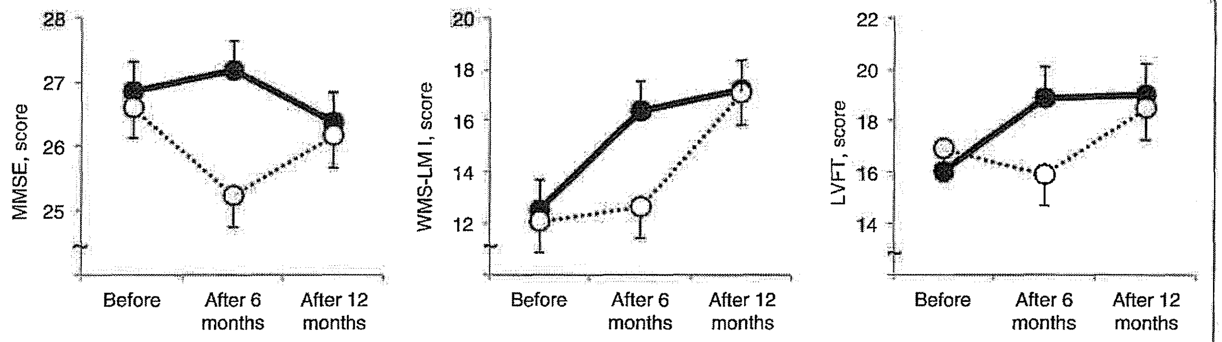

Figure 2 Changes in the MMSE, WMS, and LVFT scores. MMSE; mini-mental state examination, WMS-LM I; Logical Memory I subtest of the Wechsler memory scale-revised, LVFT; letter verbal fluency test. Panels showed change in MMSE, WMS-LM I, and LVFT scores before, after 6 months, and after 12 months intervention. 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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References

1. Ganguli M, Dodge HH, Shen C, DeKosky ST: Mild cognitive impairment, amnestic type: an epidemiologic study. *Neurology* 2004, 63(1):115–121.
2. Lopez OL, Jagust WJ, DeKosky ST, Becker JT, Fitzpatrick A, Dulberg C, Breitner J, Lyketsos C, Jones B, Kawas C, *et al*: Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1. *Arch Neurol* 2003, 60(10):1385–1389.
3. Ritchie K, Artero S, Touchon J: Classification criteria for mild cognitive impairment: a population-based validation study. *Neurology* 2001, 56(1):37–42.
4. Di Carlo A, Baldereschi M, Amaducci L, Maggi S, Grigoletto F, Scarlato G, Inzitari D: Cognitive impairment without dementia in older people: prevalence, vascular risk factors, impact on disability. The Italian Longitudinal Study on Aging. *J Am Geriatr Soc* 2000, 48(7):775–782.
5. Graham JE, Rockwood K, Beattie BL, Eastwood R, Gauthier S, Tuokko H, McDowell I: Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet* 1997, 349(9068):1793–1796.
6. Manly JJ, Bell-McGinty S, Tang MX, Schupf N, Stern Y, Mayeux R: Implementing diagnostic criteria and estimating frequency of mild cognitive impairment in an urban community. *Arch Neurol* 2005, 62(11):1739–1746.
7. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B: Current concepts in mild cognitive impairment. *Arch Neurol* 2001, 58(12):1985–1992.
8. Palmer K, Wang HX, Backman L, Winblad B, Fratiglioni L: Differential evolution of cognitive impairment in nondemented older persons: results from the Kungsholmen Project. *Am J Psychiatry* 2002, 159(3):436–442.
9. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, *et al*: Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004, 256(3):240–246.
10. Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, Wetterholm AL, Haglund A, Zhang R, Schindler R: 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. *Dement Geriatr Cogn Disord* 2006, 21(5–6):353–363.
11. Amieva H, Letenneur L, Dartigues JF, Rouch-Leroyer I, Sourgen C, D'Alchee-Biree F, Dib M, Barberger-Gateau P, Orgogozo JM, Fabrigoule C: Annual rate and predictors of conversion to dementia in subjects presenting mild cognitive impairment criteria defined according to a population-based study. *Dement Geriatr Cogn Disord* 2004, 18(1):87–93.
12. Tabert MH, Manly JJ, Liu X, Pelton GH, Rosenblum S, Jacobs M, Zamora D, Goodkind M, Bell K, Stern Y, *et al*: Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment. *Arch Gen Psychiatry* 2006, 63(8):916–924.
13. Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M: Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented. *Neurology* 2000, 55(12):1847–1853.
14. Visser PJ, Verhey FR, Hofman PA, Scheltens P, Jolles J: Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment. *J Neurol Neurosurg Psychiatry* 2002, 72(4):491–497.
15. Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W: Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann Intern Med* 2006, 144(2):73–81.
16. Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, Plymate SR, Fishel MA, Watson GS, Cholerton BA, *et al*: Effects of aerobic exercise on mild cognitive impairment: a controlled trial. *Arch Neurol* 2010, 67(1):71–79.
17. Hamer M, Chida Y: Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. *Psychol Med* 2009, 39(1):3–11.
18. Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, *et al*: Ageing, fitness and neurocognitive function. *Nature* 1999, 400(6743):418–419.
19. Lautenschlager NT, Cox KL, Flicker L, Foster JK, Van Bockxmeer FM, Xiao J, Greenop KR, Almeida OP: Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA* 2008, 300(9):1027–1037.
20. Masley SC, Weaver W, Peri G, Phillips SE: Efficacy of lifestyle changes in modifying practical markers of wellness and aging. *Altern Ther Health Med* 2008, 14(2):24–29.
21. Okumiya K, Matsubayashi K, Wada T, Kimura S, Doi Y, Ozawa T: Effects of exercise on neurobehavioral function in community-dwelling older people more than 75 years of age. *J Am Geriatr Soc* 1996, 44(5):569–572.
22. Scherder EJ, Van Paasschen J, Deijen JB, Van Der Knokke S, Orlebeke JF, Burgers I, Devriese PP, Swaab DF, Sergeant JA: Physical activity and executive functions in the elderly with mild cognitive impairment. *Aging Ment Health* 2005, 9(3):272–280.
23. van Uffelen JG, Chinapaw MJ, van Mechelen W, Hopman-Rock M: Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial. *Br J Sports Med* 2008, 42(5):344–351.
24. Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F: Physical activity, including walking, and cognitive function in older women. *JAMA* 2004, 292(12):1454–1461.
25. Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K: A prospective study of physical activity and cognitive decline in elderly women: women who walk. *Arch Intern Med* 2001, 161(14):1703–1708.
26. Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L: Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst Rev* 2008, (3):CD005381.
27. van Uffelen JG, Chin APMJ, Hopman-Rock M, van Mechelen W: The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review. *Clin J Sport Med* 2008, 18(6):486–500.
28. Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, Browndyke JN, Sherwood A: Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosom Med* 2010, 72(3):239–252.
29. Colcombe S, Kramer AF: Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci* 2003, 14(2):125–130.
30. Morris JC: The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993, 43(11):2412–2414.
31. Petersen RC: Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004, 256(3):183–194.
32. Wechsler D, Stone C: *Wechsler Memory Scale manual.* New York: Psychological Corp; 1973.
33. Aisen PS, Petersen RC, Donohue MC, Gamst A, Raman R, Thomas RG, Walter S, Trojanowski JQ, Shaw LM, Beckett LA, *et al*: Clinical Core of the Alzheimer's Disease Neuroimaging Initiative: progress and plans. *Alzheimers Dement* 2010, 6(3):239–246.
34. Schulz KF, Altman DG, Moher D: CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010, 340:c332.
35. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975, 12(3):189–198.
36. Wechsler D: *Wechsler Adult Intelligence Scale—III.* San Antonio: The Psychological Corporation; 1997.
37. Nutter-Upham KE, Saykin AJ, Rabin LA, Roth RM, Wishart HA, Pare N, Flashman LA: Verbal fluency performance in amnestic MCI and older adults with cognitive complaints. *Arch Clin Neuropsychol* 2008, 23(3):229–241.
38. Lonie JA, Herrmann LL, Tierney KM, Donaghey C, O'Carroll R, Lee A, Ebmeier KP: Lexical and semantic fluency discrepancy scores in aMCI and early Alzheimer's disease. *J Neuropsychol* 2009, 3(Pt 1):79–92.
39. Stroop JR: Studies of interference in serial verbal reactions. *J Exp Psychol* 1935, 18:643–662.
40. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E: Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999, 56(3):303–308.
41. Woollacott M, Shumway-Cook A: Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture* 2002, 16(1):1–14.
42. Chenery HJ, Murdoch BE, Ingram JCL: An investigation of confrontation naming performance in Alzheimer's dementia as a function of disease severity. *Aphasiology* 1996, 10:423–441.
43. Nicholas M, Obler LK, Au R, Albert ML: On the nature of naming errors in aging and dementia: a study of semantic relatedness. *Brain Lang* 1996, 54:184–195.
44. Herrmann MJ, Langer JB, Jacob C, Ehlis AC, Fallgatter AJ: Reduced prefrontal oxygenation in Alzheimer disease during verbal fluency tasks. *Am J Geriatr Psychiatry* 2008, 16(2):125–135.
45. Gao S, Hendrie HC, Hall KS, Hui S: The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. *Arch Gen Psychiatry* 1998, 55(9):809–815.

46. Hsiung GY, Sadovnick AD, Feldman H: Apolipoprotein E epsilon4 genotype as a risk factor for cognitive decline and dementia: data from the Canadian Study of Health and Aging. *CMAJ* 2004, 171(8):863–867.
47. Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, Tylavsky FA, Newman AB: The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA* 2004, 292(18):2237–2242.

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A Significant Relationship between Plasma Vitamin C Concentration and Physical Performance among Japanese Elderly Women

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Background. Maintenance of physical performance could improve the quality of life in old age. Recent studies suggested a beneficial relationship between antioxidant vitamin (eg, vitamin C) intake and physical performance in elderly people. The purpose of this study was to examine the relationship between plasma vitamin C concentration and physical performance among Japanese community-dwelling elderly women.

Methods. This is a cross-sectional study involving elderly females residing in an urban area in Tokyo, Japan, in October 2006. We examined anthropometric measurements, physical performance, lifestyles, and plasma vitamin C concentration of participants.

Results. A total of 655 subjects who did not take supplements were analyzed. The mean age (±standard deviation) of participants was 75.7 ± 4.1 years in this study. The geometric mean (geometric standard deviation) of plasma vitamin C concentration was 8.9 (1.5) μg/mL. The plasma vitamin C concentration was positively correlated with handgrip strength, length of time standing on one leg with eyes open and walking speed, and inversely correlated with body mass index. After adjusting for the confounding factors, the quartile plasma vitamin C level was significantly correlated with the subject's handgrip strength (p for trend = .0004) and ability to stand on one leg with eyes open (p for trend = .049).

Conclusions. In community-dwelling elderly women, the concentration of plasma vitamin C related well to their muscle strength and physical performance.

Key Words: Plasma vitamin C—Physical performance—Elderly women—Japanese.

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PHYSICAL performance and physical ability are the most important indicators of health status in elderly people and are also closely related to the quality of life. Declines in physical performance and physical activity, whether from specific disease, fall, fracture, poor nutrition, or aging itself, are associated with future disability, morbidity, and death (1,2).

In recent years, many studies have examined the roles of diet, protein, and vitamins in physical performance and physical activity(3–5). Several studies have associated low serum albumin concentration with deteriorated muscle strength and function (6,7). Some other studies have examined the relationship between serum vitamin D level and physical performance such as muscle mass, muscle strength, handgrip, walking speed, and functional capacity (8,9). Cesari et al. (3) examined the relationship between antioxidant vitamin intake (vitamin C, vitamin E, β-carotene, and retinol) and physical performance in elderly people and showed significant positive correlations between most antioxidants, especially vitamin C, and higher skeletal muscular strength in this group of people.

There are a number of mechanistic hypotheses about the potential beneficial effects of antioxidant vitamins(10–12). Vitamin C, vitamin E, β-carotene, and retinol are important antioxidants that are not synthesized by humans and, therefore, are mainly supplied via dietary intake. Vitamin C (ascorbic acid) is a water-soluble antioxidant present in the cytosol and extracellular fluid and can directly react with free radicals such as superoxide ($O_2\cdot^-$) and hydroxyl radicals ($\cdot OH$) (13,14). Each one of these oxygen-derived intermediates is considered highly reactive because of their unstable electron configurations, which could attract electrons from other molecules, resulting in another free radical that is capable of reacting with yet another molecule. This chain reaction is thought to contribute to lipid peroxidation, DNA damage, and protein degradation during oxidative stress. Oxidative damage is thought to play an important role in the age-related decline of functional activity in human skeletal muscle (15). Concentration of plasma vitamin C, which has potent antioxidant activity, is known to increase after exercise (4).

An increase in the amount of blood vitamin C content has been used as an indicator of increased oxidative reaction (11). Previous studies have examined the effects of vitamin C supplementation on physical performance and exercise (4,11). Although findings from some of the previous studies do not support any beneficial effect of increased antioxidant intake on physical performance, other studies have shown improved recovery from exercise with antioxidant intake and have also shown a preventive role of antioxidant supplementation against oxidative damage. These studies were carried out on athletes after heavy exercise. So far, however, there has been no study examining the relationship between physical performance and blood levels of vitamin C, which may be a more direct marker of the antioxidative ability of the human body.

The present study, to the best of our knowledge, is the first report that examines the relationship between plasma vitamin C concentration and physical performance in Japanese community-dwelling elderly women.

SUBJECTS AND METHODS

Study Subjects

The present cross-sectional study was carried out as part of a project involving mass health examination of community-dwelling people ("Otasha-kenshin" in Japanese) aged 70 years and older living in Itabashi-ku, Tokyo. "Otasha-kenshin," which literally means "health examination for successful aging," is a comprehensive health examination program for community-dwelling older adults aimed at preventing geriatric syndromes including falls and fractures, incontinence, mild cognitive impairment, depression, and undernutrition (16).

The eligible subjects were all female residents, aged between 70 and 84 years, living in the Itabashi area, an urban part of Itabashi-ku, Tokyo, Japan in October 2006. The population of women belonging to this age range and residing in the Itabashi area was 5937, and they were recruited by invitation through postal mail. Of them, 1,112 women applied for admission and 957 women ultimately participated in this study. The participants who were taking vitamin C supplements (n = 238) were excluded from the primary analyses for examination of the relationship between plasma vitamin C and physical performance because intake of supplements could strongly influence the plasma vitamin C level. Thus, data from 655 subjects were ultimately used for the primary analysis. However, data from the 238 supplement users were also used for subanalysis to determine whether any relationship exists between vitamin C supplementation and physical performance.

All participants were examined at the Tokyo Metropolitan Institute of Gerontology's hall. Physical performance, blood examinations, lifestyle assessments, and anthropometric measurements were performed as described below (9).

The present study was approved by the ethics review committee of the Tokyo Metropolitan Institute of Gerontology. All subjects gave written informed consent.

Anthropometric Measurements

Height and weight of each participant were measured, and body mass index was defined as weight/height^2 (kg/m^2). Body composition measurements (percent body fat) were obtained by segmental bioelectrical impedance using eight tactile electrodes according to the manufacturer's instructions (In Body 3.0; Biospace, Seoul, Korea). Measurements for the triceps surae muscles were taken between the knee and the ankle, at the level of maximum circumference of the medial and anterior calf of the left leg of each participant at sitting position.

Physical Performance

Physical performance was assessed by muscle strength (handgrip strength), balance capability, and usual and maximal walking speeds, without prior practice before the actual measurements. These assessments are routinely conducted for the elderly community as described previously (9). Handgrip strength (kg) was measured once for the dominant hand with the subjects in a standing position using a Smedley's Hand Dynamometer (Yagami, Tokyo, Japan). Grip devices were calibrated with known weights. Subjects held the dynamometer at thigh level and were encouraged to exert the strongest possible force. Balance capability was measured in terms of the length of time standing on one leg, that is, we asked the subjects to look straight ahead at a dot 1 m in front of them and to stand on the preferred leg with their eyes open and hands down alongside the trunk. The time until balance was lost (or maximum 60 seconds) was recorded. We used the better of two trials in the analysis. To determine the walking speed, participants were asked to walk on a flat surface at their "usual and maximum walking speeds." Two marks were used to delineate the start and end of a 5-m path. The start mark was preceded by a 3-m approach to ensure that the participants achieved their pace of usual or maximum before entering the test path. The participants were also instructed to continue walking past the end of the 5-m path for a further 3 m to ensure that their walking pace was maintained throughout the test path. The time taken to complete the 5-m walk was measured by an investigator and used for analysis. Walking test at maximum speed was repeated twice, and the faster speed was recorded for the test.

All physical performance tests were performed between 9 AM and 4 PM during the day. We have no data on the reproducibility of the measurements. To reduce interexaminer variation, each test was conducted by the same staff member specifically trained for this study.

Blood Examinations

Blood samples (nonfasting) were collected from the subjects between 9 am and 4 pm during the day. There was no difference in mean plasma vitamin C concentration with regard to the time of collection (data not shown). Venous blood samples were drawn into Ethylene diamine tetraacetic acid tubes. Plasma was then obtained by centrifugation at 3,000 rpm for 15 min at 4°C and subsequently used for biochemical assays. Plasma was treated with Ethylene diamine tetraacetic acid to prevent the spontaneous vitamin C degradation. Next, 100 μl of the plasma was dispensed into storage tubes, to which 450 μl of 3% metaphosphoric acid solution was added, and the mixture was stored at −80°C until further use. Vitamin C concentration was determined by an High performance liquid chromatography-electrochemical detection–based method (17). The analysis was carried out centrally in our laboratory. Serum albumin concentration was measured by the Bromocresol Green method (Special Reference Laboratories Inc., Tokyo, Japan). The coefficient of variation for serum albumin found using this method was less than 1% (9).

Lifestyle Assessment

Information regarding the participants' general health (such as medical history, smoking habits, alcohol drinking habits, regular exercise habits, vegetable intake, fruit intake and use of vitamin C supplement) was collected by interview, and history of medical conditions including hypertension, stroke, heart attack, diabetes mellitus, and hyperlipidemia was self-reported.

Alcohol drinking habits of the subjects were classified as nondrinker, current drinker, or ex-drinker. Smoking habits of the subjects were classified using three categories: never smokers, current smokers, and ex-smokers. The frequency of vegetable and fruit intake was asked using four categories: almost every day, once every two days, once or twice per week, and almost never. Subsequently, for analysis, the categories were summarized as almost every day and others.

Statistical Analysis

Data were summarized as mean and standard deviation or percentage values. The data of plasma vitamin C concentration was logarithmically transformed to approximate a normal distribution and was summarized as the geometric mean and geometric standard deviation.

Table 1. Characteristics of Study Subjects ($N = 655$)

Characteristic	Mean (*SD*)
Age (y)	75.7 (4.1)
Height (cm)	149.1 (5.7)
Weight (kg)	51.0 (8.3)
Body mass index (kg/m^2)	22.9 (3.4)
Triceps surae muscle (cm)	33.1 (2.8)
Plasma vitamin C (μg/ml)*	8.9 (1.5)
Serum albumin (mg/dL)	4.3 (0.2)
Body composition	
Percent body fat (%)	32.2 (7.0)
Physical performance tests	
Handgrip strength (kg)	18.7 (4.4)
One leg standing with eyes open (s)	35.2 (23.5)
Usual walking speed (m/s)	1.2 (0.3)
Maximal walking speed (m/s)	1.8 (0.4)
	%
Medical history	
Hypertension	50.7
Stroke	6.6
Heart attack	21.2
Diabetes mellitus	9.0
Hyperlipidemia	34.7
Alcohol drinking habit	
Current	25.3
Former	5.0
Never	69.6
Smoking habit	
Current	3.7
Former	5.7
Never	90.7
Regular exercise habit	
Yes	69.2
No	30.8
Vegetable intake	
Everyday	84.2
Others†	15.8
Fruit intake	
Everyday	81.8
Others†	18.2

Notes: Data of vitamin C supplement users were excluded.

*The geometric mean and geometric *SD*.

†Including participants taking vegetables/fruits not everyday or almost never.

The age-adjusted Pearson's correlation coefficient between the plasma vitamin C concentration and other factors were calculated. The least square means and SEs adjusted for potential confounders were calculated and compared between categories by analysis of covariance. To examine the relationship between plasma vitamin C concentration and physical performance, statistical adjustment was done by analysis of covariance for variables (except for other physical performance variables) that were correlated to plasma vitamin C concentration with $p < .20$. The same analyses were repeated for the 238 users of vitamin C supplement. All statistical analyses were performed using the SAS (version 9.0; SAS Institute Inc., NC).

RESULTS

Table 1 summarizes the basic characteristics of the subjects. As shown, the mean age (±standard deviation) of the

Table 2. Correlation between Plasma Vitamin C Concentration and Selected Factors ($N = 655$)

Factor	Correlation*	
	r	*p*
Age	−0.004	.91
Height	0.04	.27
Weight	−0.05	.19
Body mass index	−0.08	.054
Triceps surae muscle	0.001	.98
Serum albumin	−0.04	.33
Percent body fat	−0.12	.002
Handgrip strength	0.16	<.001
One leg standing with eyes open	0.15	<.001
Usual walking speed	0.14	<.001
Maximal walking speed	0.09	.036

Notes: Number of subjects is slightly different for the selected factors because of missing values.

*Age-adjusted Pearson's correlation coefficient between logarithm of vitamin C concentration and each factor.

subjects was 75.7 ± 4.1 years. The geometric mean (geometric standard deviation) of plasma vitamin C concentration was 8.9 (1.5) μg/mL. The prevalence of women eating vegetables everyday was 84.2% and those eating fruits everyday was 81.8%.

The age-adjusted geometric mean of plasma vitamin C concentration was significantly lower in subjects who had a medical history of hypertension (8.53 vs 9.22, $p = .0015$) and diabetes mellitus (7.59 vs 9.00, $p = .002$) as compared with those who did not. A history of stroke, heart attack, or hyperlipidemia was not associated with plasma vitamin C concentration. Subjects who took fruits every day had a significantly higher concentration of vitamin C than those who did not (9.14 vs 7.78, $p < .0001$). Vegetable intake, alcohol drinking habit and smoking habit were not related to plasma vitamin C concentration (not shown in table).

Table 2 shows the age-adjusted correlations between the plasma vitamin C concentration and selected factors. As shown, the plasma vitamin C concentration was positively but modestly correlated with handgrip strength, length of time standing on one leg with eyes open, as well as usual walking speed and maximal walking speed, and modestly inversely correlated with body mass index and percent body fat of the subjects.

Table 3 shows the relationship between plasma vitamin C concentration and each physical performance after adjusting for confounding factors. Results obtained after the adjustment for potential confounders confirmed that the plasma vitamin C concentration was correlated with the handgrip strength independently from the other factors (eg, p for trend = .0004 after adjusting for age, body mass index, percent body fat, hypertension, diabetes mellitus, and fruit intake; Table 3). There was also a significant relationship between the plasma vitamin C level and the subject's length of time standing on one leg with eyes open after adjustments for age, body mass index, percent body fat, hypertension, diabetes mellitus, and fruit intake (Table 3; p for trend = .049). We did not observe any significant association between the plasma vitamin C level and the usual or the maximal walking speed of the subjects.

A subanalysis using data from the 238 vitamin C supplement users showed almost null relationship between handgrip strength and plasma vitamin C concentration (data not shown).

DISCUSSION

A previous study has shown an association between higher daily dietary intake of vitamin C and skeletal muscle strength in elderly people (3). Results described in the present study indicated that plasma vitamin C concentration was positively related with muscle and physical performance in community-dwelling elderly women. To the best of our knowledge, this is the first study showing a significant

Table 3. Relationship between Plasma Vitamin C Concentration and Physical Performance Adjusted for Potential Confounder

	Quartile of plasma vitamin C level				
	Q1	Q2	Q3	Q4	
Physical performance	Mean ± *SE*	Mean ± *SE*	Mean ± *SE*	Mean ± *SE*	*p* for trend
Handgrip strength (kg), *N*	154	159	154	152	
Age adjusted	17.70 ± 0.34	18.75 ± 0.33	18.75 ± 0.34	19.60 ± 0.34	.0001
Multivariate adjusted*	17.83 ± 0.34	18.83 ± 0.32	18.89 ± 0.33	19.60 ± 0.33	.0004
One leg standing with eyes open† (s), *N*	162	163	164	161	
Age adjusted	31.44 ± 1.71	33.98 ± 1.70	37.70 ± 1.70	37.83 ± 1.71	.003
Multivariate adjusted*	33.39 ± 1.74	34.08 ± 1.67	37.63 ± 1.67	37.50 ± 1.70	.049
Usual walking speed (m/s), *N*	146	154	145	147	
Age adjusted	1.13 ± 0.02	1.19 ± 0.02	1.23 ± 0.02	1.21 ± 0.02	.008
Multivariate adjusted*	1.18 ± 0.02	1.19 ± 0.02	1.22 ± 0.02	1.21 ± 0.02	.23
Maximal walking speed (m/s), *N*	146	154	154	147	
Age adjusted	1.70 ± 0.03	1.76 ± 0.03	1.82 ± 0.03	1.76 ± 0.03	.15
Multivariate adjusted*	1.76 ± 0.03	1.77 ± 0.03	1.80 ± 0.03	1.75 ± 0.03	.94

Notes: Values are least squares mean and *SE* adjusted for the factors by analysis of covariance. Q1–Q4: first to fourth quartile groups of plasma vitamin C concentration, respectively.

*Adjusted for age, body mass index, percent body fat, hypertension, diabetes mellitus and **fruit intake**.

†Length of time standing on one leg with eyes open.

correlation between plasma vitamin C concentration and handgrip strength and ability to stand on one leg with eyes open. We, however, were unable to find any relationship between skeletal muscle mass and plasma vitamin C concentration. Handgrip strength has been found to correlate well with the strength of other muscle groups and is thus a good indicator of overall strength (18). Consistent with this idea, handgrip strength was found to be a strong and consistent predictor of all-cause mortality and morbidity of Activities of Daily Living in middle-aged people (19). The handgrip test is considered an easy and inexpensive screening tool to identify elderly people at risk of disability. Handgrip strength, an indicator of overall muscle strength, is thought to predict mortality through mechanisms other than underlying disease that could cause muscle impairment (18,19). The one leg standing test is one of the balance tests (20). The test is a clinical tool to assess postural steadiness in a static position by quantitative measurement. Many studies have shown that the decreased one leg standing time is associated with declines in Activities of Daily Living and increases in other morbidities including osteoporosis and fall (20).

Our findings suggest that vitamin C may play an important role in maintaining physical performance and thereby may help to improve healthy life expectancy in the elderly. However, the usual and maximal walking speeds did not relate to plasma vitamin C concentration. Walking speed test may be an efficient tool in screening older persons with higher risk of mortality and may easily identify high-risk groups in the community (21). Walking is a rhythmic, dynamic, and aerobic activity of the large skeletal muscles that confers multifarious benefits with minimal adverse effects. Muscles of the legs, limbs, and lower trunk are strengthened, and the flexibility of their joints are preserved (22). One of the reasons why walking speed was not related to vitamin C concentration may be because walking requires coordinated movements of arms, legs, and many parts of the body rather than a simple muscle and balance function. Previous reports showed that walking balance function did not correlate with standing balance function (23). Although we did not find any clear association between walking and plasma vitamin C concentration in this study, vitamin C may still have effects on relatively simple strength and balance functions.

One of the possible explanations for the observed relationship between vitamin C and physical performance, especially handgrip strength and the ability to stand on one leg with eyes open, may be the potential protective effects of the antioxidant vitamins against muscle damage (4,11). Vitamin C is a six-carbon lactone that is synthesized from glucose in the liver of most mammalian species, but not in humans (12). Vitamin C is an antioxidant because, by donating its electrons, it prevents other compounds from being oxidized (12). Thus, vitamin C readily scavenges reactive oxygen and nitrogen species, thereby effectively protects other substrates from oxidative damage (10,24). Although habitual exercise reduces systemic inflammation and oxidative stress as the production of endogenous antioxidants are enhanced, acute exercise increases the generation of oxygen-free radicals and lipid peroxidation (4,25). Strenuous physical performance can increase oxygen consumption by 10- to 15-folds over the resting state to meet the energy demands and results in muscle injury (26). Prolonged submaximal exercise was shown to increase the amount of both whole-body and skeletal muscle lipid peroxidation by-products; in the case of the former, the increase was indicated by greater exhalation of pentane but not of ethane (4,27,28). Supplementation with vitamin C was shown to decrease the exercise-induced increase in the rate of lipid peroxidation (27,28). Several studies suggested that oxidative damage may play a crucial role in the decline of functional activity in human skeletal muscle with normal aging (15). Consistent with this idea, several studies showed significantly lower plasma vitamin C level in the elderly population than in the younger adult population (29–31). Because the plasma vitamin C levels in these apparently healthy elderly persons rose markedly after an oral dose of vitamin C, their initially low plasma levels can be attributed to the low intake rather than to an age-related physiological defect.

In fact, the relationship between handgrip strength and plasma vitamin C concentration was significantly different between supplement users and nonusers, that is, an almost null relationship in the former and a positive relationship in the latter (data not shown). This finding suggested that vitamin C supplementation did not have any beneficial effect on the physical performance and muscle strength despite the increased plasma level of vitamin C. A number of studies reported that vitamin C supplement users had significantly higher blood vitamin C concentration than non-users (29, 32, 33). Several studies have examined the effects of exercise on changes in the serum vitamin C concentration (34–36). Some other experimental studies have shown that vitamin C supplementation can reduce symptoms or indicators of exercise-induced oxidative stress (37–40). However, the results regarding vitamin C supplementation are equivocal, and most well-controlled intervention studies report no beneficial effect of vitamin C supplementation on either endurance or strength performance (41,42). Likewise, vitamin C restriction studies showed that a marginal vitamin C deficiency did not affect the physical performance (43). Although evidence from a number of studies show that vitamin C is a powerful antioxidant in biological systems in vitro, its antioxidant role in humans has not been supported by currently available clinical studies.

Vitamin C is especially plentiful in fresh fruits and vegetables. Plasma vitamin C concentration may be merely a marker for intake of other nutrients that are abundant in fruits and vegetables. However, the statistical adjustment for fruit intake did not attenuate the relationship between plasma vitamin C and physical performance (Table 3), suggesting that vitamin C did have some beneficial effects independently of other nutrients. A number of biochemical, clinical, and observational epidemiologic studies have indicated that diets rich in fruits, vegetables, and vitamin C may be of benefit for the prevention of chronic diseases such as cardiovascular disease and cancer (44,45). Several cohort studies have examined associations between plasma vitamin C concentration and mortality from stroke or coronary heart disease (30,46,47). The effects of vitamin C supplementation are, however, still unclear. A pooled study suggested reduced incidences of coronary heart disease events with higher intake of vitamin C supplement (48), while another study showed that a high intake of vitamin C supplement is associated with an increased risk of mortality due to cardiovascular diseases in postmenopausal women with diabetes (49). A randomized placebo controlled 5-year trial, however, did not show any significant reduction in the mortality from, or incidence of, any type of vascular disease or cancer (50). These studies, in fact, have failed to demonstrate any benefit from such supplementation.

There are a number of potential weaknesses in our study that should be mentioned here. The subjects used in this study were not selected randomly from the study population, and they may be relatively healthy elderly women who were able to come to the health examination hall from their homes. A previous study assessed the correlation of antioxidants with physical performance and muscular strength (3) and demonstrated that a higher daily intake of vitamin C and carotene associated with skeletal muscle strength. However, we have no data regarding the presence of other dietary antioxidants in blood such as vitamin E, retinol, and carotene. In our questionnaire, participants were asked to respond "Yes" or "No" to whether they took supplements, and not about the frequency and quantity of intake of the supplements. Thus, we were unable to examine the reason why plasma vitamin C was not related to the handgrip strength in the supplement users by considering the dose of vitamin C they took.

This study was a cross-sectional study and, therefore, does not provide cause/effect relationships, although we demonstrated a significant correlation between physical performance and concentration of plasma vitamin C. Therefore, longitudinal follow-up studies and controlled clinical trials are necessary to confirm the role of plasma vitamin C and physical performance of the elderly women. These limitations should be considered in future studies.

In conclusion, we found a strong correlation of a higher plasma vitamin C concentration with handgrip strength and one leg standing time in community-dwelling elderly women. Although the elderly are prone to vitamin C deficiency, and they appear to have a higher dietary requirement for vitamin C, the beneficial effects of vitamin C supplementation to maintain physical performance in elderly people are equivocal and thus, need further in-depth studies.

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REFERENCES

1. Fried LP. Epidemiology of aging. *Epidemiol Rev.* 2000;22:95–106.
2. Bartali B, Salvini S, Turrini A, et al. Age and disability affect dietary intake. *J Nutr.* 2003;133:2868–2873.
3. Cesari M, Pahor M, Bartali B, et al. Antioxidants and physical performance in elderly persons: the Invecchiare in Chianti (InCHIANTI) study. *Am J Clin Nutr.* 2004;79:289–294.
4. Evans WJ. Vitamin E, vitamin C, and exercise. *Am J Clin Nutr.* 2000;72:647S–652S.
5. Houston DK, Cesari M, Ferrucci L, et al. Association between vitamin D status and physical performance: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci.* 2007;62:440–446.
6. Corti MC, Guralnik JM, Salive ME, Sorkin JD. Serum albumin level and physical disability as predictors of mortality in older persons. *JAMA.* 1994;272:1036–1042.
7. Baumgartner RN, Koehler KM, Romero L, Garry PJ. Serum albumin is associated with skeletal muscle in elderly men and women. *Am J Clin Nutr.* 1996;64:552–558.
8. Howard C, Ferrucci L, Sun K, et al. Oxidative protein damage is associated with poor grip strength among older women living in the community. *J Appl Physiol.* 2007;103:17–20.
9. Kwon J, Suzuki T, Yoshida H, Kim H, Yoshida Y, Iwasa H. Concomitant lower serum albumin and vitamin D levels are associated with decreased objective physical performance among Japanese community-dwelling elderly. *Gerontology.* 2007;53:322–328.
10. Carr AC, Frei B. Toward a new recommended dietary allowance for vitamin C based on antioxidant and health effects in humans. *Am J Clin Nutr.* 1999;69:1086–1107.
11. Clarkson PM, Thompson HS. Antioxidants: what role do they play in physical activity and health? *Am J Clin Nutr.* 2000;72:637S–646S.
12. Padayatty SJ, Katz A, Wang Y, et al. Vitamin C as an antioxidant: evaluation of its role in disease prevention. *J Am Coll Nutr.* 2003; 22:18–35.
13. Nishikimi M. Oxidation of ascorbic acid with superoxide anion generated by the xanthine-xanthine oxidase system. *Biochem Biophys Res Commun.* 1975;63:463–468.
14. Bielski BH, Richter HW, Chan PC. Some properties of the ascorbate free radical. *Ann N Y Acad Sci.* 1975;258:231–237.
15. Pansarasa O, Castagna L, Colombi B, Vecchiet J, Felzani G, Marzatico F. Age and sex differences in human skeletal muscle: role of reactive oxygen species. *Free Radic Res.* 2000;33:287–293.
16. Suzuki T, Iwasa H, Yoshida H, et al. [Comprehensive health examination ("Otasha-Kenshin") for the prevention of geriatric syndromes and a bed-ridden state in the community elderly. 1. Differences in characteristics between participants and non-participants]. *Nippon Koshu Eisei Zasshi.* 2003;50:39–48.
17. Sato Y, Uchiki T, Iwama M, Kishimoto Y, Takahashi R, Ishigami A. Determination of dehydroascorbic acid in mouse tissues and plasma by using Tris(2-carboxyethyl)phosphine hydrochloride as reductant in metaphosphoric acid/ethylenediaminetetraacetic acid solution. *Biol Pharm Bull.* 2010;33:364–369.
18. Rantanen T, Guralnik JM, Foley D, et al. Midlife hand grip strength as a predictor of old age disability. *JAMA.* 1999;281:558–560.

19. Rantanen T, Volpato S, Ferrucci L, Heikkinen E, Fried LP, Guralnik JM. Handgrip strength and cause-specific and total mortality in older disabled women: exploring the mechanism. *J Am Geriatr Soc.* 2003;51:636–641.
20. Michikawa T, Nishiwaki Y, Takebayashi T, Toyama Y. One-leg standing test for elderly populations. *J Orthop Sci.* 2009;14:675–685.
21. Rolland Y, Lauwers-Cances V, Cesari M, Vellas B, Pahor M, Grandjean H. Physical performance measures as predictors of mortality in a cohort of community-dwelling older French women. *Eur J Epidemiol.* 2006;21:113–122.
22. Morris JN, Hardman AE. Walking to health. *Sports Med.* 1997;23: 306–332.
23. Shimada H, Obuchi S, Kamide N, Shiba Y, Okamoto M, Kakurai S. Relationship with dynamic balance function during standing and walking. *Am J Phys Med Rehabil.* 2003;82:511–516.
24. Halliwell B. Vitamin C: antioxidant or pro-oxidant in vivo? *Free Radic Res.* 1996;25:439–454.
25. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol.* 2005;98:1154–1162.
26. Clarkson PM. Antioxidants and physical performance. *Crit Rev Food Sci Nutr.* 1995;35:131–141.
27. Gee DL, Tappel AL. The effect of exhaustive exercise on expired pentane as a measure of in vivo lipid peroxidation in the rat. *Life Sci.* 1981;28:2425–2429.
28. Davies KJ, Quintanilha AT, Brooks GA, Packer L. Free radicals and tissue damage produced by exercise. *Biochem Biophys Res Commun.* 1982;107:1198–1205.
29. Blanchard J, Conrad KA, Mead RA, Garry PJ. Vitamin C disposition in young and elderly men. *Am J Clin Nutr.* 1990;51:837–845.
30. Fletcher AE, Breeze E, Shetty PS. Antioxidant vitamins and mortality in older persons: findings from the nutrition add-on study to the Medical Research Council Trial of Assessment and Management of Older People in the Community. *Am J Clin Nutr.* 2003;78:999–1010.
31. Jacob RA, Otradovec CL, Russell RM, et al. Vitamin C status and nutrient interactions in a healthy elderly population. *Am J Clin Nutr.* 1988;48:1436–1442.
32. Sinha R, Block G, Taylor PR. Determinants of plasma ascorbic acid in a healthy male population. *Cancer Epidemiol Biomarkers Prev.* 1992;1:297–302.
33. Newton HM, Schorah CJ, Habibzadeh N, Morgan DB, Hullin RP. The cause and correction of low blood vitamin C concentrations in the elderly. *Am J Clin Nutr.* 1985;42:656–659.
34. Gleeson M, Robertson JD, Maughan RJ. Influence of exercise on ascorbic acid status in man. *Clin Sci (Lond).* 1987;73:501–505.
35. Camus G, Felekidis A, Pincemail J, et al. Blood levels of reduced/oxidized glutathione and plasma concentration of ascorbic acid during eccentric and concentric exercises of similar energy cost. *Arch Int Physiol Biochim Biophys.* 1994;102:67–70.
36. Duthie GG, Robertson JD, Maughan RJ, Morrice PC. Blood antioxidant status and erythrocyte lipid peroxidation following distance running. *Arch Biochem Biophys.* 1990;282:78–83.
37. Maxwell SR, Jakeman P, Thomason H, Leguen C, Thorpe GH. Changes in plasma antioxidant status during eccentric exercise and the effect of vitamin supplementation. *Free Radic Res Commun.* 1993;19: 191–202.
38. Jakeman P, Maxwell S. Effect of antioxidant vitamin supplementation on muscle function after eccentric exercise. *Eur J Appl Physiol Occup Physiol.* 1993;67:426–430.
39. Kaminski M, Boal R. An effect of ascorbic acid on delayed-onset muscle soreness. *Pain.* 1992;50:317–321.
40. Bryer SC, Goldfarb AH. Effect of high dose vitamin C supplementation on muscle soreness, damage, function, and oxidative stress to eccentric exercise. *Int J Sport Nutr Exerc Metab.* 2006;16: 270–280.
41. Thompson D, Williams C, Kingsley M, et al. Muscle soreness and damage parameters after prolonged intermittent shuttle-running following acute vitamin C supplementation. *Int J Sports Med.* 2001; 22:68–75.
42. Gey GO, Cooper KH, Bottenberg RA. Effect of ascorbic acid on endurance performance and athletic injury. *Jama.* 1970;211:105.
43. van der Beek EJ, van Dokkum W, Schrijver J, Wesstra A, Kistemaker C, Hermus RJ. Controlled vitamin C restriction and physical performance in volunteers. *J Am Coll Nutr.* 1990;9:332–339.
44. Ness AR, Powles JW. Fruit and vegetables, and cardiovascular disease: a review. *Int J Epidemiol.* 1997;26:1–13.
45. Genkinger JM, Platz EA, Hoffman SC, Comstock GW, Helzlsouer KJ. Fruit, vegetable, and antioxidant intake and all-cause, cancer, and cardiovascular disease mortality in a community-dwelling population in Washington County, Maryland. *Am J Epidemiol.* 2004;160:1223–1233.
46. Yokoyama T, Date C, Kokubo Y, Yoshiike N, Matsumura Y, Tanaka H. Serum vitamin C concentration was inversely associated with subsequent 20-year incidence of stroke in a Japanese rural community. The Shibata study. *Stroke.* 2000;31:2287–2294.
47. Gale CR, Martyn CN, Winter PD, Cooper C. Vitamin C and risk of death from stroke and coronary heart disease in cohort of elderly people. *BMJ.* 1995;310:1563–1566.
48. Knekt P, Ritz J, Pereira MA, et al. Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts. *Am J Clin Nutr.* 2004;80:1508–1520.
49. Lee DH, Folsom AR, Harnack L, Halliwell B, Jacobs DR Jr. Does supplemental vitamin C increase cardiovascular disease risk in women with diabetes? *Am J Clin Nutr.* 2004;80:1194–1200.
50. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360:23–33.

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A Lower Prevalence of Self-Reported Fear of Falling Is Associated with Memory Decline among Older Adults

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Key Words
Elderly · Fear of falling · Memory · Falls · Cognitive decline

Abstract

Background: In spite of a number of reports about various factors associated with the fear of falling (FoF) among older adults (such as age and physical function), the relationship between FoF and cognitive decline remains unclear. ***Objective:*** To determine which cognitive function is related with the prevalence of FoF in older adults. ***Methods:*** Participants were 101 older adults (mean age 75.1 years; 48.5% males). Of these, 54 older adults (53.4%) were classified as the fear group on the basis of the presence of FoF. Age, gender, the Timed Up and Go test (TUG), fall history, the Alzheimer's Disease Assessment Scale, the Wechsler Memory Scale-Revised-Logical Memory I (WMS-LM I), the delayed memory test, digit symbol coding, digit span and verbal fluency were measured as potential relevant factors. ***Results:*** Logistic regression analysis revealed that TUG [odds ratio (OR) 1.43, 95% confidence interval (CI) 1.12–1.83; p = 0.004], WMS-LM I (OR 1.20, 95% CI 1.07–1.35; p = 0.002) and fall history (OR 4.38, 95% CI 1.53–12.51; p = 0.006) were independently associated with FoF. ***Conclusions:*** The results suggest that a lower prevalence of self-reported FoF is associated with memory decline among older adults. Insensitivity to FoF may be one of the characteristics of psychological change with memory decline.

Introduction

Fear of falling (FoF) refers to a lack of self-confidence that normal activities can be performed without falling [1]. Other authors define FoF as a general concept that describes low fall-related efficacy (low confidence in avoiding falls) and being afraid of falling [2]. The prevalence of FoF ranges from 33 to 40%, is higher in women and increases with age [3, 4]. FoF is associated with poor health status [2, 5], functional decline [6, 7], psychological problems [8, 9] and restriction of activities [4, 10]. It is considered important to reduce FoF by targeting down-

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stream factors, such as increasing physical functioning [11]. In spite of a number of reports about various factors associated with FoF, there is no literature examining the relationship between FoF and cognitive functions that inevitably decline with age.

Several aspects of age-related decline of cognitive function are well documented and contribute to the deterioration of the ability to carry out tasks in activities of daily living. For example, memory difficulty is related to slower performance of timed instrumental activities of daily living tasks [12]. Additionally, cognitive impairment is one of the key factors contributing to accidental falls [13]. Recent evidence indicates that even mild cognitive decline is a risk factor for falls [14]. In seniors with Mini-Mental State Examination (MMSE) scores greater than 24 out of 30, baseline cognitive performance was found to be linearly and inversely associated with the rate of falling over 8 years [14]. Within the multiple domains of cognitive function, impaired executive function and memory decline are predictive of accidental falls in older adults [14–16] and are prevalent even in healthy, community-dwelling seniors without dementia (MMSE score >24) [17, 18]. FoF has been recognized as an important psychological factor associated with accidental falls and restricting everyday functioning [19–21]. In addition to studying the risk of falling, investigation of FoF may also be key to the medical management of older adults with mild cognitive decline. Cognitive function includes several domains, such as general, memory, processing speed, language and executive function. However, no previous studies have reported which cognitive declines contribute to the experience of FoF in older adults.

The purpose of this study is to determine the relationship between FoF and potential correlates in older adults with cognitive decline and to identify which cognitive declines are associated with FoF. This investigation is critical to the exploration of psychological factors associated with accidental falls and restricting everyday functioning, enabling the planning of future rehabilitation programs that prevent falls and maintain activities in older adults with cognitive decline.

Methods

Participants

The participants were recruited from two volunteer databases (n = 1,543), which included elderly participants aged 65 years and over who were selected by random sampling or attended a health check in Obu. In the first eligibility assessment for this study, 528 potential participants were enrolled. One hundred and sixty-five participants responded to the second eligibility assessment, and 108 participants completed the assessment and met the inclusion criteria. The inclusion criteria were that they had to be living independently in the community, Japanese-speaking and able to participate in the examinations, and they had to have adequate hearing and visual acuity. In addition, general cognitive function was found to be intact in all 108 participants, whose MMSE scores were in the range of 24–30 [22]. Seven participants were excluded based on the following exclusion criteria: a history of major psychiatric illness, other serious neurological or musculoskeletal diagnoses or depression (Geriatric Depression Scale score ≥10 [23]). The final sample used for analysis consisted of 101 older adults (mean age 75.1 years; 48.5% males; mean educational history 10.7 years). This study was approved by the ethics committee of the National Center for Geriatrics and Gerontology. All participants provided written informed consent.

Measurements

Demographic data were recorded, including age, gender, educational history and number of medications. FoF was assessed by a fourth-ordered choice, closed-ended question about participants' general FoF. The question was phrased as follows: 'Are you afraid of falling?' Participants who responded 'very much' or 'somewhat' were assigned to the fear group; participants who responded 'a little' or 'not at all' were assigned to the no-fear group [24] , which had a high test-retest reliability of up to 0.9 in a sample of 44 randomly selected individuals [25].

The participants also completed a standardized questionnaire that recorded the number of times they had fallen in the past year. A fall was defined as an event where a person unintentionally comes to rest on the ground, floor or another lower level [26]. Falls resulting from extraordinary environmental factors (e.g. traffic accidents or falls while riding a bicycle) were excluded from the count. On the basis of their fall history, participants were divided into two groups, namely fallers (1 or more falls) and nonfallers (0 falls).

The participants underwent 3 clinical measurements to assess physical performance, namely the Timed Up and Go Test (TUG), the one-leg standing test and the 5-meter walking test, in the presence of an experienced physiotherapist. The TUG [27] involves rising from a chair, walking 3 m, turning around, walking back to the chair and sitting down. Participants were instructed to complete the task at their usual pace. The score represented the time in seconds that the participant needed to complete the assessment. Less time taken to accomplish this task indicated better balancing and gait ability. The shorter time measured in the two trials was recorded as the TUG score. In the one-leg standing test, the participants were asked to stand on their preferred leg as long as possible with their arms hanging down and with eyes open. One-leg standing balance was measured as the time (0–120 s) participants could stand on one leg. The longer time measured in the two trials was recorded as the one-leg standing test score. In the 5-meter walking test, participants were asked to walk along a straight, level path at their 'normal walking speed'. Walking time was calculated using a stopwatch to measure the time taken to cover the central 5 m of the walkway (2 m at the start and finish were used for acceleration and deceleration). The walking time score was calculated as the shorter time in seconds for completion of two trials.

All neuropsychological tests were conducted by well-trained speech therapists, and each score was rechecked by a single speech

Table 1. Demographic and clinical characteristics of study participants

	Fear group (n = 54)	No-fear group (n = 47)	p value	Effect size
Age, years	76.2 ± 6.8 (65–93)	73.7 ± 6.7 (69–94)	0.071	0.37
Education, years	10.5 ± 2.2	11.0 ± 2.8	0.251	0.20
Males	20 (37.0)	29 (61.7)	0.013	0.25
Number of medications	2.8 ± 2.2	2.0 ± 2.3	0.087	0.36
GDS score	3.3 ± 2.4	2.7 ± 2.2	0.232	0.26
Fall history	21 (38.9)	9 (19.1)	0.030	0.22
TUG, s	9.7 ± 2.6	8.5 ± 2.1	0.013	0.51
One-leg standing test, s	31.3 ± 23.7	41.1 ± 23.2	0.041	0.42
5-Meter walking time, s	5.0 ± 1.8	4.6 ± 1.1	0.12	0.27

Values are means ± SD (range) or numbers of participants (%). GDS = Geriatric Depression Scale. Effect sizes are based on Cohen's d (t test) or ϕ (χ^2).

therapist who was blinded to the other data of the participants in this study. General cognitive function was evaluated using the Alzheimer's Disease Assessment Scale (ADAS) [28]. The ADAS was designed specifically to evaluate cognitive and behavioral dysfunctions characteristic of Alzheimer's disease. On this test, the scores range from 0 to 70 points, with fewer points indicating a better score.

Memory function was evaluated by the Logical Memory I (story A only) from the Japanese version of the Wechsler Memory Scale-Revised (WMS-LM I) [29]. On this task, a short story that consisted of 25 segments was read aloud to the participant, who was instructed to recall details of the story immediately. On this test, the scores ranged from 0 to 25 points, with more points indicating a better score. The delayed memory test was also conducted, which is a three-word recall test in the MMSE [22]. In this study, delayed memory was converted to categorical variables, i.e. 0 (1 or more mistakes with the three words) or 1 point (all three words correct).

Processing speed was assessed by using a version of the digit symbol coding subtest of the Wechsler Adult Intelligence Scale III [30]. In the test, participants copied symbols that are paired with numbers. Using the key provided at the top of the exercise form, the participant drew the symbol under the corresponding number. The score for digit symbol coding was the number of correct symbols drawn within 120 s. One point is given for each correctly drawn symbol completed within the time limit, for a maximum score of 133.

Executive function was assessed using the Trail Making Test, part B [31]. Participants were required to navigate a series of alternating numbers and letters and connect them in alternating sequential order. The time required to complete each task was recorded, with more time indicating worse performance.

We also conducted a digit span forward test and a digit span backward test. Both tests are a subset of the Wechsler Adult Intelligence Scale III [30] and require participants to repeat a series of verbally presented digits of increasing length in forward and backward order. Performance on the digit span task strongly depended upon working memory, cognitive regulation and manipulation, all of which are components of executive function. The score recorded, ranging from 0 to 14, was the number of successful sequences.

Verbal fluency is composed of letter fluency and category fluency [32]. The participants were asked to generate as many words as possible within 1 min, consisting of an initial letter (letter fluency) and an animal name (category fluency) [33]. Verbal fluency is an evaluation of expressive language ability and executive function [32–34]. The score was the number of successful words (except for some proper nouns).

Statistical Analysis

Unpaired t tests or χ^2 tests (for gender, fall history and delayed memory) were used to evaluate the differences in measurements between the fear and no-fear groups. Cohen's d (t test) or ϕ (χ^2) values were calculated as measures of effect size.

Logistic regression analysis, performed as a stepwise analysis, was carried out to examine whether the potential determinants were independently associated with FoF. In this analysis, the presence or absence of FoF was used as the dependent variable (no-fear = 0, fear = 1), and age and variables that showed a significant difference between the fear and no-fear groups were employed as independent variables. Gender and fall history were created as categorical variables (male = 0, female = 1; nonfaller = 0, faller = 1). Statistical analyses were conducted using software package SPSS version 11.0 (SPSS Inc., Chicago, Ill., USA), and $p < 0.05$ was accepted as significant.

Results

Fifty-four older adults out of 101 participants (53.4%) were classified into the fear group, and 47 older adults (46.6%) were classified into the no-fear group. Table 1 shows the differences in demographic variables and physical performance test scores between the fear and no-fear groups. There were no significant differences in age, educational history or number of medications. The fear group had a lower number of males than the no-fear group (fear group 37.0%, no-fear group 61.7%; p = 0.013),

Table 2. Cognitive characteristics of study participants

	Fear group (n = 54)	No-fear group (n = 47)	p value	Effect size
MMSE score	26.9 ± 2.2	27.2 ± 1.6	0.565	0.16
ADAS score	6.0 ± 3.5	6.2 ± 2.5	0.853	0.07
WMS-LM I score	8.5 ± 4.3	6.6 ± 4.6	0.033	0.43
Score of 1 on the delayed memory test	35 (64.8)	20 (42.6)	0.029	0.22
TMT-B, s	192.6 ± 82.9	180.6 ± 118	0.573	0.12
Digit symbol coding score	46.1 ± 15.2	48.1 ± 16.2	0.526	0.13
Digit span forward score	4.9 ± 0.1	4.9 ± 0.3	0.063	0
Digit span backward score	4.5 ± 0.8	4.5 ± 0.7	0.851	0
Letter fluency score	5.3 ± 3.1	6.1 ± 3.7	0.270	0.24
Category fluency score	15.1 ± 4.9	14.7 ± 4.4	0.691	0.09

Values are means ± SD or numbers of participants (%). TMT-B = Trail Making Test, part B. Effect sizes are based on Cohen's d (t test) or ϕ (χ^2).

while the number of fallers among the fear group was significantly higher than among the no-fear group (fear group 38.9%, no-fear group 19.1%; p = 0.03). With regard to physical performance tests, the fear group exhibited better scores on the TUG (p = 0.013) and one-leg standing test (p = 0.041) than the no-fear group. There were no significant differences in 5-meter walking time (p = 0.12).

Among several domains of cognitive function, only memory function showed significant differences between the groups. The fear group had significantly more points on the WMS-LM I (p = 0.033) than the no-fear group. More participants in the fear group than in the no-fear group scored 1 point on the delayed memory test (p = 0.029). There were no statistically significant differences in the MMSE, ADAS, digit symbol coding subtest, Trail Making Test, part B, digit span forward test, digit span backward test, letter fluency and category fluency between the groups (table 2).

Age, gender, fall history, TUG, WMS-LM I and delayed memory were entered into a stepwise logistic regression model. Logistic regression analysis revealed that TUG [odds ratio (OR) 1.43, 95% confidence interval (CI) 1.12–1.83; p = 0.004], WMS-LM I (OR 1.20, 95% CI 1.07–1.35; p = 0.002) and fall history (OR 4.38, 95% CI 1.53–12.51; p = 0.006) were independently associated with FoF, accounting for age and gender. Age, gender and delayed memory did not show a statistically significant relationship (table 3). The model was well calibrated between declines of observed and expected risk (Hosmer-Lemeshow $\chi^2 = 5.4$, p = 0.72).

Table 3. Factors associated with FoF in stepwise logistic regression

Factor	OR	95% CI	p value
TUG	1.43	1.12–1.83	0.004
WMS-LM I	1.20	1.07–1.35	0.002
Fall history	4.38	1.53–12.51	0.006
Age	–	–	0.32
Gender	–	–	0.13
Delayed memory test	–	–	0.16
One-leg standing test	–	–	0.27

Discussion

This is the first study to clarify the relationship between cognitive decline and experience of FoF. It is in line with studies that show the prevalence of FoF is higher in females and in individuals with worse physical function (i.e. worse scores on the TUG and one-leg standing tests) and a history of falls [25, 35]. The results of the present study revealed that memory function was also significantly associated with FoF, which indicates that a lower prevalence of FoF is associated with memory decline among older adults, although there were no significant associations between FoF and other cognitive functions (i.e. general, processing speed, language and executive function). Interestingly, it can be suggested that worse physical function is likely to cause FoF, while worse memory function is likely to inhibit FoF in older adults.

Among the various cognitive functions, memory decline may influence FoF specifically. It might be difficult for nondemented participants with memory decline to recall detailed images of accidental falls. Memory decline is the initial symptom of dementia. Older adults with even very mild dementia are inclined to underestimate their functional deficits and have poor insight into depressive symptoms and behavioral changes, which is regarded as 'anosognosia' [36]. In the present study, it is possible that participants with memory decline may also have underestimated functional deficits, the risk of accidental falls and 'post-fall syndrome', which may lead to insensitivity to FoF. We considered that insensitivity to FoF may be one of the characteristics of psychological changes in older adults with memory decline.

Low prevalence of FoF might reduce the effect of rehabilitation programs on fall prevention and the maintenance of activities in older adults with memory decline. It was reported that multimedia patient education to prevent falls was not effective for patients with impaired cognitive function, although the same education reduced falls among patients with intact cognitive function [37]. These authors suggested that cognitive impairment can limit the ability of patients to adhere to planned safety-promoting behaviors. Arai et al. [38] reported that exercise intervention for physical function outcome might be beneficial to older adults with lower confidence for performing various activities without falling compared with those with higher confidence. It is possible that FoF in a way contributes to safety-promoting behaviors and adherence to exercise intervention. Therefore, insensitivity to FoF may be one of the factors reducing the effect of education and exercise intervention to prevent falls. It is possible that education and an exercise program specifically designed to address their cognitive needs and insensitivity to FoF is more beneficial for preventing falls among participants with memory decline.

This study has several limitations. Firstly, the sample size was relatively small. Secondly, as with other cross-sectional studies, the design of the current study limits the interpretation of the results with regard to causality between memory decline and FoF. A longitudinal study will be necessary to examine the causal relationship between memory decline, future fall incidence and expression of FoF. Thirdly, we did not collect data on certain factors that may influence FoF, such as perception of health [4] and emotional support [39]. These and other factors should be examined in future FoF studies.

In conclusion, memory decline is a specific aspect of cognition influencing experience of FoF in addition to physical function and fall history. The major implication of this study is that FoF was not only associated with worse physical performance but also memory function, which indicates that a lower prevalence of FoF is associated with memory decline among older adults. Insensitivity to FoF may be one of the characteristics of psychological change in older adults with memory decline. Future research is needed to clarify the causal relationship between memory decline, future fall incidence and expression of FoF.

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References

1 Tinetti ME, Richman D, Powell L: Falls efficacy as a measure of fear of falling. J Gerontol 1990;45:P239–P243.
2 Cumming RG, Salkeld G, Thomas M, Szonyi G: Prospective study of the impact of fear of falling on activities of daily living, SF-36 scores, and nursing home admission. J Gerontol A Biol Sci Med Sci 2000;55:M299–M305.
3 Austin N, Devine A, Dick I, Prince R, Bruce D: Fear of falling in older women: a longitudinal study of incidence, persistence, and predictors. J Am Geriatr Soc 2007;55:1598–1603.
4 Zijlstra GA, van Haastregt JC, van Eijk JT, van Rossum E, Stalenhoef PA, Kempen GI: Prevalence and correlates of fear of falling, and associated avoidance of activity in the general population of community-living older people. Age Ageing 2007;36:304–309.
5 Howland J, Peterson EW, Levin WC, Fried L, Pordon D, Bak S: Fear of falling among the community-dwelling elderly. J Aging Health 1993;5:229–243.
6 Arfken CL, Lach HW, Birge SJ, Miller JP: The prevalence and correlates of fear of falling in elderly persons living in the community. Am J Public Health 1994;84:565–570.

7 Petrella RJ, Payne M, Myers A, Overend T, Chesworth B: Physical function and fear of falling after hip fracture rehabilitation in the elderly. Am J Phys Med Rehabil 2000;79: 154–160.

8 Lawrence RH, Tennstedt SL, Kasten LE, Shih J, Howland J, Jette AM: Intensity and correlates of fear of falling and hurting oneself in the next year: baseline findings from a Roybal Center fear of falling intervention. J Aging Health 1998;10:267–286.

9 Vellas BJ, Wayne SJ, Romero LJ, Baumgartner RN, Garry PJ: Fear of falling and restriction of mobility in elderly fallers. Age Ageing 1997;26:189–193.

10 Howland J, Lachman ME, Peterson EW, Cote J, Kasten L, Jette A: Covariates of fear of falling and associated activity curtailment. Gerontologist 1998;38:549–555.

11 Delbaere K, Crombez G, Vanderstraeten G, Willems T, Cambier D: Fear-related avoidance of activities, falls and physical frailty. A prospective community-based cohort study. Age Ageing 2004;33:368–373.

12 Owsley C, Sloane M, McGwin G Jr, Ball K: Timed instrumental activities of daily living tasks: relationship to cognitive function and everyday performance assessments in older adults. Gerontology 2002;48:254–265.

13 Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. J Am Geriatr Soc 2001;49:664–672.

14 Anstey KJ, von Sanden C, Luszcz MA: An 8-year prospective study of the relationship between cognitive performance and falling in very old adults. J Am Geriatr Soc 2006;54: 1169–1176.

15 Nevitt MC, Cummings SR, Hudes ES: Risk factors for injurious falls: a prospective study. J Gerontol 1991;46:M164–M170.

16 van Schoor NM, Smit JH, Pluijm SM, Jonker C, Lips P: Different cognitive functions in relation to falls among older persons. Immediate memory as an independent risk factor for falls. J Clin Epidemiol 2002;55:855–862.

17 Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, Belleville S, Brodaty H, Bennett D, Chertkow H, Cummings JL, de Leon M, Feldman H, Ganguli M, Hampel H, Scheltens P, Tierney MC, Whitehouse P, Winblad B: Mild cognitive impairment. Lancet 2006;367:1262–1270.

18 Royall DR, Cabello M, Polk MJ: Executive dyscontrol: an important factor affecting the level of care received by older retirees. J Am Geriatr Soc 1998;46:1519–1524.

19 Delbaere K, Close JC, Brodaty H, Sachdev P, Lord SR: Determinants of disparities between perceived and physiological risk of falling among elderly people: cohort study. BMJ 2010;341:c4165.

20 Deshpande N, Metter EJ, Lauretani F, Bandinelli S, Guralnik J, Ferrucci L: Activity restriction induced by fear of falling and objective and subjective measures of physical function: a prospective cohort study. J Am Geriatr Soc 2008;56:615–620.

21 Gagnon N, Flint AJ, Naglie G, Devins GM: Affective correlates of fear of falling in elderly persons. Am J Geriatr Psychiatry 2005;13: 7–14.

22 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.

23 Yesavage JA: Geriatric depression scale. Psychopharmacol Bull 1988;24:709–711.

24 Maki BE, Holliday PJ, Topper AK: Fear of falling and postural performance in the elderly. J Gerontol 1991;46:M123–M131.

25 Chu CL, Liang CK, Chow PC, Lin YT, Tang KY, Chou MY, Chen LK, Lu T, Pan CC: Fear of falling (FF): psychosocial and physical factors among institutionalized older Chinese men in Taiwan. Arch Gerontol Geriatr 2011; 53:e232–e236.

26 Koski K, Luukinen H, Laippala P, Kivela SL: Physiological factors and medications as predictors of injurious falls by elderly people: a prospective population-based study. Age Ageing 1996;25:29–38.

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 Rosen WG, Mohs RC, Davis KL: A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364.

29 Wechsler D: Wechsler Memory Scale – Revised Manual. San Antonio, The Psychological Corporation, 1987.

30 Wechsler D: Wechsler Adult Intelligence Scale – III. San Antonio, The Psychological Corporation, 1997.

31 Kortte KB, Horner MD, Windham WK: The trail making test, part B: cognitive flexibility or ability to maintain set? Appl Neuropsychol 2002;9:106–109.

32 Benton AL: Differential behavioral effects in frontal lobe disease. Neuropsychologia 1968; 6:53–60.

33 Nemoto T, Kashima H, Mizuno M: Contribution of divergent thinking to community functioning in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2007;31: 517–524.

34 Lezak MD: Neuropsychological Assessment, ed 4. New York, Oxford University Press, 2004.

35 Scheffer AC, Schuurmans MJ, van Dijk N, van der Hooft T, de Rooij SE: Fear of falling: measurement strategy, prevalence, risk factors and consequences among older persons. Age Ageing 2008;37:19–24.

36 Starkstein SE, Jorge R, Mizrahi R, Robinson RG: A diagnostic formulation for anosognosia in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2006;77:719–725.

37 Haines TP, Hill AM, Hill KD, McPhail S, Oliver D, Brauer S, Hoffmann T, Beer C: Patient education to prevent falls among older hospital inpatients: a randomized controlled trial. Arch Intern Med 2011;171:516–524.

38 Arai T, Obuchi S, Inaba Y, Nagasawa H, Shiba Y, Watanabe S, Kimura K, Kojima M: The effects of short-term exercise intervention on falls self-efficacy and the relationship between changes in physical function and falls self-efficacy in Japanese older people: a randomized controlled trial. Am J Phys Med Rehabil 2007;86:133–141.

39 Murphy SL, Williams CS, Gill TM: Characteristics associated with fear of falling and activity restriction in community-living older persons. J Am Geriatr Soc 2002;50:516–520.

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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 ≥ 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.