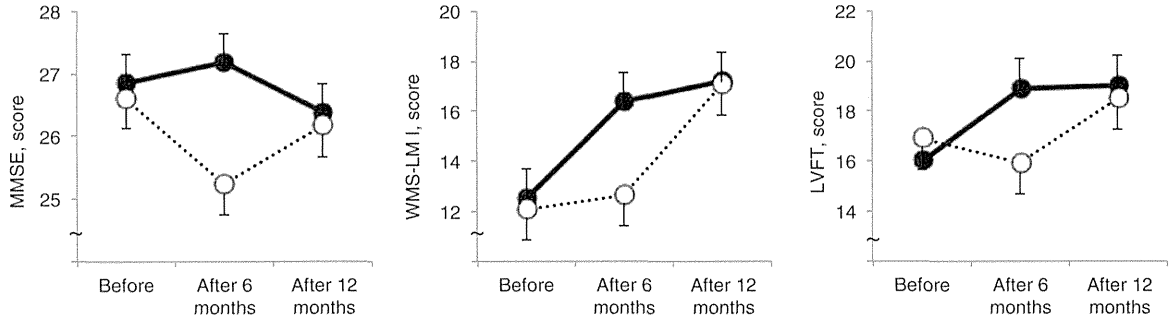

Figure 2 Changes in the MMSE, WMS, and LVFT scores. MMSE; mini-mental state examination, WMS-LM I; Logical Memory I subtest of the Wechsler memory scale-revised, LVFT; letter verbal fluency test. Panels showed change in MMSE, WMS-LM I, and LVFT scores before, after 6 months, and after 12 months intervention. Solid and dashed lines indicate the exercise and control groups, respectively. Group mean and standard errors are shown in older adults with amnestic mild cognitive impairment. The linear mixed models revealed significant group × time interactions in MMSE ($P = 0.04$), WMS-LM I ($P = 0.03$), and LVFT ($P = 0.02$).

months compared to before intervention ($P < 0.05$) and there was significant differences between the groups at after 6 months ($P < 0.05$).

For the WMS-LM I, there was a group × time interaction ($P = 0.03$); there were an overall effect of time and no main effect of group (Figure 2). In the post hoc analysis, the exercise group showed significant increase in the WMS-LM I score after 6 and 12 months compared to before intervention ($P < 0.05$) and the control group showed significant increase after 12 months compared to before intervention and after 6 months ($P < 0.05$). There was a significant difference between the groups at 6 months ($P < 0.05$).

On the LVFT, there was a group × time interaction ($P = 0.02$); there were an overall effect of time and no main effect of group (Figure 2). In the post hoc analysis, There were no significant differences between the times and groups.

The WMS-LM II, DSC, and SCWT-I showed main effect of time, although there were no group × time interaction and main effect of group. In the post hoc analysis, the exercise group showed significant increase in the WMS-LM II score after 6 and 12 months compared to before intervention ($P < 0.05$) and the control group showed significant increase after 12 months compared to before intervention and after 6 months ($P < 0.05$). There were no significant differences between the groups at each timepoints (Table 2).

Discussion

There was a significant group × time interaction on the MMSE, WMS-LM I, and LVFT scores. Twelve months of multicomponent exercise improved cognitive function in older adults with aMCI relative to the education control group. In particular, positive effects were observed for general cognitive function, immediate memory, and language ability, which is consistent with findings in cognitively intact adults [28]. A recent randomized controlled trial has been described as providing verification of the benefits of exercise in elderly adults with MCI [23]. In that study, 152 participants were randomly assigned to an aerobic exercise group and a non-aerobic exercise group, and to a vitamin B group and a placebo group, and a one-year intervention was carried out. The participants exercised twice weekly for 60 minutes each time. For the aerobic exercises, they walked together in groups. The results showed that aerobic exercise has no significant effect in improving cognitive function. However, these results were based on an intention-to-treat analysis, which included 30 participants who did not attend the exercise sessions. Had those elderly adults who had a high attendance rate among the aerobic exercise group been included in the analysis, then the results would have shown increased memory and attention, confirming the effectiveness of aerobic exercise in elder adults with MCI, though only to a limited extent. In another recent report, when elderly adults with MCI (a mean age of 70 years) engaged in aerobic exercise four times every week over the course of six months with a heart rate reserve of 75% to 85%, executive function significantly improved [16].

The present study shows that significant interactions were observed in general cognitive function, immediate memory, and verbal fluency between the groups, although intervention effects on delayed memory, processing speed, and executive control did not reach significance. Lautenschlager et al. reported that physical activity and behavioral interventions improve general cognitive function [19]. The multicomponent exercise training used in the current study also included aerobic exercise and behavioral interventions, such as self-monitoring of home-based exercise. Our results further

supported the idea that a composite approach including aerobic exercise and behavioral interventions can have beneficial effects on cognitive function in aMCI patients.

Older adults with aMCI exhibit greater decreases in memory function than in other cognitive functions, relative to healthy older adults [40]. The cognitive deficits in aMCI increase the risk of conversion from MCI to AD [11,12]. Enhancing cognitive function, especially memory, in MCI may prevent conversion from MCI to AD in older adults. Our multicomponent exercise program involved cognitive loads during exercise. In other words, exercise was conducted under multitask conditions such as dual-task stimulation or while learning tasks during the exercises [41]. Our multicomponent exercise program, involving aerobic exercise, muscle strength, and additional cognitive demand, has some advantages for improving cognitive function over aerobic exercise alone, including possibly increasing logical memory in older adults with aMCI. The WMS-LM I scores in the education control group increased significantly at 12 months compared to before and after 6 months. The education control group received reports of the results of the three assessments and lectures regarding health. We suggest that these educational approaches may be useful in maintaining healthy behavior, such as starting cognitive training or intellectual activities. In fact, the subjects in the control group had fewer cessations of intellectual activity, e.g. culture lessons, than the exercise group during the 12-month period (−9% vs. −19%).

Baker et al. reported that high intensity aerobic exercise increased VFT scores in older women with MCI [16]. Early in the dementia process, the ability to consciously access lexical information about a target word is impaired while the overall semantic system is intact [42], whereas later in the disease, the integrity of the entire system is compromised, resulting in impaired name recall in structured tasks and spontaneous conversation [42,43]. Fluency tests tap into lexical and semantic retrieval operations and may be able to measure these specific aspects of language breakdown in aMCI patients. In a functional neuroimaging study using near infrared spectroscopy, patients with AD showed decreased brain activation patterns compared with healthy controls during the conduct of VFT. Significant correlations between brain activation and performance in the LVFT for dementia patients were found [44]. In the present study, multicomponent exercise provided positive effects on LVFT scores in the aMCI subjects, who had a higher risk of dementia [45].

The present study has several limitations. The small sample size means that replication with a larger group of adults with MCI would be beneficial. Other limitations include unknown group differences in the risk factors of cognitive decline and AD, such as apolipoprotein E ε4 genotypes [46], and inflammation [47], although there were no significant differences between the groups in hypertension, diabetes mellitus, medications, biomarkers of lipid metabolism, physical performance, instrumental ADL functioning, and depressive moods. In addition, it is possible that the improvement in the exercise group resulted from the social contact that the intervention group received. This possibility cannot be completely excluded with the present design and should be addressed in future studies.

Conclusions

Twelve months of exercise improved cognitive function in older adults with aMCI relative to the education control group. In particular, positive effects were observed for general cognitive function, immediate memory, and language ability. A future follow-up investigation is required to determine whether the effect is associated with prevention or delayed onset of dementia in older adults with aMCI.

Abbreviations

aMCI: Amnestic mild cognitive impairment; AD: Alzheimer's dementia; CDR: Clinical dementia rating; WMS-LM: Wechsler memory scale-logical memory; ADL: Activities of daily living; CONSORT: Consolidated standards of reporting trials; MMSE: Mini-mental state examination; DSC: Digit symbol-coding; LVFT: Letter verbal fluency test; CVFT: Category verbal fluency test; SCWT: Stroop color and word test; ITT: Intention-to-treat.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Conception of the idea for the study: TS and HS. Development of the protocol and organization: TS, HS, HM, TD, and DY. Acquisition of participants, study management, and statistical analysis: HS, HM, TD, DY, KT, YA, KU, SL, and HP. All authors contributed to the interpretation of the data and drafting the article and provided final approval of the version to be published. All authors read and approved the final manuscript.

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Original Research Article

Effects of Exercise Intervention on Vascular Risk Factors in Older Adults with Mild Cognitive Impairment: A Randomized Controlled Trial

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Key Words
Cholesterol · Rehabilitation · Cognitive impairment · Metabolic profiles · Dementia · Vascular risk factors · Physical activity

Abstract
Aims: The purpose of this study is to clarify the effects of exercise intervention on vascular risk factors in older adults with mild cognitive impairment (MCI). ***Methods:*** Community-dwelling older adults who met the definition of MCI using the Petersen criteria (n = 100; mean age = 75.3 years) were randomly allocated to the exercise (n = 50) or education control group (n = 50). Participants in the exercise group exercised under the supervision of physiotherapists for 90 min/day, 2 days/week, 80 times for 12 months. Anthropometric profiles, blood markers, blood pressure, and physical fitness (the 6-min walking test) were measured. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and TC/HDL-C risk ratio measurements were taken from blood samples. ***Results:*** The exercise group showed significantly reduced TC and TC/HDL-C risk ratio after training compared with baseline levels ($p < 0.001$, $p = 0.004$). However, no significant reduction was found for the control group ($p = 0.09$, $p = 0.09$). Physical fitness also significantly improved after exercise intervention compared with the control group ($p < 0.0001$). ***Conclusion:*** Exercise intervention was associated with positive changes in important vascular risk factors related to cognitive decline and vascular disease in older adults with MCI.

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Introduction

Cognitive problems in older adults range from mild impairment to severe dementia. The transitional stage between normal aging and dementia has been designated as mild cognitive impairment (MCI) [1, 2]. Individuals with MCI have been found to have a 10–15 times higher risk of developing Alzheimer's disease (AD), although up to 40% will not develop dementia [3]. It is of great importance to recognize and treat patients at the earliest stage of the disease [4]. Recent studies have reported beneficial effects of physical activity or exercise on cognitive health, such as cognitive function [5–7], brain volume, and activation [8, 9], in older adults with and without cognitive impairment.

Vascular risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus, are associated with both the occurrence and progression of AD dementia [10–13]. It has also been found that vascular risk factors increase the risk of MCI [14, 15] and the risk of conversion from MCI to AD [16]. Li et al. [16] also reported that treatment (i.e., medication) of vascular risk factors was associated with a reduced risk of AD dementia, which suggests that active interventions for vascular risk factors might reduce the progression from MCI to AD dementia.

There is a growing body of evidence showing that regular physical activity has therapeutic and protective effects against dementia [17, 18] and cardiovascular disease [19] in older adults. Several studies have suggested that aerobic or resistance exercises have positive effects on vascular risk factors in healthy older adults, for example increases in high-density lipoprotein cholesterol (HDL-C) [20] as well as decreases in total cholesterol (TC), TC/HDL risk ratio, and triglyceride (TG) [21–23]. It is possible that improvements of metabolic profiles by exercise may lead to a decrease in the risk of dementia or vascular disease. However, it remains unclear whether exercise intervention affects vascular risk factors in older adults with MCI.

The identification and subsequent management of risk factors at the MCI stage could be an important strategy for preventing and delaying progression to AD. Considering the observed influence of the cardiovascular system and metabolic profile on the risk of developing dementia, it is important to know the potential benefits derived from exercise in terms of metabolomics. The purpose of this study was to investigate the effects of exercise intervention on vascular risk factors in older adults with MCI.

Participants and Methods

Participants

In this 12-month randomized controlled trial, subjects were randomly allocated to the exercise or education control group at the end of a baseline assessment. Study personnel involved in the collection of outcome measures were blinded to the randomization assignment. The Ethics Committee of the National Center for Geriatrics and Gerontology (Obu, Japan) approved the study protocol. The purpose, nature, and potential risks of the experiments were fully explained to the subjects, and all subjects gave written informed consent before participating in the study.

Subjects in this study were recruited from our volunteer databases, which included elderly individuals (65 years and over). Participants had to be community-dwelling adults aged 65 years and older to be included in the study. A total of 528 prospective subjects with a Clinical Dementia Rating (CDR) of 0.5 [24] or who complained of memory impairment were recruited in the first eligibility assessments. A total of 135 subjects responded to the second eligibility assessments. Thirty-five out of 135 subjects were excluded, and the 100 subjects

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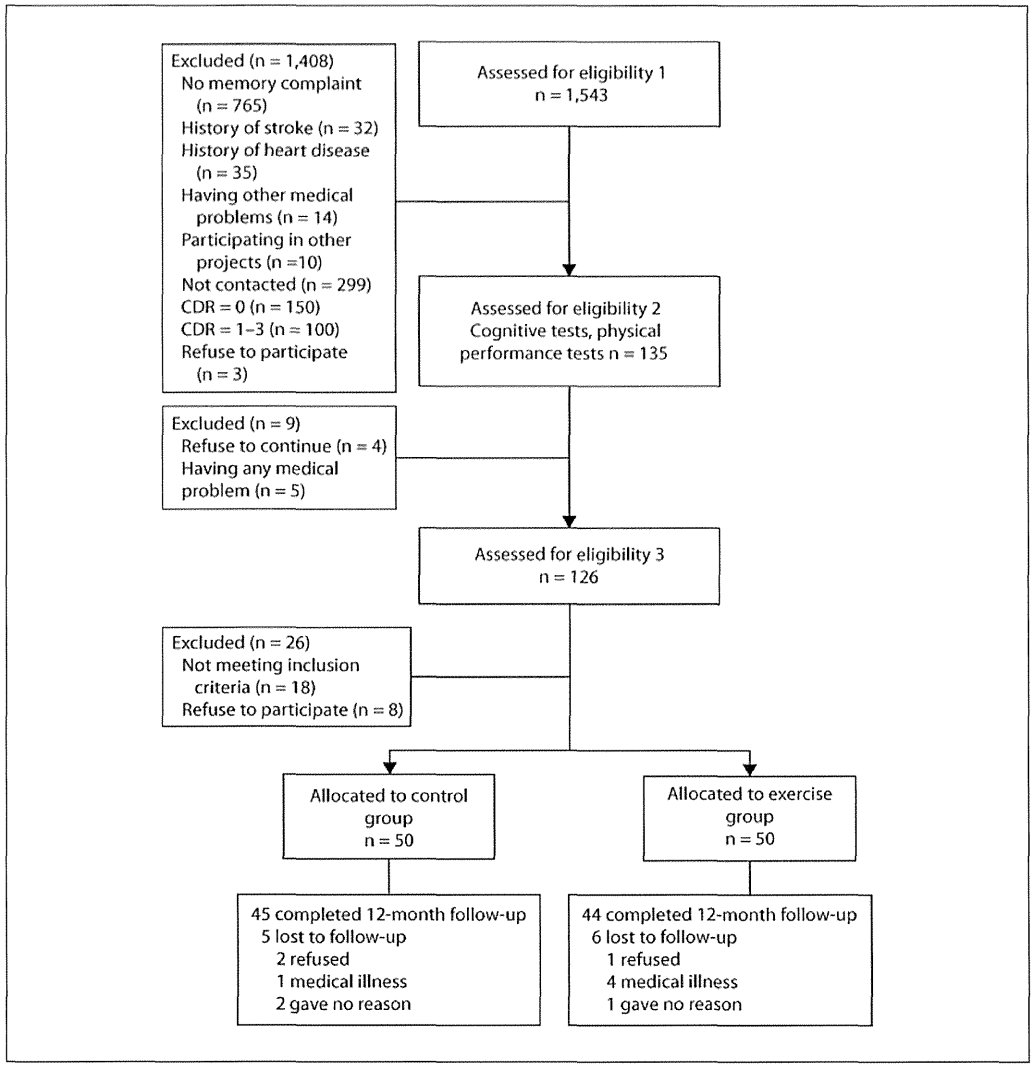

Fig. 1. Subject flow diagram from the initial contact through to study completion.

who remained met the definition of MCI using the Petersen criteria [3]. Exclusion criteria included a CDR of 0 or 1–3, a history of neurological, psychiatric, and cardiac disorders, and other severe health issues (i.e., recent myocardial infarction and unstable angina), uncontrolled hypertension, use of donepezil, impairments in basic activities of daily living, and participation in other research projects.

The Consolidated Standards of Reporting Trials (CONSORT) [25] diagram outlining the subject flow from the first contact to the study completion is shown in figure 1.

Interventions

The 12-month exercise program involved biweekly 90-min sessions with aerobic exercise, muscle strength training, postural balance retraining, and combined training. In addition, the exercise program included a focus on promoting exercise and behavior change. Two

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trained physiotherapists involved in geriatric rehabilitation conducted each intervention. Each supervised session began with a 10-min warm-up period and stretching exercise, followed by 20 min of muscle strength exercise. Then, the participants practiced aerobic exercise, postural balance retraining, and combined training for 60 min. For the aerobic exercise, participants underwent stair stepping and endurance walking. The mean intensity of the aerobic exercise was approximately 60% of the maximum heart rate.

Before and after each session of the program, the physiotherapists conducted a physical check of each participant. The participants were required to carry out daily home-based muscle strength exercises and walking, which were self-monitored using a booklet and pedometer based on the concept of promoting exercise and behavior change.

Subjects in the education control group attended three education classes about health promotion during the 12-month study period. The classes provided information regarding aging, healthy diet, oral care, brain image diagnosis, prevention of urinary incontinence, and health checks. However, the group did not receive specific information regarding exercise, physical activity, or cognitive health.

Anthropometry

Anthropometric measurements were obtained while the subjects were dressed in light clothing without shoes. Height (to the nearest 0.1 cm) and body weight (to the nearest 0.1 kg) were recorded. The body mass index (BMI) was calculated using the standard formula: weight (kg)/[height $(m)^2$].

Blood Markers and Blood Pressure

TC, HDL-C, TG, and glycosylated hemoglobin (HbA1c) were measured from blood samples, which were collected between 11 a.m. and 4 p.m. in a non-fasting state. The blood samples were kept at room temperature for 30 min to allow for clotting, then the samples were centrifuged for 15 min. Serum was harvested and stored at –25 °C until analysis. Analyses were carried out centrally in one laboratory (Special Reference Laboratories, Tokyo, Japan). Serum samples were analyzed for TC, HDL-C, TG, and HbA1c. The TC/HDL-C ratio [26] was calculated as an index of lipid-associated coronary heart disease risk and is supported by both its superior predictive power compared with TC, LDL-C, or HDL-C levels and lower within-person variability [27]. Systolic and diastolic blood pressures were measured using a standard sphygmomanometer in the sitting position after a 5-min rest.

Physical Fitness

The participants' exercise capacity was quantitatively measured using the 6-min walking test (6MWT). The 6MWT is used to measure the maximum distance that a person can walk in 6 min [28]. Participants were instructed to walk as far as possible in 6 min along a 10-meter course, performed under the supervision of a physiotherapist. This study used the distance (in meters) in the 6MWT as a measure of physical fitness.

Statistical Analysis

Baseline characteristics were compared among groups using Student's t test for quantitative variables and the χ^2 test for qualitative variables. The intervention effects on all outcome measures were determined using two-way repeated measures ANOVA, with group (exercise, control) as a between-subjects factor and time (before training, after training) as a within-subjects factor. A probability of $p < 0.05$ was considered statistically significant. Post hoc comparisons were performed to test the differences in physical function variables between before and after the training in each group. The significance level of multiple comparisons was adjusted using the Bonferroni correction ($p < 0.025$; 0.05/2), and analyses were

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Table 1. Baseline characteristics of the study subjects

	Exercise (n = 50)	Control (n = 50)	p value (t test)
Age, years	74.8 ± 7.4	75.8 ± 6.1	0.46
Men	25 (50)	26 (52)	0.84[a]
BMI	23.4 ± 3.4	22.9 ± 3.1	0.52
Educational level, years	10.9 ± 2.8	10.3 ± 2.3	0.29
Number of medications	2.5 ± 2.3	2.4 ± 2.2	0.89
GDS score	3.8 ± 3.1	3.3 ± 2.8	0.38
Physical performance			
Grip strength, kg	24.7 ± 8.1	23.5 ± 7.3	0.47
Timed up & go, s	8.8 ± 2.5	9.2 ± 2.1	0.37
Cognitive function			
MMSE score	26.8 ± 2.3	26.3 ± 2.7	0.30
ADAS-cog score	6.0 ± 2.7	6.5 ± 2.8	0.37

Values are means ± SD or n (%). GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale. [a] χ^2 test.

performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, Ill., USA). To perform the intention-to-treat analysis, a single imputation was used for all outcome measures. Missing data values were estimated using mean values for each corresponding group [29].

Results

There were no significant differences in baseline characteristics between the exercise and control groups (table 1). Figure 1 shows the flow of participants from the time of screening to study completion at 12 months. Eighty-nine (exercise group, n = 44) subjects completed the 12-month follow-up. The mean adherence to the exercise program was 78.6%, and 34 subjects (68.0%) in the exercise group attended our intervention program with more than 80% adherence.

Table 2 depicts all fitness-related variables for the exercise and control groups before and after the training. No interaction effects between group and time were detected for body weight and BMI [F(1, 98) = 0.6, p = 0.43; F(1, 98) = 0.4, p = 0.51, respectively]. Both the exercise and control groups showed reduced body weight and BMI after the intervention compared with before the intervention (exercise, $p < 0.001$; control, p = 0.01).

No interaction effects between group and time were detected for systolic and diastolic blood pressure [F(1, 98) = 1.0, p = 0.31; F(1, 98) = 3.7, p = 0.06, respectively]. Both the exercise and control groups showed reduced systolic blood pressure after intervention (exercise, p = 0.02; control, p = 0.001), but no significant change in diastolic blood pressure between before and after the intervention was observed in both groups (exercise, p = 0.09; control, p = 0.9).

A statistically significant interaction effect between group and time was found for the TC level [F(1, 98) = 5.1, p = 0.03; fig. 2a]. Post hoc comparisons revealed that the exercise group had significantly reduced TC levels compared with baseline levels ($p < 0.001$); however, no significant reduction was found for the control group (p = 0.09). There were no interaction effects between group and time for other blood markers [TC/HDL-C risk ratio, F(1, 98) = 0.77, p = 0.38; HDL-C, F(1, 98) = 0.6, p = 0.25; TG, F(1, 98) = 0.2, p = 0.78; HbA1c, F(1, 98) = 0.05, p = 0.36]. Post hoc comparisons revealed that the exercise group had a significantly reduced TC/HDL-C risk ratio after exercise training compared with before exer-

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Table 2. Fitness-related measurements according to group before and after the intervention (mean ± SD)

		Before	After	F-value 1. time effect 2. time × group	Partial η^2 1. time effect 2. time × group
Anthropometry					
Body weight, kg	exercise group	56.2 ± 9.6	55.2 ± 8.9**	19.7††	0.17
	control group	54.2 ± 8.8	53.5 ± 8.7*	0.6	0.006
BMI	exercise group	23.4 ± 3.3	22.9 ± 3.1**	19.7††	0.17
	control group	22.8 ± 3.1	22.5 ± 3.0*	0.4	0.004
Blood pressure					
Systolic, mm Hg	exercise group	144.6 ± 21.6	138.4 ± 20.3*	17.8††	0.15
	control group	142.4 ± 19.4	132.5 ± 17.5**	1.0	0.01
Diastolic, mm Hg	exercise group	74.6 ± 11.7	77.9 ± 11.1	0.24	0.014
	control group	75.1 ± 11.2	74.3 ± 9.2	3.7	0.036
Blood markers					
TC, mg/dl	exercise group	211.7 ± 36.2	193.6 ± 28.1**	19.3††	0.16
	control group	200.5 ± 34.6	194.7 ± 31.0	5.1†	0.05
TC/HDL-C risk ratio	exercise group	3.9 ± 1.0	3.7 ± 1.0**	10.8††	0.1
	control group	3.8 ± 0.9	3.7 ± 0.8	0.38	0.008
HDL cholesterol, mg/dl	exercise group	57.5 ± 16.0	55.6 ± 14.6	0.3	0.01
	control group	55.1 ± 13.2	55.2 ± 12.5	0.25	0.01
TG, mg/dl	exercise group	129.2 ± 64.7	131.8 ± 57.4	0.007	0
	control group	138.5 ± 91.5	134.7 ± 69.9	0.21	0.002
HbA1c, %	exercise group	5.6 ± 0.8	5.6 ± 0.9	1.1	0.01
	control group	5.4 ± 0.5	5.4 ± 0.4	0.05	0.001
Physical fitness					
6MWT distance, m	exercise group	378.0 ± 78.4	445.9 ± 97.8**	81.5††	0.45
	control group	363.5 ± 63.0	402.9 ± 70.7**	5.7†	0.06

* Significant difference between before and after the training within the group (Bonferroni, $p < 0.025$).
** Significant difference between before and after the training within the group (Bonferroni, $p < 0.005$).
†† $p < 0.01$; † $p < 0.05$.

cise training ($p = 0.004$), but no significant reduction was found for the control group ($p = 0.09$). There were no significant changes in HDL-C, TG, and HbA1c between before and after the intervention in both the exercise and control groups.

6MWT, our measure of physical fitness, showed significant interaction effects between group and time [$F(1, 98) = 5.7$, $p = 0.02$; fig. 2b] and was significantly increased in both the exercise and control groups compared with before the intervention (exercise, $p < 0.001$; control, $p < 0.001$).

Discussion

This study found that exercise intervention resulted in positive changes of blood markers, namely TC and TC/HDL-C levels, among older adults with MCI. Our baseline values were normal for TG and HDL-C, and borderline high for TC [30]. Numerous studies have shown that exercise improves lipid profiles among older adults. Indeed, a meta-analysis concluded that exercise could improve lipid profiles, including reducing TC and TC/HDL-C levels [31]. The multicomponent exercises in our intervention involved mainly aerobic exer-

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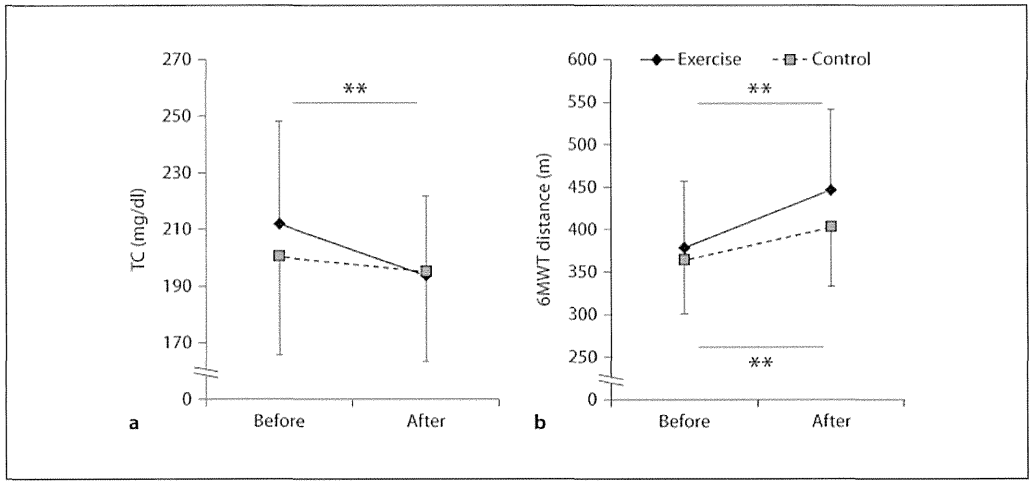

Fig. 2. The average values of TC (**a**) and 6MWT distance (**b**) in the exercise and control groups before and after the intervention. ** Significant difference between before and after the training within the group (Bonferroni post hoc test, $p < 0.005$).

cise. This type of exercise has been suggested to have positive effects on lipid profiles among older adults with coronary artery disease [32] or type 2 diabetes [33] as well as among healthy older adults [34]. Our study is the first to reveal the effectiveness of exercise intervention on vascular risk factors in older adults with cognitive impairment. Moreover, cardiorespiratory fitness also improved as a result of the increase in the 6MWT distance after exercise intervention, which is in line with previous studies reporting that exercise intervention improved cardiorespiratory functionality in healthy older adults, potentially counteracting the documented age-related decline in peak oxygen uptake [22, 23]. Previous studies have reported associations between habitual physical activity levels, increased endurance capacity, and/or chronic exercise programs and improvements in lipoprotein profiles in elderly subjects [35, 36]. In the present study, improved cardiorespiratory fitness might contribute to increased physical activity and positive changes in lipid metabolism.

From a metabolomic point of view, exercise intervention may be useful for dementia prevention in older adults with MCI. It has been reported that higher serum levels of TC lead to future cognitive decline and risk of cognitive impairment [37, 38]. It has also been reported that hypercholesterolemia independently increases the risk of conversion from MCI to AD [16]. Improved cardiorespiratory fitness and lipid metabolism may prevent vascular pathologies such as atherosclerosis. Furthermore, cholesterol is known to interact with, and modulate the generation of, Aβ, which alters cholesterol dynamics in neurons leading to tauopathy [39]. In addition, hypercholesterolemia promotes Aβ production by activating the activity of β- and γ-secretases [40]. The increased Aβ burden resulting from hypercholesterolemia may ultimately promote the development of AD [16]. The Aβ-modulating role of cholesterol may contribute to cognitive dysfunction, although conclusive evidence of the pathophysiological mechanism in dyslipidemias has not been provided yet [39]. In the current study, we also found that decreased TC levels were associated with an improvement in logical memory scores after exercise intervention [unpubl. data]. Therefore, exercise intervention may prevent cognitive decline and the incidence of dementia in older adults with MCI by improving cholesterol metabolism and risk factors (i.e., TC and TC/HDL-C levels) in older adults with MCI.

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Cholesterol is not only a risk factor for cognitive impairment, but is also regarded as a vascular risk factor in such diseases as coronary heart disease and cerebrovascular disease [41]. It has been reported that TC is positively associated with ischemic heart disease mortality in both middle- and old-aged patients [42]. Independent of the mechanism underlying lipid changes, a reduction of 1% in TC level has been shown to reduce the risk for coronary artery disease by 2% [43], which implies that our exercising participants have reduced their risk of coronary artery disease by approximately 17%. Additionally, there is a growing body of evidence showing that regular physical activity has therapeutic and protective effects against cerebrovascular disease in older adults [19]. Exercise intervention may have the potential to prevent incidences of vascular disease and related mortality in older adults with MCI. Overall, exercise is a beneficial and inexpensive practice that is associated with numerous benefits for cognitive and metabolic health with minimal adverse effects.

Study Limitations

There are several limitations to the current study. First, blood samples were collected in a non-fasting state. Although it has been reported that lipoprotein and apolipoprotein levels are not considerably different between fasting and non-fasting states, with the exception of TG, a fasting sample is preferred for precise assessment and management of cardiovascular risk [44]. Second, the intervention of this study lacked nutrient intake assessment and dietary control. It is possible that changes in nutrient intake contributed to decreases in body weight, systolic blood pressure in both groups, and unchanged HDL-C levels, which have been shown to decrease with low total and saturated fat diets [45]. To ascertain that the observed changes were due to exercise rather than other possible factors, a randomized controlled trial with control of nutrient intake in older adults with cognitive impairment and abnormal metabolic profiles, such as metabolic syndrome, should be conducted.

Conclusions

We investigated the effects of exercise intervention on vascular risk factors in older adults with MCI. The main finding of this study is that exercise intervention reduced TC levels and TC/HDL-C risk ratios among older adults with MCI. Reduction of these vascular risk factors may contribute to reduced cognitive decline and prevention of dementia, vascular disease, and related mortality in the future.

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Disclosure Statement

The authors have no conflict of interest to declare.

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Brain Atrophy and Trunk Stability During Dual-Task Walking Among Older Adults

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Background. Dual-task walking is believed to be more cognitively demanding than normal walking and alters trunk movement among older adults. However, the possible association between brain atrophy and spatiotemporal gait parameters, particularly during dual-task walking, is poorly understood. In this study, we examined the relationship between dual-task walking and brain atrophy.

Methods. One hundred ten elderly adults (aged 65–94 years, women $n = 55$) underwent magnetic resonance imaging scanning and gait experiments under normal and dual-task walking conditions. Linear accelerations of the trunk were measured in vertical, anteroposterior, and mediolateral directions using a triaxial accelerometer attached to the lower trunk. Gait speed, stride length, and cadence were recorded. The harmonic ratio, a measure of trunk stability, was computed separately in each direction to evaluate the smoothness of trunk movement during walking. Brain atrophy was quantitatively assessed using magnetic resonance image data.

Results. Gait speed, stride length, cadence, and harmonic ratio in all directions were lower in dual-task walking than in normal walking ($p < .05$). The dual-task–related changes in harmonic ratio were independently correlated with brain atrophy adjusted for subject characteristics only in the vertical direction ($p < .05$).

Conclusions. Our findings support the hypothesis that dual-task walking is more cognitively demanding than normal walking. Decreased trunk stability during dual-task walking is associated with brain atrophy. Additional studies are necessary to elucidate the effects of regional brain atrophy on the control of walking.

Key Words: Brain atrophy—Gait analysis—Dual-task walking—Acceleration.

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SUCCESSFUL locomotion is thought to require stability during gait. During normal walking, control of trunk movement is prioritized and contributes to head stability to maintain gait stability (1). Age-related gait changes among older adults induce trunk instability, which is reflected in reduced smoothness of trunk motion (2,3), and is more pronounced during more challenging walking tasks than during normal walking (4). Walking is a motor task that requires consecutive movement and adaptability to a changing environment. Successful locomotion not only requires input from the neuromuscular system but also from high-order cognitive systems such as executive function.

The performance of executive function has been associated with gait performance, and this relationship is stronger during more challenging walking tasks such as dual-task walking (5,6,7). To investigate the cognitive demands of walking, dual-task walking has been researched, for example, walking while performing a cognitive task or walking while talking. Dual-task walking markedly increased the variability of lower limb gait variables in older adults with cognitive impairment (8,9) and even in healthy older adults (10,11,12). Additionally, dual-task walking affected trunk movement in healthy older adults (7,13,14,15). Cognitive demands during dual-task walking affect spatiotemporal gait parameters. Dual-task–related changes (DTC) in gait variables correlate with both mobility and cognitive function in healthy older adults with normal gait performance (5). Moreover, dual-task training involving mobility tasks improved not only mobility function but also cognitive function (16, 17). Thus, dual-task walking may require and activate more multidomain neural resources in the brain than normal walking.

Emerging evidence suggests that age-related changes in the brain are linked to mobility deficits. Examples of these age-related changes include structural changes and changes to the biochemistry in the brain (18). Changes in the white matter (19,20,21) or the volume of gray matter (21,22,23), that is, macrostructural changes seen on magnetic resonance images (MRI), are also associated with changes in gait parameters. MRI-based measures of atrophy are a neurodegeneration marker, and they correlate with cognitive deficits and disease progress (24). However, a consensus has not been reached on which specific gait parameters are related to brain atrophy. Furthermore, it is still unclear if DTC in gait variables, including trunk movement, are related to MRI-based markers.

The purpose of this study was to investigate the relationships between brain atrophy and spatiotemporal gait parameters during normal and dual-task walking in older adults. We hypothesized that DTC in spatiotemporal gait parameters in older adults are related to brain atrophy described by MRI-based markers. To acquire quantitative gait variables including variables describing trunk movement and for a variety of conditions, we used a triaxial accelerometer that minimizes restrictions of walking movements (25). Brain atrophy was quantitatively and automatically calculated using a voxel-based analysis system from MRI (26,27).

Methods

Participants

One hundred thirty-five people were recruited from our volunteer database, which included older adults aged 65 and older. The inclusion criteria required that participants were living independently in the community and had adequate speech, hearing, and visual acuity to participate in the examinations. Exclusion criteria included having a history of major psychiatric illness, serious neurological or musculoskeletal diagnoses, or depression [Geriatric Depression Scale score $\geq$ 10 (28)]. Each participant underwent gait experiments and assessments including a face-to-face interview with a clinical nurse, a cognitive assessment by a speech therapist, physical performance tests, and MRI scanning. One hundred ten people met the criteria and participated in this study. The following data were recorded: age, sex, body mass index, and educational history. To assess functional capacity, we used the Tokyo Metropolitan Institute of Gerontology Index of Competence (29) questionnaire (0–13 points). This questionnaire consists of three subscales and each item has 1 point: instrumental self-maintenance (five items), intellectual activity (four items), and social role (four items). General physical function was examined using grip strength and the timed up and go test (30). Grip strength was measured twice while standing, and the higher value was used. The timed up and go test is a mobility test, and participants were asked to walk 3 m, then turn around and walk 3 m, all at their self-selected normal speed in a well-lit environment. Neuropsychological function was evaluated using the Mini-Mental State Examination (31). The ethics committee of the National Center for Geriatrics and Gerontology approved this study. All participants provided written, informed consent.

Gait Analysis

Participants were checked to make sure they were wearing shoes of an appropriate size before each experiment. Then, subjects were instructed to walk on an 11-m smooth, horizontal walkway, with a 2-m space at both ends of the walkway for acceleration and deceleration. Two gait experiments were performed in order: (a) normal walking at the participant's preferred speed and (b) dual-task walking: walking while counting backward in double digits with a randomly chosen starting number between 50 and 99. The mid 5-m walking time was measured, and gait speed was expressed in meters per second. A triaxial accelerometer (MVP-RF8, acceleration range: ± 60 m/sec^2, size: 45 mm width, 45 mm depth, 18.5 mm height, weight: 60 g, sampling rate: 200 Hz; MicroStone, Nagano, Japan) was attached to the L3 spinous process using a Velcro™ belt. The accuracy of data acquisition had been confirmed in a previous study using the same type of sensor (32). Before measurements, the accelerometer was calibrated statically against gravity. After analogue to digital transformation (10-bit resolution), signals were immediately transferred to a laptop PC (Let's Note CF-W5, Panasonic, Osaka, Japan) via a Bluetooth Personal Area Network. The working range of the accelerometer to the PC was approximately 50 m. Signal processing was performed using commercially available software (MATLAB, Release 2008b, The MathWorks Japan, Tokyo, Japan). The person who processed the acceleration data was blinded to any other results. Before analysis, all acceleration data were low-pass filtered (dual pass zero lag Butterworth filtered) with a cutoff frequency of 20 Hz. Stride time was determined by a validated method reported as the interval from an initial contact event to the next ipsilateral event (33). The mean stride time was calculated from five consecutive stride times. The average stride length was determined by multiplying gait speed by mean stride duration. The harmonic ratio (HR) was used to evaluate the smoothness and stability of trunk movement during gait (3,4,34). Higher HR values indicate greater stability during walking. HR was computed using a digital Fourier transform separately in each direction (vertical: VT direction, mediolateral direction, and anteroposterior direction). The procedure for calculating HR has been reported elsewhere (3,4,34).

Brain MRI

MRI was performed on a 1.5-T system (Magnetom Vision, Siemens, Germany). Three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence was used to produce a gapless series of thin sagittal sections using a magnetization preparation rapid-acquisition gradient echo

sequence (repetition time, 1700 ms; echo time, 4.0 ms; flip angle 15°, acquisition matrix 256 × 256, 1.3 mm slice thickness). The voxel-based specific regional analysis system in this study has been validated (26,27). This system was reformatted to produce gapless 2-mm thin-slice transaxial images, and the first anatomical standardization used affine transformation. The normalized MRI images were then segmented into gray matter, white matter, cerebrospinal fluid, and other components using a modified version of the clustering algorithm, the maximum likelihood "mixture model" algorithm. The segmentation procedure involved a calculation for each voxel using a Bayesian probability of belonging to each tissue class based on a priori MRI information with a nonuniformity correction. The segmented gray matter images were then subjected to an affine and nonlinear anatomical standardization using an a priori gray matter template. The anatomically standardized gray matter images were smoothed with an isotropic Gaussian kernel 12-mm full-width at half-maximum to exploit the partial volume effects, and a spectrum of gray matter intensities was created. We compared the gray matter image of each patient with the mean and standard deviation of gray matter images of healthy volunteers using voxel-by-voxel *Z* score analysis. In the final step, the *Z* score was calculated according to the following equation:

$$Z\ \text{score} = (\text{[control mean]} - \text{[individual value]}) / \text{control } SD$$

The region of brain atrophy was defined as voxels with a *Z* score greater than 2. The brain atrophy index was defined as the proportion of the number of voxels defined atrophic relative to the total number of voxels of the entire brain.

Statistical Analysis

All analyses were performed using commercially available software (JMP8.0J for Windows, SAS Institute Japan, Tokyo, Japan). The data were normally distributed for all spatiotemporal gait parameters under both normal walking and dual-task walking conditions. Gait parameters were compared between normal walking and dual-task walking using a repeated measures analysis of variance. To assess the association between DTC in gait parameters and brain atrophy, we first confirmed the interaction of the factors brain atrophy (continuous measure) and walking condition (normal walking vs dual-task walking) for each gait parameters using a repeated multivariate analysis of covariance adjusted for covariates (covariates: age, sex, and Mini-Mental State Examination score). Covariates for the interaction were then confirmed using an analysis of variance comparing tertiles of brain atrophy. A linear regression model adjusted for gait speed was used to detect a significant association between brain atrophy and DTC in those gait parameters with a significant interaction between brain atrophy and walking condition. Independent variables included subject characteristics and DTC in gait parameters between walking conditions and were presented as percentage of changes (|dual-task walking – normal walking|/normal walking × 100). Statistical significance was set a priori at $p < .05$.

Results

The 110 subjects (50% women) were aged between 65 and 94 years with a mean body mass index of 23.1 kg/m^2. The demographic data, general physical performance, functional capacity, and brain atrophy for all subjects are summarized in Table 1. The spatiotemporal gait parameters under normal walking and dual-task walking conditions and a comparison between conditions are presented in Table 2. Gait speed was significantly lower for the dual-task walking compared with the normal walking condition even when adjusted for sex ($p = .029$). Stride length and cadence were lower for dual-task walking condition compared with the normal walking condition even when adjusted for sex and gait speed (stride length: $p < .001$, cadence: $p < .001$). The HR of trunk movement in all directions was significantly lower for the dual-task walking condition compared with the normal walking condition even when adjusted for sex and gait speed (VT direction: $p < .001$, mediolateral direction: $p = .002$, anteroposterior direction: $p < .001$). The repeated multivariate analysis of covariance revealed a significant interaction between walking condition (normal walking vs dual-task walking) and brain atrophy only for HR in VT direction (walking condition × brain atrophy: $F = 4.334$, $p = .040$). Linear regression analysis revealed that brain atrophy is independently related to DTC in HR in VT direction ($\beta = .231$, $p = .024$; Table 3).

Discussion

This study revealed that decreased trunk stability during dual-task walking is significantly associated with brain atrophy in older adults. This association was independent of other variables in a regression model. In addition, dual-task walking resulted in a change of spatiotemporal gait parameters compared with normal walking, even when adjusted for sex and gait speed. The deterioration in HR during dual-task walking

Table 1. Subject Characteristics and Percentage of Brain Atrophy

Characteristics	*M* ± *SD*
Age (y)	75.4 ± 7.1
Sex, women subjects (%)	55 (50)
Body mass index (kg/m^2)	23.1 ± 3.3
Educational history (y)	10.7 ± 2.6
Mini-Mental State Examination (total score)	26.4 ± 2.5
Grip strength (kg)	23.5 ± 7.5
Timed up and go test (seconds)	9.2 ± 2.3
Geriatric Depression Scale (total score)	3.7 ± 3.0
Tokyo Metropolitan Institute of Gerontology Index of Competence (total score)	12.2 ± 1.1
Brain atrophy (%)	7.6 ± 4.2

Notes: Values are mean ± *SD* and numbers (proportion) for sex. Brain atrophy was calculated using a specific voxel-based regional analysis system for MRI data.

Table 2. Paired Comparison of Spatiotemporal Gait Parameters for Normal Walking and Dual-Task Walking

Variables	Normal Walking ($M \pm SD$)	Dual-Task Walking ($M \pm SD$)	Mean Difference (95% CI)	p Value	Adjusted p Value*
Gait speed (m/s)	1.10 ± 0.26	1.04 ± 0.31	−0.05 (−0.10, −0.01)	.022	.029†
Stride length (m)	1.13 ± 0.21	1.19 ± 0.41	0.06 (−0.01, 0.13)	.103	<.001
Cadence (steps/min)	115.8 ± 12.3	107.6 ± 17.8	−8.0 (−12.21, −3.80)	<.001	< .001
Harmonic ratio					
Vertical	2.84 ± 0.86	2.44 ± 0.81	−0.38 (−0.64, −0.12)	.005	<.001
Mediolateral	2.12 ± 0.65	1.95 ± 0.53	−0.19 (−0.36, −0.01)	.036	.002
Anteroposterior	3.13 ± 1.04	2.61 ± 0.83	−0.53 (−0.79, −0.25)	<.001	<.001

Notes: CI = confidence interval.
*Adjusted for sex and gait speed.
†Adjusted only for sex.

was observed in all three directions. However, the association between brain atrophy and DTC in HR was only present in VT direction.

Both the motor system and the cognitive system act reciprocally to ensure successful locomotion. To investigate this interaction, many experiments have been conducted using the dual-task method (10,11,12). DTC in gait parameters among older adults as a result of cognitive motor interference reflect an adaptation to a more challenging conditions and the fact that locomotion requires high-order cognitive processing such as executive function (5,6,7). Dual tasking generally affects spatiotemporal gait parameters including lower extremity (10,12) and trunk movement (7,13,14,15). Our results were consistent with reported dual-task changes for spatiotemporal gait measures, although the magnitude of changes varied among gait variables, type of tasks, or task difficulty (10,12). Dual tasking decreases HR as indicated by decreased smoothness of trunk movement and increased trunk instability in all directions. Furthermore, decreased HR may be caused by an adaptation because similar changes in HR have been reported for walking with additional challenges (eg, walking on an irregular surface) (4). The DTC in spatiotemporal gait parameters observed in our study suggest that dual tasking influences the control of both lower extremity and trunk movement.

Table 3. A Linear Regression Model for Brain Atrophy

	Brain Atrophy	
Variables	β (*SE*)	p Value
Age	.352 (.004)	<.001
Gender	.462 (.034)	<.001
Body mass index	.240 (.007)	.010
Educational history	−.028 (.010)	.779
Mini-Mental State Examination score	−.143 (.011)	.164
Grip strength	−.082 (.005)	.540
Tokyo Metropolitan Institute of Gerontology Index of Competence	.072 (.023)	.469
Geriatric Depression Scale	.249 (.008)	.016
Dual-task–related changes of HR in VT direction	.231 (.062)	.024
R^2		.362

Notes: HR = harmonic ratio; VT = vertical. A linear regression model was used to examine the association between dual-task–related changes of the gait parameter and brain atrophy, adjusted for gait speed.

MRI-based measures of brain atrophy are valid parameters because macrostructural brain abnormalities inevitably lead to neurodegeneration, neuropsychological deficits, tangle deposition, and microstructural loss (24). The macrostructural brain abnormalities associated with gait are hyperintensities of the white matter (19,20,21) and atrophy of the gray matter (21,22,23). The brain volume in the sensorimotor and frontoparietal regions including the prefrontal lobes is associated with step time and double support time during normal gait (22), and the differences between intracranial and brain volume were independently related to slower gait speed in women after adjusting for covariates (21). While one study reported that hippocampal volume is related to gait speed (23), results of another study suggest that gait performance among older adults is not necessarily related to atrophy in the memory domain including the hippocampus (22). The latter study also reported a weak association between gait measures and brain volume in the cerebellum or basal ganglia structures—regions that play key roles in the control of balance. A consensus has not been reached on the relationship between quantitative MRI-based measures of brain atrophy and gait variables. The results of our study indicate that DTC in trunk movement is significantly related to brain atrophy measured using the voxel-by-voxel method, which has been validated in other studies (26,27). Rosano and colleagues (22) suggested that gait variables under several conditions, including difficult conditions, should be investigated to clarify the task-specific network in the brain. Our initial results indicate that DTC in trunk movement might be associated with brain atrophy.

The control of trunk movement contributes to successful locomotion and is under continuous active neural control (1). The neural network may prioritize trunk stability to increase head stability during walking (35). Additionally, dual-task walking requires successful allocation of attention to both walking and the other task, which relies on executive function. In fact, dual-task decrements of gait measures are related to cognitive performance such as executive function (5,6,7), and both mobility and cognitive function are enhanced by dual-task intervention training as shown by results of randomized clinical trials (16,17). Because dual-task walking requires the

simultaneous control of walking and an additional task, the demand on neural resources for postural adjustments during walking may be greater for dual-task walking compared with normal walking. The analysis of HR during dual-task walking revealed an association between DTC in HR and brain atrophy; however, there was no relationship between DTC in other gait variables and brain atrophy. These results suggest that HR during dual-task walking may be a biomechanical marker for identifying a decline in brain volume.

Although dual-task walking decreased HR for trunk movement in all directions, an association between brain atrophy and DTC in HR was only observed in VT direction. These observations agree with results of other studies that HR data for lower trunk acceleration may represent different phenomena depended on the direction (2,36). Menz and colleagues (2) reported that directional specificity in HR in older adults was greater while walking under more challenging conditions. Results of their study suggested that the HR value of the lower trunk in VT direction had the ability to detect instability under challenging conditions. In another study, Brach and colleagues (3) suggested that HR in anteroposterior direction represents age-related changes that are not even affected by gait speed. The directional specificity of HR was not fully clarified, and further evidence for this specificity is required. Nevertheless, the results of our study indicate that brain atrophy is more likely to be related to trunk instability in the VT direction than in the anteroposterior and mediolateral directions induced by dual-task walking.

One limitation of this study is the relatively small sample size. Additionally, some physical dimensions, such as fitness level (37) and static postural instability (38), may have acted as confounding factors but were not included in this study. Furthermore, the effects of executive function and attention as confounding factors could influence dual-task gait performance (6,12) and should be considered to generalize these results. Moreover, the type and/or difficulty of dual-task walking in this study could have affected the results. Hence, dual-task walking using other types of cognitive tasks (eg, verbal fluency) should further be investigated. Finally, in this study, we measured atrophy of the entire brain. It is likely that regional atrophy assessed by MRI and other macrostructural measures (eg, white matter lesions) will provide a better insight into the mechanistic relationship between brain atrophy and gait function.

Conclusion

Brain atrophy correlated with a decline in the control of trunk movement during dual-task walking. This result indicates that dual-task walking induces trunk instability because additional cognitive resources are required compared with that during normal walking. Further studies are needed to clarify the effects of regional structural brain loss on the control of trunk movement and limb control during walking.

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