (pulse pressure [PP], blood pressure [BP], pulsatility index) measures in older people harboring moderate to severe CSVD, as evidenced by confluent white matter hyperintensity and/or ≥2 lacunes on magnetic resonance imaging. We further investigated interactions between treatment conditions and hemodynamics measures.

Results: Fifty-three and 54 subjects were randomized into the active and control group, respectively. There was no between-group difference in any of the clinical outcomes. The active group had a greater between-group reduction in systolic BP and PP than the control group. Within-group comparison showed that global cognition of the active group remained similar at end of the study compared to baseline, whereas it declined significantly in the control group. We observed "diverging" interaction effects in that greater reduction in systolic BP/PP was associated with greater improvement in memory functions and global cognition but worsening in processing speed in the active group. Side effects were comparable between the two groups.

Discussion: Future study should investigate the mechanisms of the diverging impacts of aerobic exercise upon different cognitive domains so that the benefit–risk ratio of aerobic exercise in older people harboring more advanced CSVD can be better defined.

KEYWORDS
aerobic exercise, cerebral small vessel disease, cognitive impairment, randomized controlled trial

1 | BACKGROUND

Sporadic cerebral small vessel disease (CSVD) is a common cause of dementia and stroke.[1] Other symptoms that may co-occur include mood and gait problems.[1] It commonly evolves over years through a subclinical stage before the development of disabling events.[2] Those with more severe CSVD are at higher risk of incident dementia.[3] Ideally, intervention should target the subclinical stage for the prevention of disabling events.

Age and high blood pressure (BP) are the two most important interrelated etiological risk factors for CSVD.[4] With age, both aorta and cerebral small vessels undergo loss of elasticity. An increase in aortic stiffness leads to pulsatile flow being transmitted to the cerebral small vessels, causing further damage to the small vessels. In older people, an increase in pulse pressure (PP) and/or systolic BP reflects aortic stiffness.[5] The associated change of cerebral microcirculation includes a rise in pulsatility index (PI) of the intracranial large arteries that can be derived by transcranial doppler ultrasound (TCD). Studies showed an intercorrelation between the increase in these hemodynamic measures with worsening of CSVD and cognition.[6–8]

Clinical studies have shown that aerobic exercise in older people can improve aortic stiffness and cerebral microcirculatory function.[9–11] Many studies found an association between physical activity and less CSVD.[12] However, some found no[12] or even a negative association.[13] Overall, longitudinal studies involving younger subjects without advanced CSVD at baseline were more likely to show a positive association.[12] In another study, a J-shaped relationship was found in that physical activity beyond a limit was associated with an increase in CSVD.[14] A plausible explanation for this relationship was that as BP drops further with increasing physical activity, cerebral perfusion may drop if underlying cerebral autoregulation is impaired, which is common among older people with advanced CSVD.[15,16]

A systematic review has shown that aerobic exercise preferentially improves executive function and processing speed among healthy older people.[17] However, its impact in patients with Alzheimer's disease dementia was less consistent[18] and some yielded a negative effect upon cognition.[19] Taking together, the benefit–risk ratio of aerobic exercise upon the brain and cognition may be influenced by age, the intensity of exercise, and severity or types of underlying brain pathologies.

Given the benefit and risk of aerobic exercise in older people harboring moderate to advanced CSVD are unknown, we conducted this randomized controlled trial (RCT) exploring the short-term effects (24 weeks) of aerobic dance training (ADT) on clinical (cognition, mood, motor functions) and hemodynamic measures in this high-risk group. We also examined the potential interaction between the treatment group and hemodynamics upon clinical measures.

RESEARCH IN CONTEXT

1. Systematic review: Some clinical studies showed that physical activity is associated with less sporadic cerebral small vessel disease (CSVD) and better cognition in healthy older people. However, some showed a J-shaped association between physical activity and CSVD and that physical activity might even worsen cognition in patients with dementia. As reviewed using PubMed, the benefits and risks of aerobic exercise in older people harboring moderate-to-severe CSVD are unknown.

2. Interpretation: There was no difference in the change in cognition between the aerobic and control groups. The improvement in processing speed was not observed in the aerobic group and there was a "reverse" interaction between treatment condition and hemodynamics upon processing speed.

3. Future directions: Future study should investigate the mechanisms of the diverging impacts of aerobic exercise upon different cognitive domains so that the benefit–risk ratio of aerobic exercise in older people harboring more advanced CSVD can be better defined.

2 | METHODS

2.1 | Study design and participants

The CU-AEROBIC (The Chinese University of Hong Kong–Aerobic Exercise in Older People with Subclinical SporadIc Cerebral Small Vessel Disease) study is a rater-blind RCT involving 110 participants who were randomized in a 1:1 ratio into ADT or control group using computer-generated randomization codes. Inclusion criteria were (1) age $\geq$ 65 years; (2) community-dwelling; (3) presence of moderate to severe CSVD, defined by a global score of $\geq$ 2 of the Age-Related White Matter Changes rating scale on magnetic resonance imaging (MRI)[20,21] and/or $\geq$2 lacunes; and (4) written informed consent. Exclusion criteria were (1) history of stroke, (2) history of known cognitive disorder and/or Mini-Mental State Examination score less than education adjusted cutoff for dementia, (3) other significant neurological/psychiatric comorbidities, (4) physical impediments hindering participation in exercise training, and (5) contraindication for MRI.

Approximately half of the participants (n = 59) were recruited from another community project,[22] in which a brain MRI was performed upon 801 community-dwelling older people. We recruited additional participants from elderly centers. We arranged MRI for eligible subjects (n = 361) using a brief 10-minute MRI protocol (supporting information). Eventually, another 48 subjects with MRI evidence of moderate to severe CSVD were recruited.

2.2 | MRI quantitative data

Quantification of baseline white matter hyperintensity (WMH) was processed using AccuBrain (BrainNow Medical Technology Company Ltd.), a cloud-based automated brain quantification tool.[23] Please see supporting information for MRI acquisition details.

2.3 | Data collection

Data collection took place at baseline and weeks 12, 24, and 36.

2.3.1 | Cognitive functions

The 60-minute protocol of the National Institute of Neurological Diseases and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Neuropsychological Battery was administered,[24] which evaluates executive function (color trail test [CTT] 2, animal fluency test), processing speed (CTT1, Symbol-Digit Modalities Test [SDMT]), memory: verbal learning (Hong Kong List Learning Test [HKLLT] learning), verbal delayed recall (HKLLT 30-minute delayed recall), recognition memory (HKLLT 30-minute delayed recognition) and non-verbal delayed recall (Rey-Osterrieth Complex Figure Copy Test [RCFT] 30-minute delayed recall), visuospatial function (RCFT), and language (modified Boston naming test [mBNT]). Performances on individual cognitive tests were combined into a single composite summary z-score to reflect global cognition (60-minute protocol summary score). We administered the Montreal Cognitive Assessment (MoCA) at baseline.

2.3.2 | Mood and motor functions

Depressive symptoms were measured using the 15-item Geriatric Depression Scale (GDS).[25] The Mini-Balance Evaluation Systems Test (Mini-BESTest) was used to assess dynamic balance performance.[26] The Timed Up & Go test (TUG) was used to examine functional mobility.[27] The 6-minute walk test was used to determine walking capacity.[28] Performances on individual motor function tests were combined into a single composite summary z-score to reflect global motor function.

Daily physical activities outside training sessions were recorded using the self-report International Physical Activity Questionnaire (IPAQ; http://www.ipaq.ki.se/publications.htm). To avoid rater bias, the research assistant performing the assessment was blind to treatment allocation and encouraged not to discuss with the participants the interventions.

2.3.3 | Hemodynamics and apolipoprotein E genotyping

We obtained PP and systolic and diastolic BP at each study visit. We derived cerebral PI of the right and left middle cerebral artery (MCA) via TCD at each study visit (supporting information). Apolipoprotein E (APOE) polymorphisms were assayed by TaqMan genotyping.[3]

2.4 | Treatment condition

The active intervention lasted for 24 weeks and consisted of 60 minutes per session, targeting an age-specific heart rate reserve of 70%. In groups of 5, participants practiced the dance led by a physiotherapist once per week for the first 2 months and twice per week between months 3 and 6. Participants in the control group received a weekly 3-hour group-based (group of five participants) program containing stretching exercises and health education (supporting information).

2.5 | Sample size estimation

The sample size was estimated based on the hypothesized mediation model.[29] This estimation was based on testing the mediation effect in a linear regression model. Assuming that in the full model the regression coefficient of the mediator (i.e., TCD PI) = 1.8, the standard deviation of mediator, derived from the same sample of community older people with significant CSVD was 0.17, the standard deviation of the error term in full model = 1, and a point-biserial correlation of 0.4 between training effect and PI measures, a sample size of 100 was required to demonstrate a significant mediation model at power = 0.8 and 5% significance level. Assuming a dropout rate of 10%, a total sample size of 110 was needed.

2.6 | Statistical and efficacy analyses

Group comparison was conducted using independent sample t test, Chi-squared test, or Fisher exact Test where appropriate. For cognitive measures, the treatment effect was analyzed using analysis of covariance (ANCOVA) with age, years of education, and IPAQ scores entered as covariates. All outcome measures were analyzed using intention-to-treat (ITT) with the last observation carried forward to handle missing data, as well as per-protocol analysis. For details of the mediation model, please see supporting information. Statistical analysis was performed using IBM SPSS version 25.0. Statistical significance was determined at $P < .05$.

2.6.1 | Primary outcomes

Primary outcomes were the between-group comparison of the change in cognition between baseline and week 24. Percentage change was used to represent the change from baseline to subsequent visits. We performed a similar analysis of the above outcomes at other time points as well (see supporting information).

2.6.2 | Secondary outcomes

Secondary outcomes were the between-group comparisons of the change in mood, motor functions, and hemodynamic measures between baseline and week 24.

2.6.3 | Tertiary outcomes

Tertiary outcomes included a within-group comparison of all clinical measures. Other tertiary outcomes included the interaction effects between treatment condition and change in hemodynamics upon a change in cognitive, mood, and motor measures while controlling for age and years of education at week 24 using linear regression models. We also investigated whether effects of ADT upon a change in cognitive, mood, and motor measures were mediated through hemodynamic change via a standard mediation model with age and years of education entered as covariates (see supporting information). Linear regression models were conducted to examine the interaction effects between treatment condition and baseline WMH volume and *APOE ε*4, respectively, upon a change in clinical outcomes at week 24.

2.7 | Safety monitoring

Randomized subjects who had received at least one session of intervention were included in the safety analysis. Any adverse events were monitored throughout the study (see supporting information).

The study was approved by the Human Research Ethics Committee of the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (Ref. 2015.677-T) and was registered with ClinicalTrials.gov (NCT02730065).

3 | RESULTS

Fifty-four and 56 subjects were randomized into the ADT and control group, respectively. The intervention started in October 2016 and lasted for 24 weeks. Three subjects withdrew from the study without receiving the allotted intervention, leaving 53 and 54 in the ADT and control groups, respectively. A further four and six randomized subjects discontinued after receiving at least one allotted intervention, leaving 49 and 48 subjects who had completed the whole study

in the ADT and control groups, respectively (see Figure 1). There was no difference in any of the demographics, medical history, imaging features, and baseline outcome measures between ADT and control group (see Table 1). The mean age, MoCA score, and WMH volume for the whole ITT population were 75.66 ($\pm$5.08 standard deviation [SD]), 22.38 ($\pm$4.00 SD), and 8.34 ($\pm$8.09 SD) mL (see Figure 2), respectively. An example FLAIR image illustrating moderate WMH volume in the ADT group is illustrated in Figure S1 in supporting information.

3.1 | Primary outcomes

There was no significant between-group difference in cognitive change from baseline at week 24 (see Table 2) or at other time points (see supporting information).

3.2 | Secondary outcomes

Between-group comparisons on hemodynamic measures showed that there was a significant reduction from baseline in systolic BP in the ADT group ($P = .038$) and a trend favoring the ADT group in the reduction of PP from baseline ($P = .055$) compared to the control group. There was no between-group difference in diastolic BP and MCA PI.

Per-protocol analysis also showed no significant between-group difference at any timepoint in all clinical outcomes. For PP, its change between baseline and week 24 was associated with ADT became significant ($P = .047$) and this effect persisted until week 36 ($P = .021$, per protocol) (see Table 2 and supporting information).

3.3 | Tertiary outcomes

The within-group comparison showed that global cognition of the ADT group increased significantly at week 12 and remained similar to that of baseline at other time points, whereas global cognition of the control group declined significantly at weeks 12 and 24 compared to baseline (see Figure 2A).

Executive domain (CTT2) exhibited significant improvement at weeks 24 and 36 compared to baseline for both ADT and control group, whereas animal fluency test exhibited significant improvement at week 36 compared to baseline only in the ADT group (see Figure 2B).

Performance in all memory subdomains (verbal learning, verbal delayed recall, recognition memory, non-verbal delayed recall; see Figure 2D) showed significant improvement at weeks 12, 24, and 36 for both groups. Language domain (mBNT) improved significantly only for the ADT group (at weeks 24 and 36; see Figure 2E). There was no within-group difference in visuospatial functions for both groups at any time point (see Figure 2F).

Interestingly, improvement in processing speed was observed mainly in the control group. Performance in CTT1 of the control group improved at weeks 24 and 36, while CTT1 performance improved only
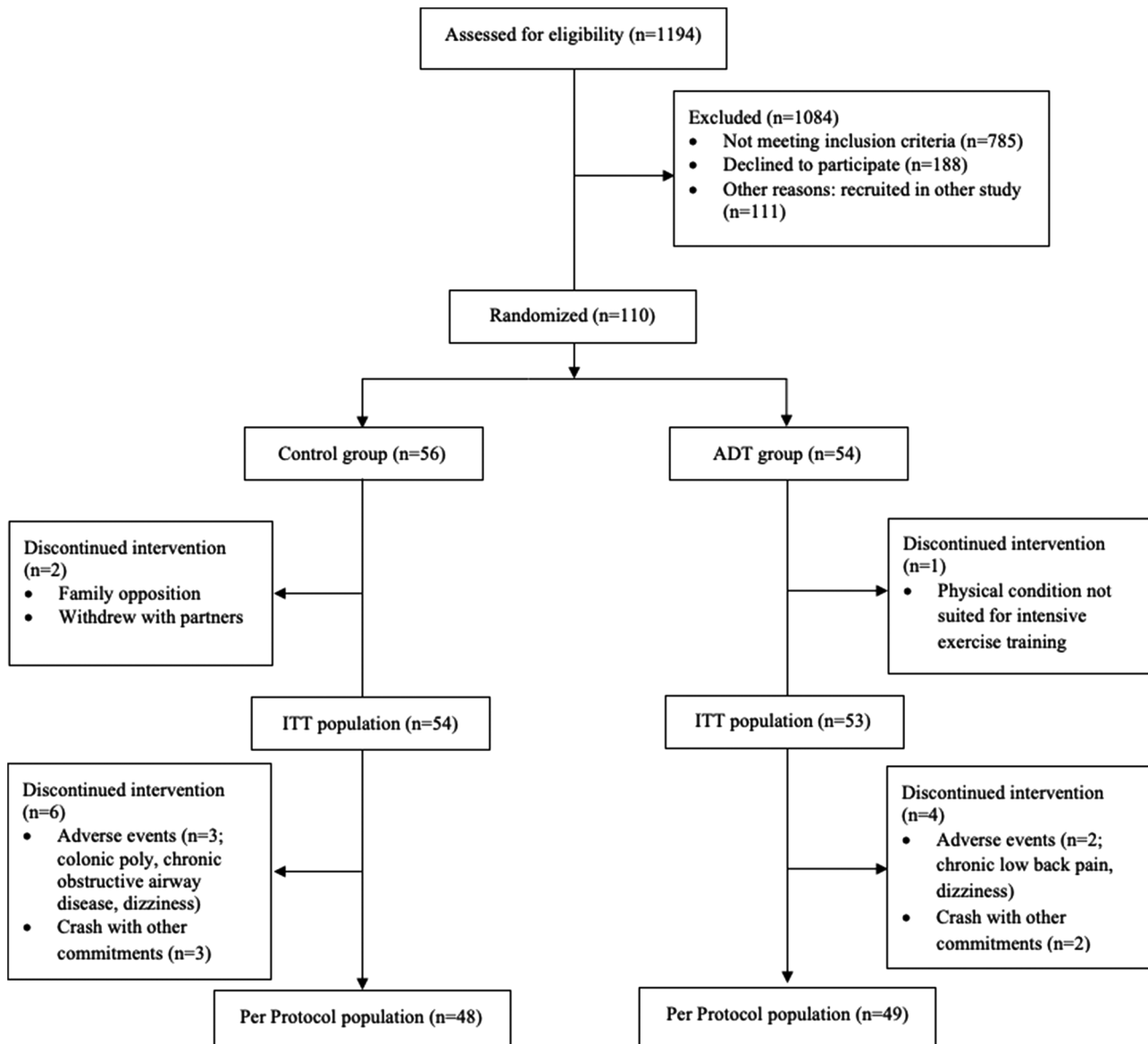
FIGURE 1 CONSORT (Consolidated Standards of Reporting Trials) flow diagram

at week 36 for the ADT group. Performance of SDMT improved at all time points only for the control group (see Figure 2C).

The ADT group reported significantly fewer depressive symptoms at weeks 12 and 24 compared to baseline, whereas the control group improved only at week 36 (Figure 3A). Motor functions showed improvements on the Mini-BESTest (see Figure 3B) at weeks 24 and 36 for both groups. The control group showed improvement in the TUG test at week 24, while there was no apparent change in the TUG test for the ADT group (see Figure 3B). There was no significant difference found for the 6-minute walk test and the global motor function for both groups at any time point (see Figure 3B). The per-protocol analysis yielded similar results to that of ITT analysis in all the above comparisons.

We investigated the interaction between treatment condition and change in PP and systolic BP, respectively, upon clinical measures that

yielded significant changes in between- or within-group comparisons. Specifically, we found a greater reduction in PP was associated with greater improvement in recognition memory and verbal delayed recall, while a greater reduction in systolic BP was associated with greater improvement in verbal delayed recall in the ADT group. In the per-protocol analysis, the interaction between PP and ADT group upon recognition memory and verbal delayed recall remained significant. In addition, a greater reduction in systolic BP was also found to associate with greater improvement in global cognition in the ADT group. Interestingly, we found a greater reduction in PP/systolic BP was associated with a greater worsening in processing speed (CTT1) in the ADT group.

We found no significant mediating effect between relevant hemodynamic measures (i.e., PP and systolic BP) and treatment conditions upon any of the relevant clinical outcomes at week 24 in the ITT and per-protocol analysis.

TABLE 1 Baseline characteristics of participants

	Control (n = 54)	ADT (n = 53)	*P*
Demographics			
Age in years	76.1 ± 4.9	75.2 ± 5.2	.340
Female, n(%)	35 (64.8%)	36 (67.9%)	.734
Education years	7.9 ± 5.7	8.3 ± 5.2	.763
Vascular risk factors			
Hypertension, n(%)	45 (83.3%)	44 (83%)	.965
Hyperlipidemia, n(%)	22 (40.7%)	24 (45.3%)	.635
Diabetes mellitus, n(%)	10 (18.5%)	11 (20.8%)	.771
Smoking, n(%)	1 (1.9%)	1 (1.9%)	.999
Body weight (kg)	59.3 ± 10.3	56.9 ± 8.4	.190
Genetic profile			
APOE ε4 carriers	12 (23.1%)	9 (19.1%)	.633
Cognitive measures			
Global cognition			
MoCA total	22.2 ± 4.1	22.6 ± 3.9	.608
60-min protocol summary score	-0.063 ± 0.651	0.053 ± 0.674	.373
Executive functions			
CTT2, s	150.0 ± 38.7	139.3 ± 44.7	.195
Animal fluency test	15.1 ± 4.0	15.8 ± 5.2	.476
Processing speed			
CTT1, s	79.8 ± 22.6	78.9 ± 30.2	.863
SDMT	26.8± 10.4	28.9 ± 12.4	.343
Language			
mBNT total	13.7 ± 1.3	13.6 ± 1.3	.750
Visuospatial functions			
RCFT copy	23.6 ± 8.1	25.4 ± 7.8	.241
Memory			
HKLLT learning	21.2 ± 6.6	22.2 ± 7.1	.452
HKLLT 30-min delayed recall	6.4 ± 3.6	6.9 ± 3.4	.447
HKLLT 30-min delayed recognition	13.1 ± 2.9	13.9 ± 1.9	.115
RCFT 30-min delayed recall	8.2 ± 6.4	9.5 ± 6.9	.326
Motor functions			
Mini-BESTest	18.2 ± 3.8	19.6 ± 4.0	.066
Timed Up & Go test	10.5 ± 2.3	9.9 ± 1.9	.152
6-min walk test, m	359.4 ± 66.5	359.9 ± 51.2	.964
Combined motor function	-0.099 ± 0.884	0.101 ± 0.757	.213
Mood			
GDS total	3.1 ± 3.0	2.6 ± 3.3	.480
Level of physical activities			
IPAQ total	3570 ± 2745	4132 ± 2720	.290
Hemodynamic measures			
Systolic blood pressure (mmHg)	139.1 ± 19.4	141.0 ± 17.1	.590
Diastolic blood pressure (mmHg)	76.9 ± 9.9	77.4 ± 9.8	.781

(Continues)

TABLE 1 (Continued)

	Control (n = 54)	ADT (n = 53)	P
Pulse pressure	62.2 (16.5)	63.6 (13.1)	.633
Right MCA PI	1.3 ± 0.3	1.4 ± 0.4	.266
Left MCA PI	1.3 ± 0.4	1.4 ± 0.4	.664
MRI measures			
Brain WMH volume (mL)	7.7 ± 6.8	9.0 ± 9.2	.419
Lacune count	0.4 ± 0.8	0.2 ± 0.5	.209

Note: Values are presented as mean ± standard deviation or % as appropriate.
Abbreviations: ADT, aerobic dance training; APOE, apolipoprotein E; CTT, Color Trails Test; GDS, Geriatric Depression Scale; HKLLT, Hong Kong List Learning Test; IPAQ, International Physical Activity Questionnaire; mBNT, modified Boston Naming Test; MCA, middle cerebral artery; mL, milliliter; MoCA, Montreal Cognitive Assessment; PI, pulsatility index; RCFT, Rey Complex Figure Test; SDMT, symbol digit modalities test; WMH, white matter hyperintensity.

There was no interaction between treatment condition and WMH volume upon relevant clinical measures at week 24. The interaction between treatment condition and APOE polymorphism was significant in that APOE ε4 carriers had significantly less improvement in verbal delayed recall than ε4 non-carriers in the ADT group. The per-protocol analysis yielded similar results to that of ITT analysis in the above analysis.

The IPAQ outside of training sessions did not differ between or within group at any time point for both ITT and per-protocol analysis.

3.4 | Safety

Rates of any adverse events were comparable between the two groups (supporting information). An event of plantar fasciitis that did not lead to study discontinuation occurred in the ADT group and was the only event that was considered possibly related to ADT.

4 | DISCUSSION

The CU-AEROBIC study investigated the benefit and risk of aerobic exercise upon cognition, mood, and motor functions in older people with subclinical moderate to severe CSVD and the interaction between treatment condition and hemodynamics upon clinical outcomes. The study showed two important findings. First, the ADT might have improved certain cognitive functions. Although there was no significant between-group difference in change from baseline for all the clinical outcomes, within-group comparison showed that the ADT group exhibited significant improvements in memory, executive, and language functions compared to baseline. Overall, global cognition remained stable in the ADT group, but it declined in the control group. Consistent with previous RCTs,[10,11] the aerobic group achieved a greater reduction in PP/systolic BP compared to that in the control group. We observed interaction in that a greater reduction in PP/systolic BP was associated with greater improvement in memory functions and global cognition. Taken together, these findings suggested that among older people harboring advanced CSVD, the prescribed ADT may reduce aor-

tic stiffness, thereby conferring benefits upon certain cognitive functions.

The second important finding was that improvement in processing speed was not observed in the ADT group and there was a "reverse" interaction between treatment condition and hemodynamics upon processing speed. Recent findings on the effects of exercise among healthy older people showed that improvement in processing speed should be most consistently observed.[17] Such improvement was noted among our controls likely due to practicing effect. More intriguingly, the interaction effect showed that reduction in PP/systolic BP was associated with worsening in processing speed in the ADT group.

The exact mechanisms explaining this lack of improvement in processing speed and the diverging impacts of a reduction in PP/systolic BP upon varying cognitive domains are unknown. We postulated that on one hand, reduction in PP/systolic BP may improve cognition because of a reduction in pulsatile flow or improved endothelial functions; on the other hand, it may lead to reduced cerebral perfusion if there is impairment of the cerebral autoregulation, which might be present in our subjects.[15,16] A previous study showed that certain brain regions, in particular caudate and putamen, are more vulnerable to ischemia than other brain regions when cerebral perfusion drops.[30] Because caudate and putamen are strategic structures that regulate performance in processing speed,[31,32] a slight drop in cerebral perfusion may therefore preferentially impair processing speed, negating the potential positive effect of aerobic exercise upon cognition. Further, a mechanistic study that incorporates assessment for cerebral perfusion, autoregulation, and vasoreactivity is required to investigate these potential diverging impacts after aerobic exercise in subjects with advanced CSVD.

We did not observe any between-group difference nor interaction effects between the treatment group and hemodynamics in any of the mood and motor measures. Although this might suggest that aerobic exercise had no apparent impact upon these functions, the scales that we used may not be able to capture subtle changes among older people with relatively normal mood and gait functions. For future trials targeting subclinical CSVD, we proposed to use more sensitive mood (e.g., 30-item GDS)[33] and motor measures (e.g., electronic walkways).

We found that APOE ε4 carriers had less gain on memory function from ADT. Although this finding was consistent with some studies,[34]
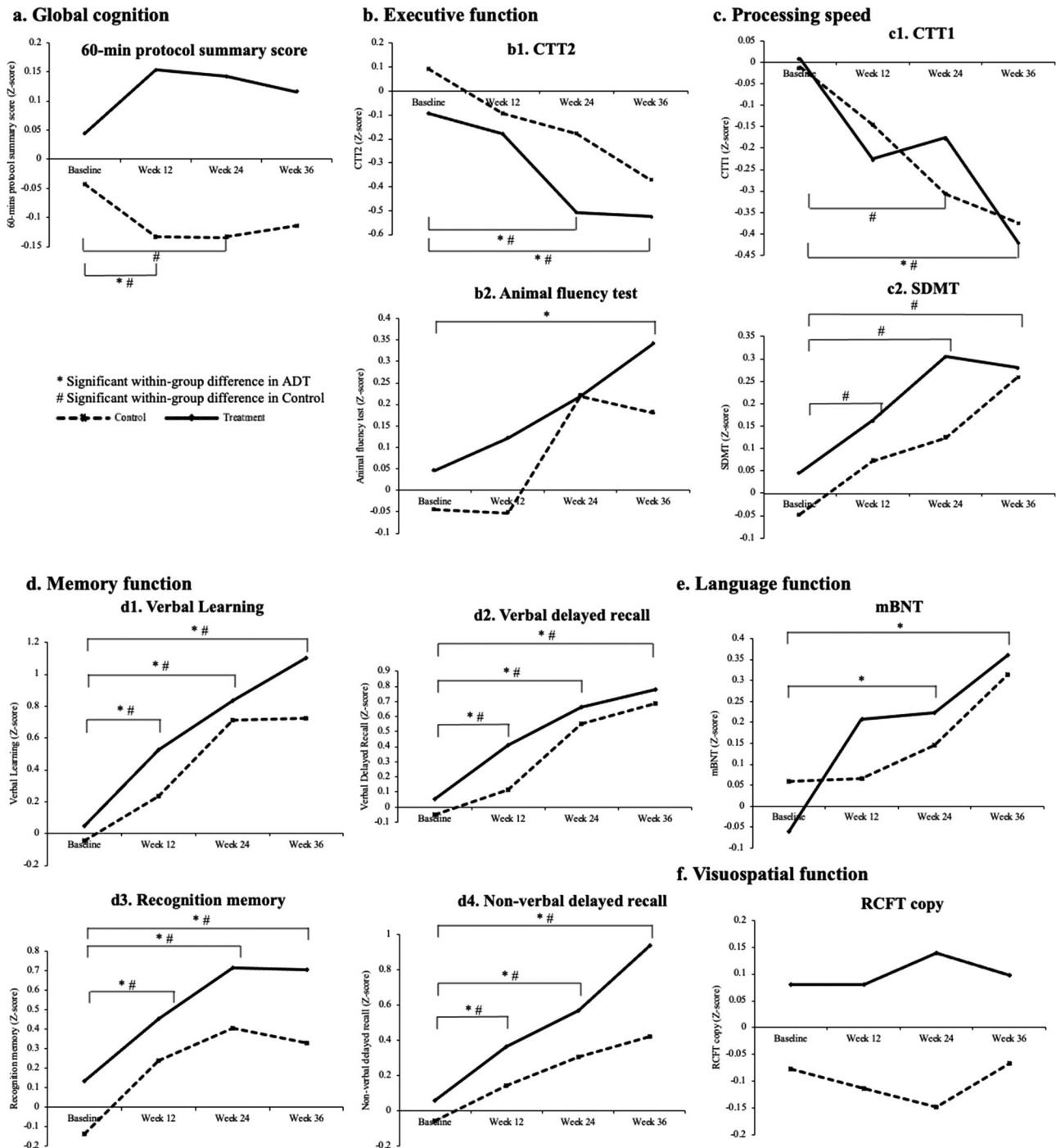
FIGURE 2 Illustrated the within-group differences in general cognition (2a) and specific cognitive domains (2b-f). * denote significant within-group difference in the ADT group while # denote significant within-group difference in control

others suggested the contrary.[35] These conflicting findings probably suggest that the interaction between *APOE ε4* and physical activity upon cognition is complex and multiple factors may influence the interaction. The presence of CSVD could be one of these factors that may reduce cognitive gain after aerobic exercise among *APOE ε4* carriers.

The strengths of the CU-AEROBIC study include the use of an extensive neuropsychological battery that is sensitive to CSVD and that we evaluated separate cognitive domains. We included hemodynamic measures as surrogates for the vascular status of large arteries and cerebral small vessels. Our study has a few limitations. Although we attempted to obtain PI for all subjects using TCD, we failed to obtain PI for 42% of the ITT population because of the absence of the temporal window. This high percentage of missing data would reduce power to see significant effects, hence the finding of a lack of impacts of ADT upon PI will need to be interpreted with caution. Ideally, phase-contrast MRI angiography should be used as it can provide a more comprehensive picture of cerebral hemodynamics, including pulsatility of the arteries, veins, and cerebrospinal fluid space, as

TABLE 2 Group comparison on percentage change from baseline at Week 24

		Control		ADT		
		Mean (SD)	n	Mean (SD)	n	P
Cognition						
Global cognitive						
60-min summary score						
	Intention-to-treat	−28.2 (188.4)	53	17.8 (454.8)	53	.445
	Per-protocol	−31.5 (191.5)	47	19.8 (478.3)	48	.436
Executive Functions						
CTT2, s						
	Intention-to-treat	−7.5 (23.2)	54	−10.6 (25.2)	53	.529
	Per-protocol	−6.9 (20.9)	46	−8.4 (18.9)	46	.730
Animal fluency test						
	Intention-to-treat	9.8 (32.4)	54	11.7 (50.7)	53	.922
	Per-protocol	9.5 (32.9)	47	12.6 (53.2)	48	.882
Processing speed						
CTT1, s						
	Intention-to-treat	−5.5 (18.7)	54	1.8 (23.6)	53	.071
	Per-protocol	−6.4 (19.9)	47	2.1 (24.8)	48	.061
SDMT						
	Intention-to-treat	35.9 (231.2)	54	9.7 (27.9)	53	.434
	Per-protocol	41.3 (247.7)	47	10.5 (29.2)	48	.417
Memory						
HKLLT Learning						
	Intention-to-treat	26.8 (36)	54	24.8 (30.4)	53	.924
	Per-protocol	30.2 (37.3)	47	25.6 (29.8)	48	.659
HKLLT 30-min delayed recall						
	Intention-to-treat	50.4 (118.2)	49	31.5 (59.2)	51	.374
	Per-protocol	59.6 (125.4)	42	34.4 (60.8)	47	.286
HKLTT 30-min delayed recognition						
	Intention-to-treat	14.1 (33.4)	54	11.8 (18.1)	53	.696
	Per-protocol	16.4 (35.3)	47	12.9 (18.7)	48	.578
RCFT 30-min delayed recall						
	Intention-to-treat	61.3 (182.3)	48	76 (197)	50	.800
	Per-protocol	70.1 (193.5)	42	84.1 (203.3)	46	.854
Language						
mBNT total						
	Intention-to-treat	0.3 (7.9)	54	2.7 (8.1)	53	.118
	Per-protocol	0.2 (8.4)	47	3.0 (8.5)	48	.105
Visuospatial Functions						
RCFT copy						
	Intention-to-treat	−0.6 (30)	53	68.3 (459.3)	52	.308
	Per-protocol	−0.9 (32.2)	46	73.7 (478)	48	.335
Motor functions						
Mini-BESTest						
	Intention-to-treat	9.4 (16.5)	54	8.7 (16.8)	53	.814
	Per-protocol	10.9 (17.3)	47	8.1 (14.9)	48	.409

(Continues)

TABLE 2 (Continued)

		Control		ADT		
		Mean (SD)	**n**	**Mean (SD)**	**n**	**P**
Timed Up & Go test						
	Intention-to-treat	−3.3 (11.6)	54	−2.1 (14.9)	53	.626
	Per-protocol	−3.8 (12.4)	47	−2 (15.5)	48	.536
6-min walk test, m						
	Intention-to-treat	1.2 (10.3)	54	2.1 (14.2)	53	.718
	Per-protocol	1.6 (11)	47	2.5 (14.9)	48	.729
Combined motor function						
	Intention-to-treat	−84.2 (518.4)	54	−23.1 (438.8)	53	.512
	Per-protocol	−96.1 (555.4)	47	−25.8 (461.5)	48	.504
Mood						
GDS total						
	Intention-to-treat	−0.9 (71.8)	41	−16.4 (75.4)	40	.348
	Per-protocol	−1.0 (75.7)	37	−15.8 (79.2)	35	.420
Level of physical activities						
IPAQ total						
	Intention-to-treat	80.5 (147.5)	54	66.8 (262.9)	53	.741
	Per-protocol	93.5 (153.9)	47	71.5 (275.7)	48	.634
Hemodynamic measures						
Systolic blood pressure (mmHg)						
	Intention-to-treat	0.6 (14.0)	54	−5.9 (17.7)	53	.038
	Per-protocol	1.2 (14.5)	47	−4.2 (12.6)	47	.060
Diastolic blood pressure (mmHg)						
	Intention-to-treat	1.5 (16.3)	54	−2.5 (17.8)	53	.227
	Per-protocol	2.1 (17.3)	47	−0.6 (12.2)	47	.384
Pulse pressure						
	Intention-to-treat	1.0 (21.1)	54	−7.1 (21.6)	53	.055
	Per-protocol	2.0 (21.7)	47	−7.1 (22.3)	47	.047
Right MCA PI						
	Intention-to-treat	-6.4 (13.1)	40	−5.7 (14.7)	39	.832
	Per-protocol	-7.2 (13.4)	34	−6.5 (15.6)	34	.832
Left MCA PI						
	Intention-to-treat	−4.0 (14.0)	33	−5.1 (14.4)	36	.742
	Per-protocol	−4.5 (14.5)	30	−5.9 (15.1)	32	.709

Note: Values are presented as mean (standard deviation).
Abbreviations: ADT, aerobic dance training; *APOE*, apolipoprotein E; CTT, Color Trails Test; GDS, Geriatric Depression Scale; HKLLT, Hong Kong List Learning Test; IPAQ, International Physical Activity Questionnaire; mBNT, modified Boston Naming Test; MCA, middle cerebral artery; mL, milliliter; MoCA, Montreal Cognitive Assessment; PI, pulsatility index; RCFT, Rey Complex Figure Test; SDMT, symbol digit modalities test; WMH, white matter hyperintensity.

well as cerebrovascular reactivity. Another limitation was that we did not investigate other mechanistic factors that may mediate the benefit of exercise upon various cognitive domains (e.g., memory functions). These factors may include brain-derived neurotrophic factor, glycosylphosphatidylinositol-specific phospholipase D1,[36] and inflammatory markers (e.g., C-reactive protein, interleukin-6),[37] which may influence cognition via mechanisms that may not directly relate to vas-cular mechanisms. Last, our study was too short to see if aerobic exercise can prevent incident dementia and/or stroke.

In conclusion, the CU-AEROBIC study shows that although the prescribed ADT enhance certain cognitive functions in older people with subclinical moderate to severe CSVD, the negative impact of reduced PP/systolic BP upon processing speed caution the potential risk of aerobic exercise in this group of older people. Our findings have
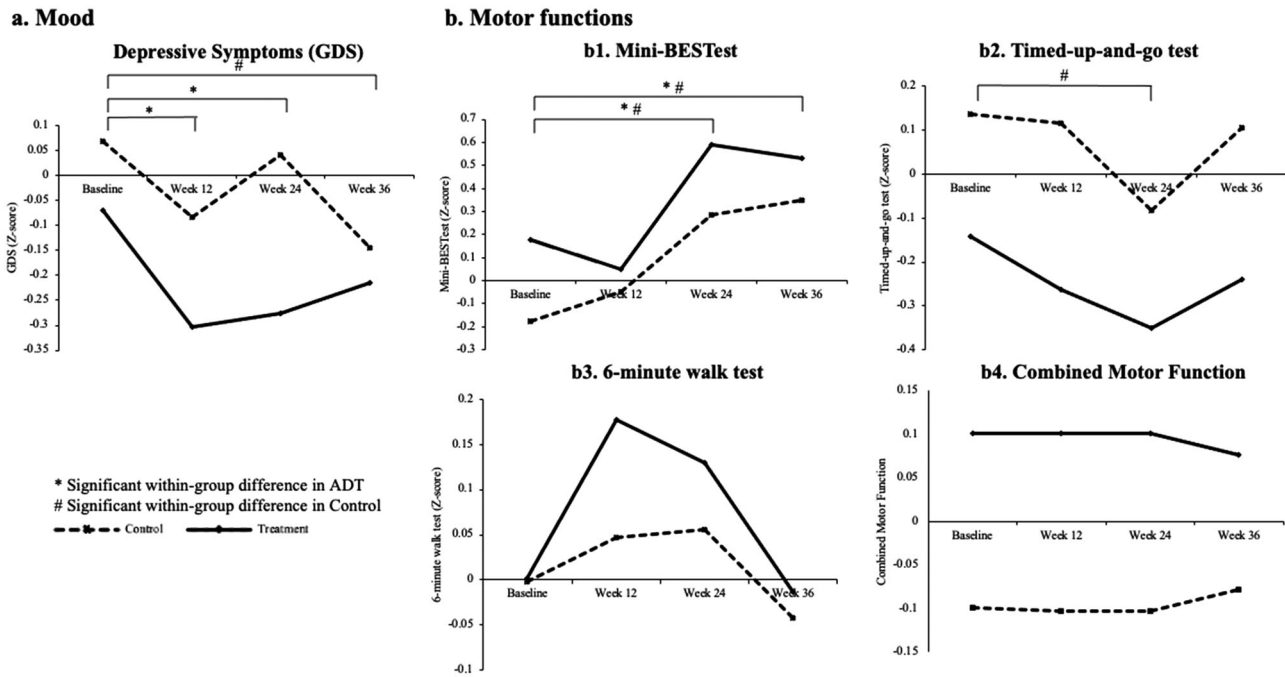
FIGURE 3 Illustrated the within-group differences in mood (3a) and motor functions (3b). * denote significant within-group difference in the ADT group while # denote significant within-group difference in control

implications in future trial design for the investigation of the benefit and risk of aerobic exercise upon cognition, mood, and motor functions in older people harboring advanced CSVD.

CONFLICTS OF INTEREST

In the past 36 months, Adrian Wong reports payment from Hong Kong Court (payment made to him). Margaret Kit Yi Mak reports conference attendance support from The Hong Kong Polytechnic University to attend the XXVI World Congress on Parkinson's Disease and Related Disorders May 1–4, 2021. Linda Chiu Wa Lam reports consulting fees from the second expert Colloquium on Early Alzheimer's Disease organized by Eisai Pharmaceutical (zoom meeting in 2020); and giving a lecture and preparing a newsletter article on mental disorders for dentists for the Hong Kong Dental Association (2020); and she is a member of the Advisory Committee on Mental Health at the Food and Health Bureau of the HKSAR government. Sin Ki Yeung reports the provision of reading materials by the professor for the submitted work. Lin Shi reports grants from Hong Kong General Research Fund and Innovation and Technology Fund. Thomas Wai Hong Leung is the president of Hong Kong Neurological Society (unpaid). Yannie Oi Yan Soo reports grants

from Hong Kong Health and Medical Research Fund (payment made to CUHK) and Emerging Markets Thrombosis Investigator-Initiated Research Program from Pfizer (payment made to CUHK); and honorarium for being a speaker from Amgen (payment made to her), honorarium for being a speaker from Daiichi and Boehringer Ingelheim (Hong Kong) Ltd (payment made to CUHK); and support for conference attendance by Hong Kong Neurological and Hong Kong Stroke Societies (no direct payment involved). Timothy Chi Yui Kwok is the director of Jockey Club Centre for positive ageing, Hong Kong; reports honorarium for attending a hearing for guardianship board, Hong Kong; and payment from Hong Kong government for expert report for coroner office; and donation for research (donation made to CUHK). Ho Ko reports grants from Croucher Innovation Award, Collaborative Research Fund of the Research Grants Council, Hong Kong and Area of Excellence Scheme of the Research Grants Council, Hong Kong (payments made to CUHK); and consulting fees from Videns Incorporation Limited. He has patents on the identifications of new potential disease-modifying therapeutics for Niemann-Pick disease type C, a method for slowing down brain aging, and new methods for achieving rapid and deep immunostaining. All other authors declare no financial disclosures or conflicts of interest.

REFERENCES

1. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*. 2019;18:684-696.
2. Silbert LC, Dodge HH, Perkins LG, et al. Trajectory of white matter hyperintensity burden preceding mild cognitive impairment. *Neurology*. 2012;79:741-747.
3. Mok VCT, Lam BYK, Wang Z, et al. Delayed-onset dementia after stroke or transient ischemic attack. *Alzheimers Dement*. 2016;12:1167-1176.

4. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9:689-701.

5. Kim EJ, Park CG, Park JS, et al. Relationship between blood pressure parameters and pulse wave velocity in normotensive and hypertensive subjects: invasive study. *J Hum Hypertens*. 2007;21:141-148.

6. Webb AJ, Simoni M, Mazzucco S, Kuker W, Schulz U, Rothwell PM. Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility. *Stroke*. 2012;43:2631-2636.

7. Mok V, Ding D, Fu J, et al. Transcranial Doppler ultrasound for screening cerebral small vessel disease: a community study. *Stroke*. 2012;43:2791-2793.

8. Wang Z, Wong A, Liu W, et al. Pulse pressure and cognitive decline in stroke patients with white matter changes. *J Clin Hypertens*. 2015;17:694-698.

9. Akazawa N, Tanahashi K, Kosaki K, et al. Aerobic exercise training enhances cerebrovascular pulsatility response to acute aerobic exercise in older adults. *Physiol Rep*. 2018;6:e13681.

10. Sikiru L, Okoye GC. Effect of interval training programme on pulse pressure in the management of hypertension: a randomized controlled trial. *Afr Health Sci*. 2013;13:571-578.

11. Ashor AW, Lara J, Siervo M, Celis-Morales C, Mathers JC. Effects of exercise modalities on arterial stiffness and wave reflection: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2014;9:e110034.

12. Sexton CE, Betts JF, Demnitz N, Dawes H, Ebmeier KP. Johansen-Berg H. A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. *NeuroImage*. 2016;131:81-90.

13. Podewils L, Guallar E, Beauchamp N, Lyketsos C, Kuller L, Scheltens P. Physical activity and white matter lesion progression: assessment using MRI. *Neurology*. 2007;68:1223-1226.

14. Moniruzzaman M, Kadota A, Segawa H, et al. Relationship between step counts and cerebral small vessel disease in Japanese men. *Stroke*. 2020;51:3584-3591.

15. Matsushita K, Kuriyama Y, Nagatsuka K, Nakamura M, Sawada T, Omae T. Periventricular white matter lucency and cerebral blood flow autoregulation in hypertensive patients. *Hypertension*. 1994;23:565-568.

16. Birns J, Jarosz J, Markus HS, Kalra L. Cerebrovascular reactivity and dynamic autoregulation in ischaemic subcortical white matter disease. *J Neurol Neurosurg Psychiatry*. 2009;80:1093-1098.

17. Gomes-Osman J, Cabral DF, Morris TP, et al. Exercise for cognitive brain health in aging: a systematic review for an evaluation of dose. *Neurol Clin Pract*. 2018;8:257-265.

18. Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for people with dementia. *Cochrane Database Syst Rev*. 2015:CD006489.

19. Lamb SE, Sheehan B, Atherton N, et al. Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. *BMJ*. 2018;361:k1675.

20. Wahlund LO, Barkhof F, Fazekas F, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32:1318-1322.

21. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822-838.

22. Lam BYK, Leung K, Yiu B, et al. Peak width of skeletonized mean diffusivity and its association with age-related cognitive alterations and vascular risk factors. *Assess Dis Monit*. 2019;11:721-729. Alzheimer's & Dementia: Diagnosis.

23. Shi L, Wang D, Liu S, et al. Automated quantification of white matter lesion in magnetic resonance imaging of patients with acute infarction. *J Neurosci Methods*. 2013;213:138-146.

24. Wong A, Xiong YY, Wang D, et al. The NINDS-Canadian stroke network vascular cognitive impairment neuropsychology protocols in Chinese. *J Neurol Neurosurg Psychiatry*. 2013;84:499-504.

25. Woo J, Ho SC, Lau J, et al. The prevalence of depressive symptoms and predisposing factors in an elderly Chinese population. *Acta Psychiatr Scand*. 1994;89:8-13.

26. Franchignoni F, Horak F, Godi M, Nardone A, Giordano A. Using psychometric techniques to improve the Balance Evaluation Systems Test: the mini-BESTest. *J Rehabil Med*. 2010;42:323-331.

27. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39:142-148.

28. ATSCoPSfCP. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166:111-117.

29. Vittinghoff E, Sen S, McCulloch CE. Sample size calculations for evaluating mediation. *Stat Med*. 2009;28:541-557.

30. Payabvash S, Souza LC, Wang Y, et al. Regional ischemic vulnerability of the brain to hypoperfusion: the need for location specific computed tomography perfusion thresholds in acute stroke patients. *Stroke*. 2011;42:1255-1260.

31. Botzung A, Philippi N, Noblet V, Loureiro de Sousa P, Blanc F. Pay attention to the basal ganglia: a volumetric study in early dementia with Lewy bodies. *Alzheimers Res Ther*. 2019;11:108.

32. Hong Z, Ng KK, Sim SK, et al. Differential age-dependent associations of gray matter volume and white matter integrity with processing speed in healthy older adults. *Neuroimage*. 2015;123:42-50.

33. Williams JR, Hirsch ES, Anderson K, et al. A comparison of nine scales to detect depression in Parkinson disease: which scale to use?. *Neurology*. 2012;78:998-1006.

34. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *Jama*. 2008;300:1027-1037.

35. Jensen CS, Simonsen AH, Siersma V, et al. Patients with Alzheimer's disease who carry the APOE epsilon4 allele benefit more from physical exercise. *Alzheimers Dement (N Y)*. 2019;5:99-106.

36. Horowitz AM, Fan X, Bieri G, et al. Blood factors transfer beneficial effects of exercise on neurogenesis and cognition to the aged brain. *Science*. 2020;369:167-173.

37. Low A, Mak E, Rowe JB, Markus HS, O'Brien JT. Inflammation and cerebral small vessel disease: a systematic review. *Ageing Res Rev*. 2019;53:100916.

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