kilograms/(height in meters)^2] was calculated on the basis of the current height and weight. Hand grip strength was measured using a Toei Light handgrip dynamometer (Toei Light Co., Ltd., Saitama, Japan). Both hands were tested, and the higher value was used to characterise the maximum muscle strength of the subject. Walking speed was determined by recording the time taken by a subject to walk a determined distance, such as 5 or 6 m, at his/her usual speed. The ability to rise from a chair without using the arms (chair stand) and the ability to perform 5 chair stands was evaluated. The time required to complete the tasks was recorded.

Medical information

Medical information was obtained by experienced medical doctors in each cohort. All participants were questioned about pain in both knees by asking the following questions: 'Have you experienced right knee pain on most days (and continuously on at least one day) in the past month, in addition to the current pain?' and 'Have you experienced left knee pain on most days (and continuously on at least one day) in the past month, in addition to the current pain?' Subjects who answered 'yes' were considered to have knee pain. Lumbar pain was determined by asking the following question: 'Have you experienced lumbar pain on most days (and continuously on at least one day) in the past month, in addition to the current pain?' Subjects who answered 'yes' were considered to have lumbar pain.

In some cohorts (Tokyo-1, Wakayama-1, and Wakayama-2), the participants completed the modified Mini-Mental Status Examination-Japanese version [9] for evaluating cognitive function. Physicians explained any unclear sections of this questionnaire to the participants and assessed the cognitive status on the basis of the completed questionnaire.

Radiography and radiographic assessment

In several cohorts (Tokyo-1, Wakayama-1, Wakayama-2, Hiroshima, Niigata, and Mie), the radiographic examination of knees and/or spine was performed to evaluate the OA or fractures. Plain radiographs were obtained for both knees in the antero-posterior view with weight-bearing and foot map positioning and for the spine in the antero-posterior and lateral views.

The severity of OA was radiographically determined according to the Kellgren-Lawrence (KL) grading system as follows [10]: KL0, normal joint; KL1, slight osteophytes; KL2, definite osteophytes; KL3, narrowing of joint cartilage, and large osteophytes; and KL4, bone sclerosis, narrowing of joint cartilage, and large osteophytes. In the LOCOMO study, joints exhibiting disc-space narrowing alone and no large osteophytes were graded as KL3. In each cohort, radiographs were examined by a single, experienced orthopaedic surgeon who was masked to the clinical status of the participants. If at least one knee joint was graded as KL2 or higher, the participant was diagnosed with radiographic KOA. Similarly, if at least one intervertebral joint of the lumbar spine was graded as KL2 or higher, the participant was diagnosed with radiographic LS.

BMD measurement

In the Wakayama-1, Wakayama-2, and Hiroshima cohorts, BMD of the lumbar spine and proximal femur was measured using dual energy X-ray absorptiometry (DXA) (Hologic Discovery; Hologic, Waltham, MA, USA) during the baseline examination.

OP was defined on the basis of the World Health Organization (WHO) criteria. Specifically, OP was diagnosed when the BMD T scores were lower than the mean lumbar peak bone mass—2.5 SDs [11]. In Japan, the mean BMD of the L2–L4 vertebrae among both young male and female adults has been measured using Hologic DXA [12]. In the present study, lumbar spine BMD < 0.714 g/cm^2 (for both men and women) and femoral neck BMD < 0.546 g/cm^2 (men) or <0.515 g/cm^2 (women) were considered to indicate OP.

Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA Corp., College Station, TX, USA). Differences in proportions were compared using the Chi square test. Differences in continuous variables were tested for significance using analysis of variance for comparisons among multiple groups or Scheffe's least significant difference test for pairs of groups. To test the association between the interaction between the knee pain and lumbar pain, a logistic regression model was used. First, the presence of knee pain was used as an objective variable (0: absence, 1: presence) and age (+1 year), gender (men vs. women), BMI (+1 kg/m^2), regional differences (0: rural areas including Wakayama-1, Wakayama-2, Niigata, Mie, Akita, and Gunma vs. 1: urban areas including Tokyo-1, Tokyo-2, and Hiroshima), and lumbar pain (0: no, 1: yes) were used as explanatory variables. Then, lumbar pain was used as an objective variable, and knee pain was used as an explanatory variable in the identical model. All p values and 95 % confidence intervals (CI) of two-sided analysis are presented.

Results

Table 2 shows the number of participants classified by age and gender. Most participants were aged $\geq$60 years, and

Table 2 Numbers of participants in the LOCOMO study classified by age and gender

Age strata (years)	Total (%)	Men (%)	Women (%)
≤39	125 (1.0)	49 (1.2)	76 (0.9)
40–49	483 (4.0)	183 (4.6)	300 (3.7)
50–59	963 (8.0)	320 (8.1)	643 (8.0)
60–69	3,170 (26.3)	1,161 (29.3)	2,009 (24.9)
70–79	5,041 (41.9)	1,573 (39.7)	3,468 (43.0)
80–89	2,111 (17.6)	627 (15.8)	1,484 (18.4)
≥90	126 (1.1)	46 (1.2)	80 (1.0)
Total	12,019 (100.0)	3,959 (100.0)	8,060 (100.0)

99.0 % of the participants were aged ≥40 years. Two-thirds of the participants were women, and their mean age was 1 year greater than that of the male participants.

Selected characteristics of the study populations, including age, height, weight, BMI, and proportions of participants who smoked and consumed alcohol are shown in Table 3. The participants were considered as smokers and alcohol consumers if they answered 'yes' to the question 'Are you currently smoking/drinking?' in the self-administered questionnaire. The mean values of age and BMI were significantly higher in women than in men ($p < 0.01$). The proportions of both current smokers and alcohol consumers were significantly higher among men than among women ($p < 0.001$).

Table 3 Baseline characteristics of participants in the LOCOMO study classified by age and gender

Variables	Men	Women	*p* Value (men vs. women)
Age (years)	70.0 (10.6)	71.0 (10.3)	<0.001
Height (cm)	161.1 (6.8)	148.5 (6.4)	<0.001
Weight (kg)	59.3 (9.5)	50.8 (8.6)	<0.001
BMI (kg/m^2)	22.8 (3.0)	23.0 (3.5)	0.007
Smoking (%)	34.0	4.8	<0.001
Drinking (%)	52.4	21.1	<0.001

Values are represented as mean (standard deviation)

BMI body mass index

By analysing the data at the baseline examination, we determined the prevalence of knee pain and lumbar pain. Figure 3 shows the age-sex distribution of the prevalence of knee pain and lumbar pain. Overall, the prevalence of knee pain was 32.7 % (27.9 % in men and 35.1 % in women) and that of lumbar pain was 37.7 % (34.2 % in men and 39.4 % in women). The prevalence of pain in both the knee and lumbar region were significantly higher in women than in men ($p < 0.001$). On the basis of the total age and sex distributions derived from the Japanese census in 2010 [13], our results estimate that 18,000,000 people (7,100,000 men and 10,900,000 women) aged ≥40 years would be affected by knee pain and that 27,700,000 people (12,100,000 men and 15,600,000 women) aged ≥40 years would be affected by lumbar pain.

Further, among 9,046 individuals who were surveyed on both knee pain and lumbar pain at the baseline examination in each cohort, the prevalence of both knee pain and lumbar pain was 12.2 % (10.9 % in men and 12.8 % in women). The prevalence of the coexistence of knee and lumbar pain in the participants aged <40, 40–49, 50–59, 60–69, 70–79, and ≥80 years was 4.0, 4.8, 7.4, 13.0, 13.3, and 11.7 %, respectively, (6.1, 5.3, 6.0, 10.0, 11.5, and 13.2 %, respectively, in men and 2.6, 4.6, 8.1, 14.8, 14.2, and 11.0 %, respectively, in women). The prevalence of both knee pain and lumbar pain increased with age in men, whereas that in women reached a plateau at 60–69 and 70–79 years and then declined. On the basis of the total age and sex distributions derived from the Japanese census in 2010 [13], our results estimate that 6,800,000 people

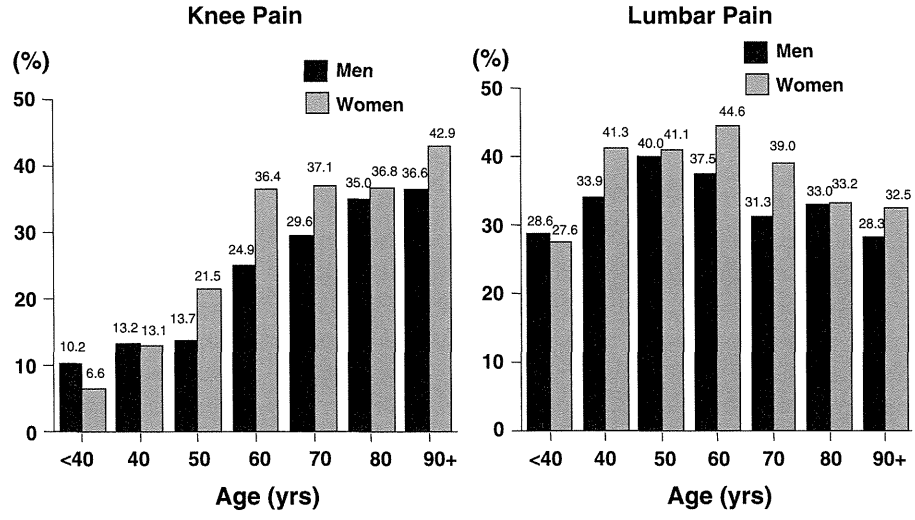

Fig. 3 Prevalence of knee pain and lumbar pain according to age and gender

Table 4 Odds ratios (OR) of potentially associated factors for the presence of knee pain/ lumbar pain vs. absence of pain

Explanatory variables	Reference	OR	95% confident interval	*p*
Knee pain (presence vs. absence)				
Age (years)	+1 year	1.045	1.039–1.051	<0.001***
Gender	0: men, 1: women	1.602	1.441–1.780	<0.001***
Region	0: urban area, 1: rural area	2.419	2.152–2.720	<0.001***
BMI (kg/m^2)	+1 kg/m^2	1.141	1.124–1.158	<0.001***
Lumbar pain	0: absence, 1: presence	1.373	1.243–1.515	<0.001***
Lumbar pain (presence vs. absence)				
Age (years)	+1 year	1.018	1.013–1.023	<0.001***
Gender	0: men, 1: women	1.130	1.023–1.248	0.016*
Region	0: urban area, 1: rural area	2.016	1.801–2.256	<0.001***
BMI (kg/m^2)	+1 kg/m^2	1.020	1.003–1.031	0.021*
Knee pain	0: absence, 1: presence	1.375	1.246–1.518	<0.001***

BMI body mass index

* $p < 0.05$, *** $p < 0.001$

(2,800,000 men and 4,000,000 women) aged ≥40 years would be affected by both knee pain and lumbar pain.

To test the association between the knee pain and lumbar pain, the presence of knee pain was first used as an objective variable (0: absence, 1: presence) and age (+1 year), gender (men vs. women), BMI (+1 kg/m^2), regional differences (0: rural areas including Wakayama-1, Wakayama-2, Niigata, Mie, Akita, and Gunma vs. 1: urban areas including Tokyo-1, Tokyo-2, and Hiroshima), and lumbar pain (0: no, 1: yes) were used as explanatory variables. Then, the presence of lumbar pain was used as an objective variable (0: absence, 1: presence) and age (+1 year), gender (men vs. women), BMI (+1 kg/m^2), regional differences (0: rural areas including Wakayama-1, Wakayama-2, Niigata, Mie, Akita, and Gunma vs. 1: urban areas including Tokyo-1, Tokyo-2, and Hiroshima), and knee pain (0: no, 1: yes) were used as explanatory variables. Table 4 shows the result of the logistic regression analysis. Higher age, female sex, higher BMI, living in a rural area, and the presence of lumbar pain significantly influenced the presence of knee pain. Similarly, higher age, female sex, higher BMI, living in a rural area, and the presence of knee pain significantly influenced the presence of lumbar pain.

Discussion

In the present study, we integrated the information of individual cohorts established for the prevention of musculoskeletal diseases, and created the nationwide large-scale cohorts comprising the LOCOMO study. By using the data of the LOCOMO study, we found that the prevalence of knee pain was 32.7 % and that of lumbar pain was 37.7 %. Both knee pain and lumbar pain were prevalent in 12.2 % of the total population. In the present study, we also clarified that the factors associated with knee or lumbar pain were age, sex, body build, and residential characteristics. In addition, the presence of knee pain affected the lumbar pain, and vice versa. This association remained even after the adjustment for the above-mentioned associated factors. To our knowledge, this is the first study to report the frequency of the knee pain and lumbar pain and to estimate the total number of prevalent subjects, by using a large-scale population-based cohort study in Japan.

With regard to musculoskeletal pain, several population-based epidemiological studies have demonstrated that chronic pain is a highly prevalent condition. Soni et al. [14] reported that the prevalence rates of self-reported knee pain using the baseline data in 1,003 participants from the Chingford Women's Study were 22.97 % in the left knee and 24.80 % in the right knee. The definition of the presence of the knee pain (based on the following two questions: 'Have you had any knee pain in either knee in the last month?' and 'How many days of pain have you experienced in the last month?') was similar but not identical to our definition used in the LOCOMO study, and the subjects' age was younger in the Chinford study than in the LOCOMO study. Therefore, we could not compare the prevalence between the Chinford and LOCOMO studies directly. However, at a glance, the prevalence seems to be higher in the Japanese population. This may be due to the fact that the prevalence of KOA (KL grades ≥2) was higher in the Japanese population than that in the Caucasian population [15]. Verhaak et al. [16] reviewed epidemiological studies on chronic benign pain among adults, including subjects aged between 18 and 75 years, and reported that the prevalence ranged between 2 and 40 % of the population. Coggon et al. did not perform a population-based study, but instead conducted a cross-sectional survey comparing the prevalence of disabling low back pain and disabling wrist/hand pain among groups of workers carrying out similar physical activities in different cultural environments in 18 countries including Japan. They

reported that the 1-month prevalence of disabling low back pain in nurses ranged from 9.6 to 42.6 %, and that of disabling wrist/hand pain in office workers ranged from 2.2 to 31.6 % [17]. We could not compare our results to those of Coggon's results directly because of the difference in the characteristics of the targeted population. However, previous reviews and reports demonstrated that the prevalence of the chronic pain varied in the population surveyed, and therefore, estimating the prevalence and number of patients in pain would require a study that comprises various regions with a large number of subjects. Our LOCOMO study contains 12,019 participants from the cohorts consisting of nine communities in different locations in Japan. Therefore, we believe that our estimation of the prevalence of knee pain and lumbar pain is appropriate, and the number of patients was sufficient.

With regard to the characteristics of subjects with chronic pain, Soni et al. [14] reported that among subjects who could be followed up for 12 years, a higher BMI was predictive of persistent knee pain (odds ratio = 1.14) and incident knee pain (odds ratio = 1.10). Verhaak et al. [16] demonstrated that chronic pain generally increased with age, with some studies reporting a peak prevalence between the ages of 45 and 65 years. These results were not consistent with our results. Moreover, we noted that living in a rural area was associated with the presence of knee pain and lumbar pain, which may be due to the difference of the primary occupation in that area. Muraki et al. [18] reported that the presence of KOA and LS was influenced by the primary occupation of the participants. According to their report, the prevalence of higher K/L grades of KOA and LS was significantly higher among agricultural, forestry, and fishery workers than among clerical workers and technical experts [18]. For occupational activities, sitting on a chair had a significant inverse association with K/L grades $\geq$2 for KOA and LS, whereas standing, walking, climbing and heavy lifting were associated with higher K/L grades for KOA [18]. An association between occupational activities and KOA was also observed in several studies [19–21]. Agricultural, forestry, and fishery workers seemed to be more common in rural areas than in urban areas. In addition, occupational activities, such as sitting on a chair, might be observed more commonly in clerical workers than in agricultural, forestry, and fishery workers. These findings might support the regional differences of pain that were observed in the present study. The main focus of the present study was pain, and not OA; however, the most probable diagnosis underlying knee pain among older people was reported to be OA [22].

There are also several reports regarding the coexistence of pain. The above-mentioned Coggon's investigation indicated that the rates of disabling pain at 2 anatomical sites—the lumbar spine and wrist/hand—covaried (r = 0.76) [17]. In their cross-sectional study, Smith et al., examined the presence and sites of chronic pain in 11,797 women. The presence of chronic pain was noted in 38 % of women; among them, the percentage of women experiencing chronic pain at 1, 2, 3, 4, and $\geq$5 sites was 23.2, 24.4, 20.0, 14.3, and 18.2 %, respectively [23]. These results showed that chronic pain coexists at other anatomical sites. In the present study, the prevalence of both knee pain and lumbar pain was 12.2 % (10.9 % in men and 12.8 % in women) among the general population. However, among the subjects with lumbar pain, 37.3 % also had knee pain (39.0 % in men and 36.6 % in women). Unfortunately, in the LOCOMO study, we were unable to collect the data regarding pain at anatomical sites other than knee pain and lumbar pain. Nevertheless, the coexistence of pain was commonly noted, which is inconsistent with previous reports.

There were several limitations in the present study. First, the current subjects do not truly represent the entire Japanese population. We should carefully consider this limitation, especially when determining the generalisability of the results. However, the LOCOMO study is the first large-scale population-based prospective study with more than 12,000 participants. Although it does not comprise the whole population of Japan, the number of participants in the cohorts established for the prevention of the musculoskeletal diseases appears to be biggest worldwide. Second, all the items of our survey in the baseline examination were not recorded in all cohorts. For example, radiographic examination of knees was performed only in Tokyo-1, Wakayama-1, Wakayama-2, Niigata, and Mie prefectures and radiographic examination of the lumbar spine was performed only in Tokyo-1, Wakayama-1, Wakayama-2, Hiroshima, and Mie prefectures. Third, the radiographic findings for OA assessment using KL scales have not been integrated yet, because of the delay in the standardisation of reading methods of the observers. Radiographs should be assessed by a single observer to omit the inter-observer variability, and if this is impossible, then the inter-observer variability among observers should be tested using the standardised criteria. Therefore, in the present study, we could not evaluate the severity of knee/spinal OA or vertebral fractures for assessing knee pain and lumbar pain. After suitable evaluation of intra-observer and inter-observer variability in the assessment of radiography findings and integration of this information, we hope to re-analyse the factors associated with the presence of chronic pain. Moreover, not only OA and fractures, but also rheumatoid arthritis and spondyloarthritis should be considered as parameters for assessing knee pain and lumbar pain. Although collection of the information on the diagnosis may be difficult on a large scale due to the associated cost, it may be possible to obtain this information in at least two cohorts.

In addition, our study has several strengths. First, as mentioned above, the large number of the integrated subjects included in the LOCOMO study is the biggest strength of this study. Moreover, we collected data from nine cohorts across Japan. By using the data of the LOCOMO study, we could compare the regional differences of specific clinical symptoms such as knee pain or lumbar pain, or particular diseases, such as KOA, LS, or OP, as well as its prognosis, such as the incidence of disability or mortality. In particular, we identified regional differences in the prevalences of knee pain and lumbar pain. In addition, we collected a substantial amount of information, via an interviewer-administered questionnaire, dietary assessment, anthropometric measurements, neuromuscular function assessment, biochemical measurements, medical history recording, radiographic assessment, and BMD measurement. However, all items were not recorded in all cohorts and the regional selection bias in each examination should be considered when interpreting the results.

In summary, by using the data of the LOCOMO study, we clarified the prevalence of knee pain and lumbar pain, their coexistence, and their associated factors.

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A Randomized Controlled Trial of Multicomponent Exercise in Older Adults with Mild Cognitive Impairment

Takao Suzuki[1]*, Hiroyuki Shimada[2], Hyuma Makizako[2], Takehiko Doi[2], Daisuke Yoshida[2], Kengo Ito[3], Hiroshi Shimokata[4], Yukihiko Washimi[5], Hidetoshi Endo[6], Takashi Kato[3]

1 Research Institute, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan, **2** Section for Health Promotion, Department for Research and Development to Support Independent Life of Elderly, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan, **3** Department of Clinical and Experimental Neuroimaging, Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan, **4** Department for Development of Preventive Medicine, Center for Development of Advanced Medicine for Dementia, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan, **5** Department of Cognitive Disorders, Hospital of National Center for Geriatrics and Gerontology, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan, **6** Department of Comprehensive Geriatric Medicine, Hospital of National Center for Geriatrics and Gerontology, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan

Abstract

Background: To examine the effect of multicomponent exercise program on memory function in older adults with mild cognitive impairment (MCI), and identify biomarkers associated with improvement of cognitive functions.

Methodology/Principal Findings: Subjects were 100 older adults (mean age, 75 years) with MCI. The subjects were classified to an amnestic MCI group (n = 50) with neuroimaging measures, and other MCI group (n = 50) before the randomization. Subjects in each group were randomized to either a multicomponent exercise or an education control group using a ratio of 1:1. The exercise group exercised for 90 min/d, 2 d/wk, 40 times for 6 months. The exercise program was conducted under multitask conditions to stimulate attention and memory. The control group attended two education classes. A repeated-measures ANOVA revealed that no group × time interactions on the cognitive tests and brain atrophy in MCI patients. A sub-analysis of amnestic MCI patients for group × time interactions revealed that the exercise group exhibited significantly better Mini-Mental State Examination ($p = .04$) and logical memory scores ($p = .04$), and reducing whole brain cortical atrophy ($p < .05$) compared to the control group. Low total cholesterol levels before the intervention were associated with an improvement of logical memory scores ($p < .05$), and a higher level of brain-derived neurotrophic factor was significantly related to improved ADAS-cog scores ($p < .05$).

Conclusions/Significance: The results suggested that an exercise intervention is beneficial for improving logical memory and maintaining general cognitive function and reducing whole brain cortical atrophy in older adults with amnestic MCI. Low total cholesterol and higher brain-derived neurotrophic factor may predict improvement of cognitive functions in older adults with MCI. Further studies are required to determine the positive effects of exercise on cognitive function in older adults with MCI.

Trial Registration: UMIN-CTR UMIN000003662

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* E-mail: suzutaka@ncgg.go.jp

Introduction

Alzheimer's disease (AD) places a considerable and increasing burden on patients, caregivers and society. The number of older adults living with AD is predicted to increase from the current 26.6 million to 106.2 million by 2050 globally. [1] The current standard of care for mild to moderate AD involves treatment with acetylcholinesterase inhibitors to improve cognitive function. The *N*-methyl-d-aspartate antagonist memantine has also been reported to improve cognitive function in patients with moderate to severe AD. [2] While these drugs improve the symptoms of AD, they do not have substantial disease-modifying effects. [3] Thus, attempts have been made to identify individuals at increased risk of AD, and to test interventions that might delay the progression of prodromal symptoms of dementia.

An association has been proposed between regular participation in physical activity, especially aerobic exercise, and a variety of cognitive benefits. [4,5,6,7,8] Several meta-analyses have reported that physical activity is associated with improvements in attention, processing speed, and executive function in older adults with and without cognitive impairments. [9,10,11] However, these studies produced some inconsistent findings, with some reporting

cognitive gains in memory function [10,11] and other study reporting equivocal results. [9]

Evidence from neuropsychological and neuroimaging studies has suggested that mild cognitive impairment (MCI) represents a clinical prodrome to degenerative dementias such as AD. [12] For example, a population-based study in Sweden reported that the relative risks of progression to dementia in a 3-year follow-up in subjects with mild, moderate, and severe cognitive impairment (without dementia), were 3.6, 5.4, and 7.0, respectively. [13] However, of the individuals with MCI, 11% remained stable, and 25% exhibited an improvement in cognitive function between baseline and follow-up observation. [13] This variation in MCI populations should be examined to facilitate the development of interventions for inhibiting the progression of dementia. Several randomized controlled trials (RCTs) have been conducted to investigate the effects of exercise or physical activity on cognitive function in older adults with MCI. [4,5,6,7,8] These studies have revealed the effects of exercise or physical activity on cognitive function, including executive function, in older adults with MCI. However, the effect of exercise on memory function in this population remains unclear.

The precise neurobiological mechanism for the improvement of cognitive functions remains unknown, however a large number of rodent studies suggest a central role of certain molecules such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1), and vascular endothelial growth factor (VEGF). The molecules have been shown to facilitate neurogenesis in the hippocampus, promote synaptic plasticity in the hippocampus and cerebral cortex, and angiogenesis and enhance growth and protection of neurovasculature. [14,15] In fact, some neuroimaging studies of human subjects revealed that aerobic exercise increased hippocampal volume, [16] and gray and white matter regions including the cingulate cortex, supplementary motor cortex, inferior frontal gyrus, and superior temporal gyrus. [17]

The present randomized trial was designed to test whether a 6-month supervised multicomponent exercise program could reduce the rate of cognitive decline, especially in memory function, and reduce the rate of brain volume decline among older adults with MCI. The multicomponent exercise program included aerobic exercise, muscle strength training, and postural balance retraining, because previous reviews suggested that combined aerobic exercise and strength training interventions improved attention and working memory to a greater extent than aerobic exercise alone. [11,18] We explored the biomarkers for identifying improvement of cognitive functions. Serum total cholesterol (T-cho), hemoglobin A1c (HbA1c), BDNF, and VEGF levels at baseline were used as potential predictors.

Methods

CONSORT checklist and the protocol for this trial is available as supporting information; see **Checklist S1** and **Protocol S1**.

Participants

Subjects in this study were recruited from two volunteer databases (n = 1,543), which included elderly individuals (65 years and over) selected either by random sampling or when they attended a medical check-up in Obu, Japan. Inclusion criteria specified that prospective participants were community-dwelling individuals aged 65 years and over. A total of 528 prospective participants with a Clinical Dementia Rating (CDR) of 0.5, or who complained of memory impairment, were recruited in the first round of eligibility assessments. Of these, 135 subjects satisfied the requirements of the second round of eligibility assessments, which included neuropsychological tests, which included language and memory tests, attention and executive function tests, clinical diagnosis, activities of daily living (ADL), educational level, and magnetic resonance imaging. Thirty-five subjects were excluded, meaning that a total of 100 subjects took part in the study (mean age, 75.4±7.1 years; 65–95 years, men n = 55, 51%). All subjects met the definition of MCI as per the Petersen criteria. [19] All MCI subjects had objective impairments in either episodic memory and/or executive functioning at least 1.5 standard deviations below the age-adjusted mean for at least one of the neuropsychological tests. Final classification of subjects was based on the above factors and consensus of a team of neuroscientists. Exclusion criteria included a CDR = 0, or a CDR of 1–3, a history of neurological, psychiatric, or cardiac disorders or other severe health issues, use of donepezil, impairment in basic activities of daily living (ADL), and participation in other research projects. Subjects were classified to an amnestic MCI group (aMCI) (n = 50) with neuroimaging measures, and other MCI group (n = 50) before the randomization. Then, the subjects in each group were randomly assigned to either a multicomponent exercise or an education control group using a ratio of 1:1. Participant characteristics at the beginning of the study are shown in **Table 1**. We confirmed that there were no significant differences in demographic characteristics, physical performance, or instrumental ADL levels between the exercise and control groups. Fifty subjects with aMCI (mean age, 76.0±7.1 years; 65–92 years, men n = 27, 54%) were selected from among the subjects to participate in a sub-analysis. All subjects included the aMCI group agreed to measure functional neuroimaging tests. This sub-analysis was limited to aMCI patients because aMCI is most likely to progress to AD.[20] Objective memory impairment to determine aMCI was defined as a lower memory score on the Wechsler Memory Scale-Revised (WMS-R) Logical Memory II. [21]

Ethics

The Ethics Committee of the National Center for Geriatrics and Gerontology approved the study protocol. The purpose, nature, and potential risks of the experiments were fully explained to the subjects, and all subjects gave written, informed consent before participating in the study. The subjects had the capacity to consent because they maintained general cognitive function and daily activities.

Interventions

The six-month, multicomponent exercise program included biweekly 90-minute sessions involving aerobic exercise, muscle strength training, postural balance retraining, and dual-task training. In addition, the exercise program included a focus on promoting exercise and behavior change. Two trained physiotherapists involved in geriatric rehabilitation conducted each intervention. Each exercise class contained 16–17 participants, and each supervised session began with a 10-min warm-up period and stretching exercise, followed by 20 min of muscle strength exercise. The subjects then practiced aerobic exercise, postural balance retraining, and dual-task training for 60 min. In the aerobic exercise and postural balance retraining, subjects underwent circuit training, including stair stepping, endurance walking, and walking on balance boards. The mean intensity of the aerobic exercise was approximately 60% of maximum heart rate which was similar to the intensity used in previous studies. [4,6] Eleven of the 40 classes during the six-month intervention period included approximately 20–30 minutes of consecutive outdoor walking. In the dual-task training sessions, subjects performed concurrent cognitive tasks during exercise. For example, the subjects in the

Table 1. Characteristics of the subjects.

	All subjects		aMCI subjects	
	Exercise (n = 50)	Control (n = 50)	Exercise (n = 25)	Control (n = 25)
Age, mean (SD), y	74.8 (7.4)	75.8 (6.1)	75.3 (7.5)	76.8 (6.8)
Men, No. (%)	25 (50.0)	26 (52.0)	13 (52.0)	14 (56.0)
Educational level, mean (SD), y	10.9 (2.8)	10.4 (2.4)	11.1 (2.4)	10.8 (2.7)
Diagnosis, No. (%)				
Hypertension (3*, 1†)	23 (46.9)	22 (45.8)	13 (52.0)	11 (45.8)
Heart disease (4*, 1†)	5 (10.2)	1 (2.1)	2 (8.0)	0 (0)
Diabetes Mellitus	8 (16.0)	3 (6.0)	5 (20.0)	3 (12.0)
Medication, 3 and over (2*, 1†)	22 (44.0)	19 (39.6)	10 (40.0)	11 (45.8)
Blood pressure, mmHg				
Systolic, mean (SD)	144.6 (21.6)	142.4 (19.4)	152.2 (21.0)	143.7 (21.3)
Diastolic, mean (SD)	74.6 (11.7)	75.1 (11.2)	77.3 (11.1)	74.3 (10.1)
Blood test				
Total cholesterol, mean (SD), mg/dL	211.7 (36.2)	200.5 (34.5)	212.6 (36.9)	202.8 (32.2)
HbA1c, mean (SD), %	5.6 (0.8)	5.4 (0.5)	5.6 (0.6)	5.4 (0.5)
BDNF, mean (SD), ng/mL	12.1 (10.0)	13.5 (10.4)	11.9 (11.3)	14.4 (12.2)
VEGF, mean (SD), pg/mL	97.6 (19.7)	103.5 (22.2)	95.9 (18.4)	96.7 (15.4)
Physical performances				
Grip strength, mean (SD), kg	24.7 (8.1)	23.5 (7.3)	25.2 (7.3)	23.1 (8.4)
One legged standing, mean (SD), s	34.6 (24.6)	31.2 (23.9)	34.0 (25.1)	29.3 (23.6)
Timed up & go, mean (SD), s	8.8 (2.5)	9.2 (2.1)	9.0 (2.2)	9.1 (2.0)
IADL subscale of TMIG index, mean (SD), score	4.8 (0.9)	4.9 (0.3)	5.0 (0.2)	4.9 (0.3)
GDS, mean (SD), score	3.8 (3.1)	3.3 (2.8)	3.0 (2.1)	2.6 (2.0)
Cognitive functions, score				
MMSE, mean (SD)	26.8 (2.3)	26.3 (2.7)	26.8 (1.8)	26.6 (1.6)
ADAS-cog, mean (SD)	6.0 (2.8)	6.5 (2.8)	6.3 (2.2)	6.8 (2.2)
WMS-LM I, mean (SD)	14.6 (6.9)	13.8 (7.4)	12.5 (5.9)	12.0 (4.9)
WMS-LM II, mean (SD)	10.5 (7.4)	9.4 (7.4)	8.2 (5.4)	6.9 (5.0)
Clinical subtype, No. (%)				
Amnestic MCI	34 (68.0)	37 (74.0)		
Non-amnestic MCI	16 (32.0)	13 (26.0)		
VSRAD				
MTA-ERC atrophy, mean (SD) (1*)	1.3 (0.9)	1.5 (1.0)	1.4 (1.0)	1.4 (1.0)
WBC atrophy, mean (SD) (1*)	7.3 (4.7)	8.3 (4.6)	7.9 (3.9)	7.4 (3.3)

Abbreviations: IADL subscale of TMIG index, instrumental activities of daily living subscale of Tokyo Metropolitan Institute of Gerontology index; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; WMS, Wechsler Memory Scale; MCI, mild cognitive impairment. *missing value in all subjects. †missing value in the aMCI subjects.

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exercise group were asked to walk while inventing their own poem, as aerobic exercise. In the ladder training exercise, subjects learned to step in consecutive square segments, and were instructed to step as quickly and accurately as possible. Before and after each session of the program, physiotherapists conducted a health check of each subject. The physiotherapists and a well-trained instructor implemented risk management for accidents and other adverse events during the program. The subjects were instructed to carry out daily home-based muscle strength exercises and walking, which were self-monitored using a booklet and pedometer based on the concept of promoting exercise and behavior change. Attendance at each session was recorded and a transportation service was provided for participants, if necessary, to help subjects maintain their participation in the program.

Subjects in the education control group attended two education classes about health promotion during the 6-month study period. The class provided information regarding healthy diet, oral care, prevention of urinary incontinence, and health checks. However, the group did not receive specific information regarding exercise, physical activity, or cognitive health.

Outcomes

Cognitive Functions. The Mini-Mental State Examination (MMSE) [22] and Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog) [23] were used to assess general cognitive function.

Modified versions of the logical memory subtest from the WMS-R [21] was used to assess memory function. In the WMS-R, two short stories (Story A and B) were read aloud to the subject, who was then instructed to recall details of the stories immediately (LM I, immediate recall) and after 30 min (LM II, delayed recall; each total recall score = 50). [21]

MRI. MRI was performed with a 1.5-T system (Magnetom Avanto, Siemens, Germany). Three-dimensional volumetric acquisition with a T1-weighted gradient echo sequence was then 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).

In analysis of brain volume, we used the voxel-based specific regional analysis system for Alzheimer's disease (VSRAD), which enables the examination of atrophy of the bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) using voxel-based morphometry. [24] The VSRAD has been shown to achieve high accuracy (87.8%) in discriminating patients in the very early stages of AD with MCI from normal control subjects using Z scores. [24] A previous VSRAD study reported that atrophy of the MTA-ERC exhibited a clear functional relationship with blood flow changes in the hippocampus, thalamus and temporal lobe, which were suggested to be closely related to inter-regional anatomical and physiological connections. [25]

Acquired MRI images were formatted to gapless, transaxial images, followed by extraction of the gray matter images using SPM2. Anatomical standardization was used to fit each individual brain to standard template MRIs in the common coordinate system of the MNI T1 MRI template. [26] The segmented gray matter images were then subjected to affine and nonlinear standardization using a template of prior gray matter. The anatomically standardized gray matter images were then smoothed again using an isotropic Gaussian kernel 12 mm in full width at half maximum, to determine the partial volume effect and create a spectrum of gray matter intensities. Gray matter intensities were equivalent to the weighted average of gray matter voxels located in the volume fixed by the smoothing kernel. Regional intensity was considered equivalent to gray matter concentration. We compared the gray matter image of each patient with the mean and standard deviation (SD) 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 score = ((control mean)−(individual value))/control SD). The Z score thus reflected the degree of atrophy in bilateral MTA-ERC. Higher Z scores indicated clearer MTA-ERC atrophy. VSRAD also automatically measured the degree of atrophy in the whole brain cortices (WBC), including the hippocampus: if the Z-score was more than 2.0 within a voxel, the area was considered to exhibit atrophy. [24] Thus, the proportion of atrophic area in the whole brain (%) was measured in the following way: 100×([the number of voxels with Z-score≥2.0]/[the number of whole brain voxels]).

Biochemical measures3. T-cho, HbA1c, BDNF, VEGF receptor 1 (VEGFR1) were used as biomarkers. Blood samples were collected between 11 am and 4 pm in a non-fasting state. The blood samples were kept at room temperature for 30 min to allow for clotting, after which the samples were centrifuged for 15 min. Serum was then harvested and stored at −25 °C until analysis. Analyses were carried out centrally in one laboratory (Special Reference Laboratories, Tokyo, Japan). BDNF and VEGFR1 were measured with the Quantikine Human kit (R&D systems, Inc. Minneapolis, MN, USA). Coefficients of variation (CVs) of BDNF in intra-assay and inter-assay precision were 2.6–3.2 and 5.5–9.8, respectively. Those of VEGFR1 were 3.8–6.2 for intra-assay and 7.6–11.3 inter-assay precision.

Sample size

Since participants were selected on the basis of memory impairments, memory was considered the most important cognitive outcome in our study. Therefore, sample size calculations were based on AVLT data. [27] A previous study reported that a sample of 34 participants per group to detect a clinically relevant effect, with 80% power. [6] To allow for a dropout of 25%, the final sample size was 85 participants.

Randomization–Sequence generation

Subjects were randomly assigned after completion of baseline assessments. Subjects were classified to an amnestic MCI group (n = 50) with neuroimaging measures, and other MCI group (n = 50) before the randomization. The subjects in each group were randomized to either a multicomponent exercise or an education control group using a ratio of 1:1. The subjects were further randomized and dichotomized into two groups, an amnestic MCI group (n = 50) with neuroimaging measures, and other MCI group (n = 50).

Randomization–Implementation and concealment

After the baseline assessment, subjects were randomized using the option "random sample of cases" in IBM SPSS statistics software (Version 19; SPSS Inc., Chicago, IL, USA). A researcher who was not aware of the aims of the study performed the randomization procedure.

Blinding

Study personnel involved in the collection of outcome measures were blinded to the randomization assignment. Several trained speech therapists blinded to group status conducted the cognitive tests, and one speech therapist recalculated all of the results.

Statistical methods

Statistical analysis was performed using IBM SPSS statistics software. For the baseline comparisons between exercise and control groups for all subjects, and for the amnestic MCI (aMCI) sub-analysis, Pearson's method, together with Chi square analysis with Fisher's exact test was used to investigate the categorical data. Kolmogorov-Smirnov tests confirmed that all continuous variables followed a normal distribution. Basic characteristics of patients were compared between the two groups using *t*-tests.

A general linear model for repeated-measures analysis of variance (ANOVA) was used to determine the group difference for the cognitive tests and VSRAD measurements. Two time points were treated as the within-subjects factor (effect over time) and the differences between the exercise and control groups were treated as the between-subjects factor. When the repeated-measures ANOVA indicated that the group × time interaction was significant, tests of simple main effects were performed to determine which group or groups differed significantly across the intervention period. Alpha level of the post-hoc analyses were adjusted for the Bonferroni method, i.e. corrected alpha = .025.

Multiple logistic regression models were used to determine the predictors of improvements in cognitive function. Dependent variables were the cognitive tests which showed significant improvements in the comparison between before and after the intervention of all subjects. Based on the results from the cognitive tests, the subjects were dichotomized into two categories; the subjects who improved their cognitive test scores (improvement

group) and the subjects who showed no improvement, or who exhibited a deterioration in their cognitive test scores (no improvement group). Biochemical variables at baseline measurements were treated as independent variables. Covariates such as age, sex, educational level, and the intervention group were included in the logistic model.

The univariate analyses and repeated-measures ANOVA were performed with all subjects grouped together as well as with a subgroup that was limited to older adults with aMCI. The logistic regression analysis was performed to determine the predictors of improvement of cognitive functions in all subjects. All statistical significance tests were two-sided, and an alpha-level of .05 was considered statistically significant.

Results

Participant flow

Figure 1 shows the flow of participants from the time of screening to study completion at 6 months. Ninety-two (exercise group, n = 47) subjects completed the 6-month follow-up. Of the 50 aMCI subjects, 47 (94%) completed the 6-month follow-up. Two of the remaining 47 subjects in the exercise group (one male, one female) missed all exercise programs, but completed the examinations before and after the intervention. The two subjects were included in the following analyses. Mean adherence to the exercise program, including the remaining 47 subjects, was 85.9%, and 38 subjects (80.9%) in the exercise group attended our intervention program with greater than 80% adherence.

Baseline data

There were no significant differences in baseline characteristics between all subjects grouped together and the aMCI group alone (**Table 1**).

Participants analyzed

Our primary analysis of cognitive function included all patients who remained at the end of the study (total n = 92; exercise group, n = 47; control group, n = 45). A total of 90 subjects (exercise group, n = 46; control group, n = 44) completed MRI scanning. When the analyses were limited to subjects with aMCI, the exercise and control groups included 24 and 23 subjects in assessments of cognitive function and MRI, respectively.

Outcomes in all MCI subjects

Table 2 shows changes in cognitive scores over the 6-month period by group. There were main effects of time in ADAS-cog ($p = .01$), WMS-LM I ($p < .01$), WMS-LM II ($p < .01$), and WBC atrophy level ($p = .03$), although no main effects of group and group × time interactions were detected on the cognitive tests and brain atrophy (**Table 2**).

Outcomes in aMCI subjects

When the analyses were limited to subjects with aMCI, the repeated-measures ANOVA for MMSE showed a significant effect of group ($p = .03$) and there was a group × time interaction in MMSE ($p = .04$) indicating benefit of the exercise over time. Tests of simple main effects revealed that the control group decreased in MMSE score ($p = .015$) after intervention. A repeated-measures ANOVA showed a significant effect of time ($p < .01$) and group × time interaction ($p = .04$) in WMS-LM I. Tests of simple main effects showed that the exercise group exhibited better WMS-LM I ($p < .01$) scores compared to baseline, but not in the control group. The repeated-measures ANOVA for WMS-LM II ($p < .01$) and MTA-ERC atrophy ($p = .03$) showed a significant effect of time. However, there were no main effects of group and no group × time interactions. A repeated-measures ANOVA showed a significant group × time interaction ($p < .05$) in WBC atrophy level. There were no main effects of group or time. Tests of simple main effects revealed that the subjects in the control group showed increased WBC atrophy ($p = .01$) after intervention, compared with their baseline scores (**Table 2, Figure 2**).

Relationships between cognitive functions and biomarkers

Paired *t*-tests revealed significant improvements in ADAS-cog ($p = .01$), WMS-LM I ($p < .01$), and WMS-LM II scores ($p < .01$) after the intervention. Multiple logistic regression analysis revealed that low T-cho level before the intervention was associated with improvement in WMS-LM I (odds ratio (OR) 0.98, 95% confidence interval (95% CI) 0.96–1.00, $p = .02$). Higher BDNF level at baseline was significantly related to improvements in ADAS-cog (OR 1.07, 95% CI 1.02–1.13, $p = .01$) independent of age, sex, educational level, and intervention (**Table 3**).

Adverse events

Four subjects (exercise group, n = 2; control group, n = 2) experienced adverse events (hospitalization for illness). Falls (as a type of minor adverse event) over a 6-month period were reported by 23/90 (26%) of subjects, with no significant differences among groups. There were no other adverse events during exercise intervention for 6-months.

Discussion

Evidence of exercise on cognitive function

Older adults with MCI have been found to exhibit greater decreases in memory function than in other cognitive functions, relative to healthy older adults. [28] The enhancement of cognitive function, especially memory function, in individuals with MCI may play a crucial role in preventing the progression from MCI to AD in older adults. Klusmann et al. reported significant effects of a multifaceted exercise program on cognitive function, finding that a 6-month exercise program resulted in improvements in delayed story recall. [29] However, their sample consisted of healthy, well-functioning females without any signs of cognitive impairment. In addition, previous studies reported that aerobic exercise or other physical activity can increase executive function in older adults with cognitive impairments, but the effects of exercise on memory function in this population remain unclear. [4,5,6,7,8] To our knowledge, this is the first study to demonstrate an improvement in logical memory following multicomponent exercise training among older adults with aMCI. The exercise group showed significant differences not only in WMS-LM I scores, but also in MMSE scores compared to the control group in aMCI populations. Our intervention study extends the results of previous studies with healthy samples, indicating the potential for an increase in memory performance and maintenance of general cognitive function in subjects exhibiting signs of cognitive decline.

A meta-analysis of aerobic exercise and neurocognitive performance demonstrated that interventions combining aerobic exercise and strength training, similar to our program, improved attention, processing speed and working memory to a greater extent than aerobic exercise alone. [11] However, the mechanism underlying this improvement remains unclear. A previous study reported that subjects with MCI improved their episodic memory performance when they were exposed to a multifactorial cognitive intervention program that included dual-task attentional and memory training. [30] Dual-task deficit is recognized as a potential

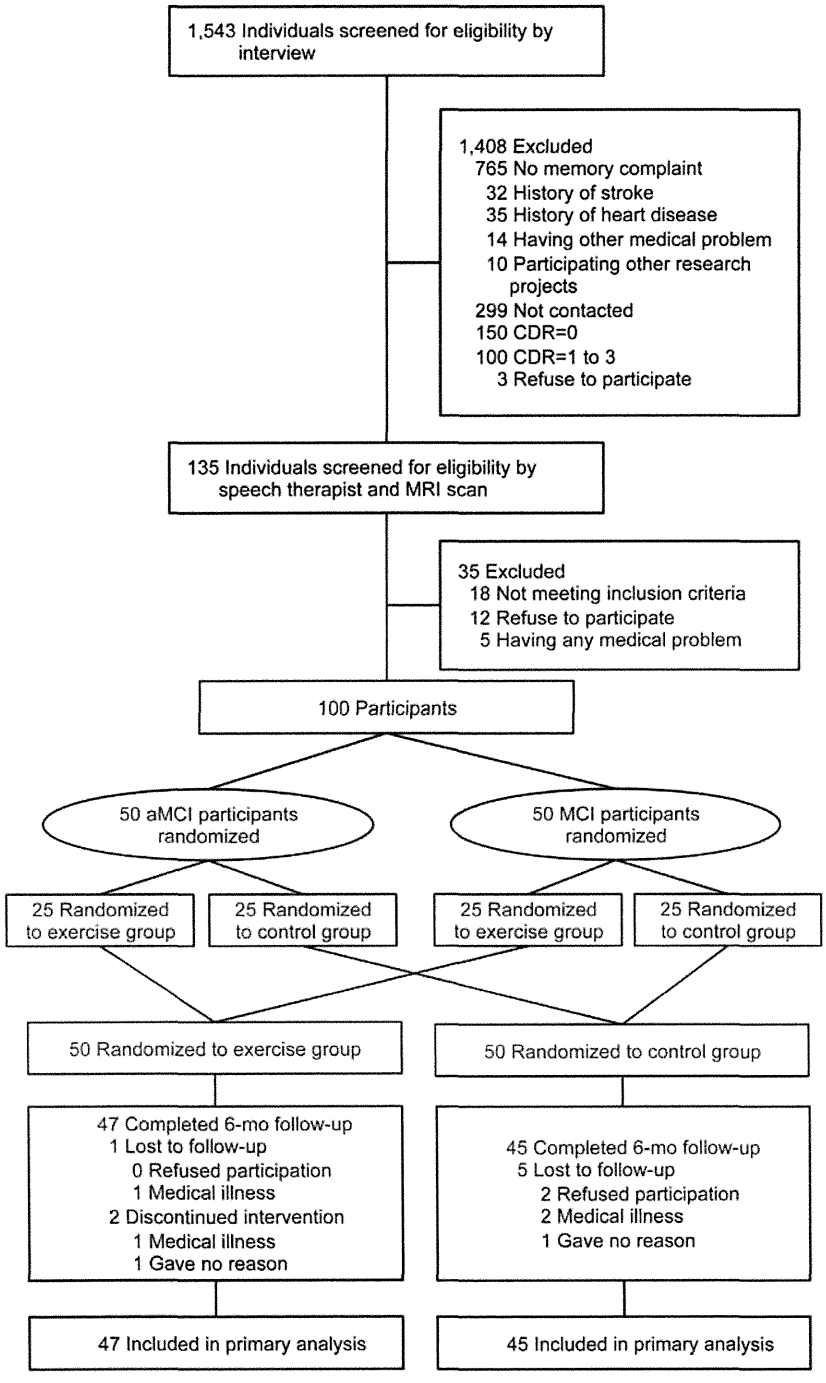

Figure 1. Subject flow diagram from initial contact through to study completion.
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early marker for dementia, [31,32] and dual-task-related changes in performance were greater in subjects with MCI compared with cognitively normal age-matched controls. [33,34] Our multicomponent program involved changes in cognitive load using dual-task stimulation and learning tasks. We believe that dual-task training may have a greater effect on various cognitive functions, for example, general and memory functions, than interventions that only focus on aerobic exercise. [7,10] However, the results from the present study do not provide direct evidence for the positive effect of dual-task training. Future studies are required to investigate the effects of dual-task training on cognitive function in the older adults with MCI.

Lautenschlager et al. reported that physical activity and behavioral intervention improved general cognition among adults with MCI. [4] The multicomponent exercise training in the current study also included encouragement for subjects to engage in more physical activity. Our results further support the notion that training involving physical activity can have a beneficial effect

Table 2. Comparison of Cognitive Function between the Exercise and Control Group.

	All subjects (n = 100)						aMCI subjects (n = 50)					
	Mean Difference From Baseline (95% CI) in All Subjects		*P* Value ANOVA for Repeated Measures			ES	Mean Difference From Baseline (95% CI) in aMCI Group		*P* Value ANOVA for Repeated Measures			ES
	Exercise Group (n = 47)	Control Group (n = 45)	Group	Time	Group × time interaction	r	Exercise Group (n = 24)	Control Group (n = 23)	Group	Time	Group × time interaction	r
MMSE	0.2 (−0.5, 0.9)	−0.3 (−1.1, 0.4)	0.18	0.79	0.32	0.11	0.3 (−0.8, 1.3)	−1.4 (−2.5, −0.3)	0.03	0.14	.04[b]	0.31
ADAS-cog	−0.8 (−1.4, −0.2)	−0.2 (−0.8, 0.4)	0.17	0.01	.16 (1)[c]	0.15	−1.2 (−2.1, −0.3)	−0.1 (−1.0, 0.8)	0.1	0.06	0.1	0.24
WMS-LM I	2.8 (1.4, 4.2)	1.0 (−0.5, 2.4)	0.29	<.01	0.08	0.19	3.8 (1.6, 5.9)	0.5 (−1.6, 2.7)	0.14	<.01	.04[a]	0.31
WMS-LM II	3.4 (2.0, 4.8)	1.9 (0.4, 3.4)[b]	0.28	<.01	0.15	0.15	3.8 (1.8, 5.7)	2.1 (0.1, 4.2)	0.11	<.01	0.26	0.17
MTA-ERC	0 (−0, 0.1)	0 (0, 0.1)	0.18	0.08	0.89	0.02	0.1 (0, 0.2)	0 (−0.1, 0.1)	0.91	0.03	0.27	0.17
WBC	0.1 (−0.4, 0.7)	0.7 (0.1, 1.2)	0.08	0.03	0.16	0.15	−0.1 (−0.8, 0.6)	0.9 (0.2, 1.6)	0.86	0.08	<.05[b]	0.29

Abbreviations: MMSE, Mini-Mental State Examination; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; WMS, Wechsler Memory Scale; MTA-ERC, medial temporal areas including the entorhinal cortex; WBC, whole brain cortices; ES, effect size.

[a]$p<.025$; significant differences before versus after intervention in the exercise group

[b]$p<.025$; significant differences before versus after intervention in the control group

[c]Missing value

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not only on memory function, but also on general cognitive function in people with aMCI. General cognitive function can be used to discriminate between people who progress to AD and those who do not. [35] Improvements of memory function and maintenance of general cognitive function suggest that multicomponent exercise can help prevent progression from MCI to AD. However, despite significant interactions, the effect sizes in general cognitive function and logical memory were small. Moreover, these interactions would not become significant if the p-values were adjusted for multiple comparisons. Further studies are required to determine the positive effects of exercise on cognitive function in older adults with MCI.

Relationship between exercise and brain atrophy

It is well established that structures in the medial temporal lobe, particularly the hippocampus and ERC, are essential for normal memory function. There is an emerging literature describing baseline structural MRI correlates of cognitive impairment in elderly adults with mild cognitive impairment (MCI) and Alzheimer's disease (AD). Some studies have identified relationships between aerobic exercise and increased brain volume [16,17] and functional connectivity between parts of the frontal, posterior, and temporal cortices [36] in healthy older adults. For example, Erickson et al. found that the hippocampus remains plastic in late adulthood and that a 1-year period of aerobic exercise was sufficient for enhancing volume. [16] Our 6-month multicomponent exercise program with MCI subjects revealed that exercise did not have a significant group × time interaction on MTA-ERC scores or WBC atrophy compared to the control group. However, there was significant group × time interaction in WBC atrophy level, when tested in a sub-analysis restricted to aMCI subjects. Post-hoc analyses revealed that the control group exhibited increased WBC atrophy after intervention, compared with their baseline scores. These results suggest that older adults with aMCI may exhibit high levels of plasticity in WBC atrophy. Further study is needed to establish our findings using large samples and detailed neuroimaging analysis.

Predictors of increasing of cognitive function

In the relationships between cognitive function and biochemical measures, low T-cho and high BDNF serum levels at baseline were associated with increased memory and general cognitive function in the MCI subjects, respectively. Serum lipoprotein levels may be a common and potentially modifiable risk factor for AD. [37] For example, a prospective study reported that lower serum levels of LDL and T-cho were associated with better cognitive performance and a lower risk of cognitive impairment in 1,037 women with cardiovascular disease. [38] Our finding extends knowledge about the relationships between T-cho and cognitive function to older adults with MCI. Animal studies have revealed that the structure and function of the hippocampus, a brain region critical for certain forms of cognition, is adversely affected by hyperlipidemia. (e.g. [39]) Abnormal lipid metabolism may be undesirable status for improvement cognitive functions, especially memory. Exercise is also a valid and feasible way to manage lipoprotein levels and regular activity may be potential strategies for preventing cognitive decline in elderly individuals. [40]

One of the main determinants of cell size is cell growth, which is modulated by certain growth factors, such as BDNF. The levels of BDNF-associated gene expression have been found to increase with physical activity. [14] BDNF expression has also been suggested to play a role in learning and synaptic plasticity. [41]

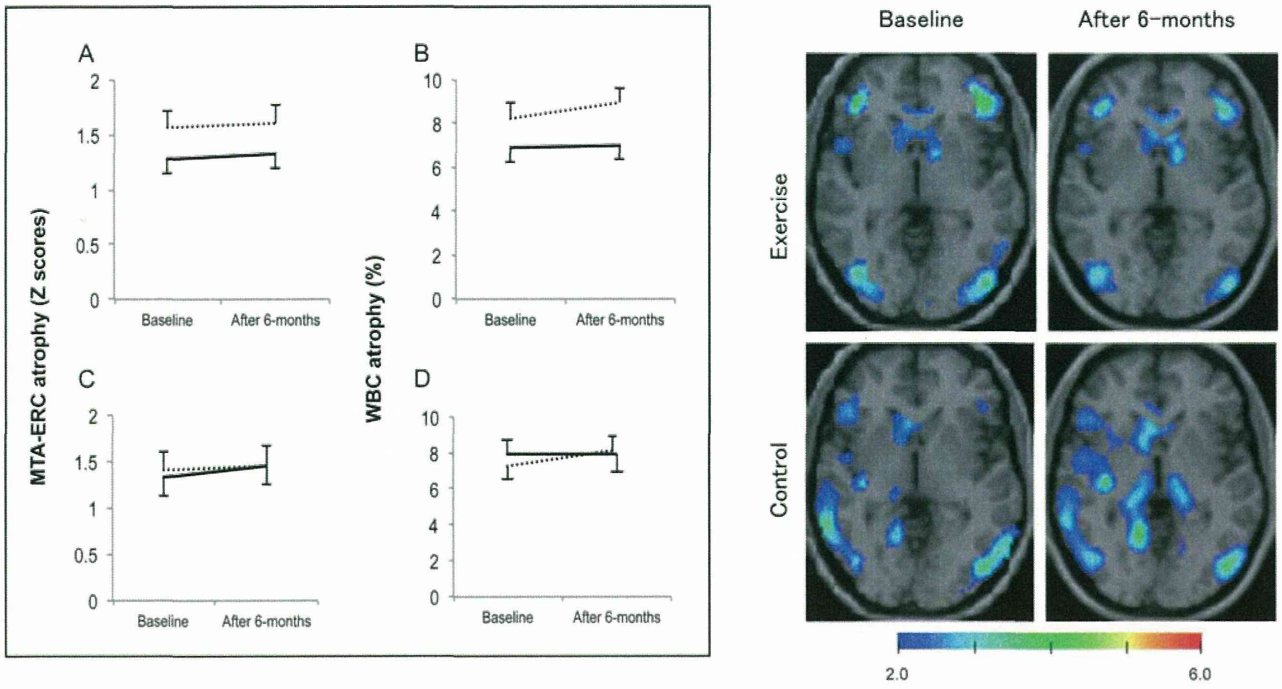

Figure 2. Change in MTA-ERC and WBC volumes in response to the 6-month intervention. Abbreviations: MTA-ERC, medial temporal areas including the entorhinal cortex; WBC, whole brain cortices. Left panel shows change in MTA-ERC and WBC volumes before and after the 6-month intervention. Solid and dashed lines indicate the exercise and control groups, respectively. Group mean differences and standard errors for MTA-ERC and WBC atrophy are shown in panels A and B, respectively, for all subjects. Panels C and D show mean differences and standard errors for MTA-ERC and WBC atrophy, respectively, for older adults with aMCI. The repeated-measures ANOVA revealed that there was a significant group × time interaction on WBC atrophy level ($p<.05$) in older adults with aMCI. Right panel shows typical images for VSRAD, indicated atrophy region, in subjects with aMCI in the exercise and control groups. The upper panel shows WBC atrophy in a man (81 years old) with aMCI who completed the 6-month exercise program. The rate of WBC atrophy decreased after the intervention (8.74% at baseline to 6.39% after the intervention). The lower panel shows WBC atrophy of a man (80 years old) with aMCI in the control group. The rate of WBC atrophy increased after the 6-month intervention period (7.19% at baseline to 10.48% after the intervention).
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The present results indicate that high serum BDNF levels have a beneficial effect on general cognitive function in older adults with MCI.

Limitations

The present study involved several limitations. The small sample size should be addressed by replication with a larger group of adults with MCI. Of the 135 potential subjects screened for eligibility in our study, 35 were excluded for not meeting inclusion criteria, refusal to participate, or medical reasons (**Figure 1**). This

Table 3. Predictors of Improvements in Cognitive Function.

	ADAS-cog	*P*	WMS-LM I	*P*	WMS-LM II	*P*
	OR (95% CI)		**OR (95% CI)**		**OR (95% CI)**	
Age, years	0.97 (0.91–1.05)	.44	0.95 (0.89–1.03)	.22	0.96 (0.90–1.04)	.34
Sex, women/men	1.00 (0.35–2.82)	1.00	0.74 (0.26–2.13)	.57	2.56 (0.85–7.66)	.09
Educational level, years	0.85 (0.70–1.04)	.11	0.93 (0.76–1.13)	.45	1.01 (0.83–1.22)	.96
Intervention, exercise group/control group	2.85 (1.10–7.37)	.03	2.27 (.90–5.72)	.08	1.98 (.77–5.12)	.16
T-cho, mg/dl	1.00 (0.98–1.02)	.96	**0.98 (0.96–1.00)**	**.02**	0.99 (0.97–1.01)	.18
HbA1c, %	0.53 (0.25–1.14)	.10	1.20 (0.57–2.53)	.64	0.61 (0.29–1.30)	.20
BDNF, ng/ml	**1.07 (1.02–1.13)**	**.01**	1.00 (0.95–1.05)	.94	1.02 (0.97–1.08)	.39
VEGFR1, pg/ml	0.99 (0.97–1.01)	.39	0.99 (0.96–1.01)	.32	1.00 (0.98–1.03)	.74

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; WMS, Wechsler Memory Scale; T cho, total cholesterol; HbA1c, hemoglobin A1c; BDNF, brain-derived neurotrophic factor (BDNF); VEGFR1, vascular endothelial growth factor receptor 1.
Missing values: ADAS-cog (n = 10), WMS-LM I (n = 9), WMS-LM II (n = 9)
doi:10.1371/journal.pone.0061483.t003

selection bias may have affected the generalizability of our findings to population-based samples. Other limitations include unknown group differences in risk factors of cognitive decline and AD, such as apolipoprotein E ε4 genotype, and inflammation, although there were no significant differences between groups in terms of *hypertension, diabetes mellitus, medications, biomarkers of lipid* metabolism, physical performance, instrumental ADL functioning, or depressive mood. In addition, it is possible that the improvement in the exercise group resulted from the social contact to which the intervention group was exposed. This possibility cannot be completely excluded with the present design, and should be addressed in future studies.

Conclusion

The current results indicate that a multicomponent exercise program can provide cognitive benefits for older adults with aMCI. The effects of exercise were most pronounced for logical memory and general cognitive function in older adults with aMCI. Exercise was found to maintain the atrophy levels of the whole brain cortex in older adults with aMCI. Improvement of cognitive function was associated with low T-cho and high BDNF levels at baseline. A future follow-up investigation is required to determine whether the observed effects are associated with prevention or delayed onset of AD in older adults with MCI.

Supporting Information

Checklist S1 CONSORT Checklist.
(DOC)

Protocol S1 Trial Protocol.
(DOCX)

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Author Contributions

Conceived and designed the experiments: TS H. Shimada. Performed the experiments: H. Shimada HM TD DY TK. Analyzed the data: H. Shimada. Contributed reagents/materials/analysis tools: KI H. Shimokata YW HE. Wrote the manuscript: TS H. Shimada HM TD DY. Review of manuscript: KI H. Shimokata YW HE TK.

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ORIGINAL ARTICLE

Using two different algorithms to determine the prevalence of sarcopenia

Daisuke Yoshida,[1,2] Takao Suzuki,[3] Hiroyuki Shimada,[1] Hyuntae Park,[4] Hyuma Makizako,[1] Takehiko Doi,[1] Yuya Anan,[1] Kota Tsutsumimoto,[1] Kazuki Uemura,[1] Tadashi Ito[1] and Sangyoon Lee[4]

[1]Section for Health Promotion, Department for Research and Development to Support Independent Life of Elderly, [4]Section for Physical Functioning Activation, Department of Functioning Activation, Center for Gerontology and Social Science, [3]Research Institute, National Center for Geriatrics and Gerontology, and [2]Japan Foundation for Aging and Health, Aichi, Japan

Aim: Several operative definitions and screening methods for sarcopenia have been proposed in previous studies; however, the opinions of researchers still differ. We compared the prevalence of sarcopenia using two different algorithms: (i) the European working group on sarcopenia in older people (EWGSOP)-suggested algorithm using gait speed as the first step; and (ii) the muscle mass and strength algorithm.

Methods: A population-based, cross-sectional survey of adults aged over 65 years was carried out. Data on a total of 4811 participants were available for analysis. Gait speed, grip strength and appendicular skeletal muscle mass were assessed to determine sarcopenia. Appendicular skeletal muscle mass was estimated from bioimpedance analysis measurements and expressed as skeletal muscle mass index. Grip strength and skeletal muscle mass index were considered to be low if they fell below the threshold of the lowest 20% of values measured in a subset of healthy subjects. We compared the prevalence rates of sarcopenia determined by the two algorithms.

Results: The prevalence rate of sarcopenia in a representative sample of older Japanese adults was 8.2% for men and 6.8% for women based on the EWGSOP algorithm. The two algorithms identified the same participants as sarcopenic, the only difference being the EWGSOP algorithm classified an additional seven participants (0.15%) into sarcopenia compared with the muscle mass and strength algorithm.

Conclusion: It is debatable whether inclusion of gait speed is necessary when screening for sarcopenia in community-dwelling older adults. Future research should examine the necessity of including gait speed in algorithms and the validity of cut-off values. **Geriatr Gerontol Int 2014; 14 (Suppl. 1): 46–51.**

Keywords: aging, prevalence, sarcopenia.

Introduction

Several changes in body composition occur with the aging process (e.g. a decrease in bone and muscle mass, and an increase in the proportion of fat).[1,2] Lower muscle mass is associated with decreased strength, and might lead to the development of functional limitations and disability in old age.[3–6] Advanced skeletal muscle loss could also potentially have an impact on quality of life, the need for supportive services and ultimately the need for long-term care in older persons.[5] Thus, it is important to develop a valid and feasible method to screen older adults for sarcopenia, and to establish a preventive strategy for sarcopenia in older people.

Although operative definitions and screening methods for sarcopenia have been proposed in previous studies, the opinions of researchers have been conflicting.[3,7–10] Recently, a European working group on sarcopenia in older people (EWGSOP) published their recommendations for a clinical definition, and consensus diagnostic criteria, for sarcopenia.[10] In that report, the EWGSOP suggested an algorithm using the presence of both low muscle mass and low muscle function, including strength and gait performance, for the diagnosis of sarcopenia. Low gait performance is the first step to identify sarcopenia in the EWSOP algorithm. Thus, it is possible that older adults with high gait

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Correspondence: Dr Daisuke Yoshida PhD, Section for Health Promotion, Department for Research and Development to Support Independent Life of Elderly, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-machi, Obu, Aichi 474-8511, Japan. Email: yoshida@ncgg.go.jp

performance would not be categorized as sarcopenic, even if they had evident muscle atrophy.

The term "sarcopenia" was coined by Rosenberg in 1989 to refer to the process of age-related loss of skeletal muscle mass.[11] Originally, "sarcopenia" derives from the Greek words *sarx* (meaning flesh) and *penia* (meaning loss), and this term is used to refer specifically to the gradual loss of skeletal muscle mass and strength that occurs with advancing age.[12] According to the original meaning, the definition and diagnosis of sarcopenia should be based on the reduction of muscle mass and strength. Furthermore, sarcopenia is a fundamental component of frailty, and it can be seen as one dimension of frailty. Frailty is a geriatric syndrome resulting from age-related cumulative declines across multiple physiological systems, and is characterized by the following five domains: unintended weight loss, self-reported exhaustion, weakness (reduced grip strength), slow gait speed and low levels of physical activity.[13] If sarcopenia patients are screened according to gait speed, sarcopenia becomes roughly synonymous with frailty, and it could confuse interpretation of both sarcopenia and frailty.

The purpose of the present study was to compare the difference in prevalence of sarcopenia determined using two different algorithms: (i) the EWGSOP algorithm, using gait speed as the first step; and (ii) the muscle mass and strength algorithm, and to examine whether gait speed should be a critical component for screening sarcopenia.

Methods

Participants

The present study was based on data collected as part of the Obu Study of Health Promotion for the Elderly (OSHPE), carried out in Obu, Aichi, Japan, from August 2011 to February 2012. OSHPE initially sent postal invitations to 14 313 persons aged 65 years and older, resident in the city of Obu. Individuals who had participated in previous studies, were hospitalized and/or in residential care, or were certified as requiring more than level 3 care needing support or care by the Japanese public long-term care insurance system were excluded from participation in OSHPE. A total of 5104 persons responded and agreed to participate in the present study (response rate: 35.7%). The overall survey consisted of face-to-face interviews on health status, physical and cognitive function tests, and body composition, among other items. Major chronic illnesses were assessed by nurses through face-to-face interviews. Chronic illnesses included in the study were hypertension, hyperlipidemia, diabetes mellitus, heart disease, stroke, Parkinson's disease, dementia, clinical depression, cancer, lung disease, osteoporosis and arthritis (rheumatoid and osteoarthritis).

Of the 5104 OSHPE participants, we excluded those with missing data on body composition, gait speed or muscle strength. Data on 4811 participants (94.3% of all participants, 2343 men and 2468 women) were available for this analysis. All participants were informed about the study procedures and provided written informed consent before participation. In addition, this study was carried out in accordance with the Helsinki Declaration, and was approved by the ethics committee of the National Center for Geriatrics and Gerontology.

Assessment of appendicular muscle mass

A multifrequency bioelectrical impedance analyzer (MC-980A; Tanita, Tokyo, Japan) was used to measure bioimpedance. This bioelectrical impedance analysis (BIA) instrument uses six electrical frequencies (1 kHz, 5 kHz, 50 kHz, 250 kHz, 500 kHz and 1000 kHz), and we calculated the impedance index, height^2 (cm) divided by resistance (Ω). The participants stood barefoot on the analyzer platform, grasping the two handgrips. Eight-point tactile electrodes made contact with the palm and thumb of each hand, and with the anterior and posterior aspects of the sole of each foot. Surface electrodes were placed on the right side of the body, on the dorsal surface of the hands and feet proximal to the metacarpal- and metatarsal-phalangeal joints, respectively, medially between the distal prominences of the radius and ulna, and between the medial and lateral malleoli at the ankle. Measurements were carried out by trained staff, and completed within 30 s.

We estimated appendicular skeletal muscle mass (ASM) using the following equations that were developed for Japanese older adults:[14]

$$\text{Men: ASM} = 0.197 \times (\text{impedance index}) + 0.179 \times (\text{weight}) - 0.019$$

$$\text{Women: ASM} = 0.221 \times (\text{impedance index}) + 0.117 \times (\text{weight}) + 0.881$$

Skeletal muscle mass index (SMI) was calculated as ASM / height.^{2}

Measurement of muscle strength

Maximal voluntary isometric strength of handgrip was measured using a hand dynamometer Grip-D (Takei, Niigata, Japan). The measurement was taken with the dominant hand in a standing position. The muscle strength test was carried out once only. Handgrip strength has been widely used to measure muscle strength and correlates well with most relevant outcomes.[15]

Measurement of gait speed

Participants were asked to walk 6.4 m (divided into two 2.0-m zones at each end, and a 2.4-m middle-zone) at their usual pace. We measured the required time (in seconds) to pass the 2.4-m middle zone to calculate gait speed (m/s). Use of a cane or walker was permitted if participants could not practice the gait test. The gait test was carried out five times, and the average value was used.

Gait speed is a valid and widely used measure of mobility limitation for both healthy and impaired older persons,[16] with high predictive validity for subsequent disability, hospitalization and mortality.[17,18]

Algorithm and cut-off values to determine sarcopenia

We used the EWGSOP-algorithm as one method to determine the individuals with sarcopenia. We also used the muscle mass and strength algorithm. The EWGSOP recommends use of normative (healthy young adult) rather than other predictive reference populations, with cut-off points (for muscle mass and strength) at two standard deviations below the mean reference value.[10] However, no reference data from a normative Japanese population were available with which to determine cut-off values for grip strength and SMI. In the absence of normative reference populations, previous studies have used healthy older adults as their reference groups (applying cut-off points derived from the lowest sex-specific quartiles[13] or quintiles[9,19]). To overcome this limitation, we selected a healthy subset of people from our study, and used their sex-specific quintile points (lowest 20%) as cut-off values. This healthy subset was defined as follows: no impairment of activities of daily living, no medical history (stroke, Parkinson's disease, Alzheimer's disease or other serious neurological diagnoses, depression), gait speed ≥1.0 m/s and Mini-Mental State Examination (MMSE) score ≥21. Participants were classified as "low level" when their grip strength or SMI values fell below the cut-off points. In the EWGSOP-algorithm, a gait speed at 0.8 m/s is used as the cut-off value.[10]

Statistical analysis

Differences in age, body mass index (BMI), SMI, gait speed, grip strength, and MMSE score were compared between those with and without sarcopenia using *t*-tests by sex. The prevalence of major chronic illnesses was also compared between those with and without sarcopenia using χ^2-tests. All analysis was carried out using commercially available software, IBM SPSS statistics (version 19; SPSS, Chicago, IL, USA), and the level of significance was as set at $P < 0.05$.

Results

Determination of the cut-off values for sarcopenia

A total of 3810 (74.6% of all participants, 1848 men and 1962 women, mean age 71.2 ± 4.9 years) were included in the healthy subset of people used to determine cut-off values. Cut-off values of grip strength were set at 28.8 kg and 18.2 kg for men and women, respectively. Similarly, cut-off values of SMI were set at 7.09 kg/m^2 in men and 5.91 kg/m^2 in women.

Prevalence and characteristics of sarcopenia

Data on a total of 4811 participants (94.3% of all participants, 2343 men and 2468 women) were available for analysis. The mean age was 72.2 ± 5.5 years in men and 72.1 ± 5.7 in women. The mean SMI was 7.71 ± 0.79 kg/m^2 in men and 6.51 ± 0.70 kg/m^2 in women.

According to the EWGSOP-algorithm, 7.5% (n = 360) of all participants were classified as having sarcopenia. The prevalence of sarcopenia was 8.2% for men and 6.8% for women, but this difference was not significant ($P = 0.09$). The prevalence of sarcopenia increased with age in both men and women, with people aged 80 years and older having the highest prevalence rates (25.0% in men and 12.2% in women, Fig. 1).

The characteristics of normal and sarcopenic participants are summarized in Table 1. Compared with the normal participants, both male and female sarcopenic participants were significantly older ($P < 0.01$) and had lower BMI ($P < 0.01$). In addition, there were significant differences in the proportions of participants with hypertension ($P < 0.01$) and osteoporosis ($P < 0.01$).

We also calculated the prevalence of sarcopenia using the muscle mass and strength algorithm, and compared the prevalence of sarcopenia determined using the two methods (Fig. 2). The present results showed that the two algorithms produced similar overall estimates of sarcopenia prevalence (7.5% *vs* 7.3% using the

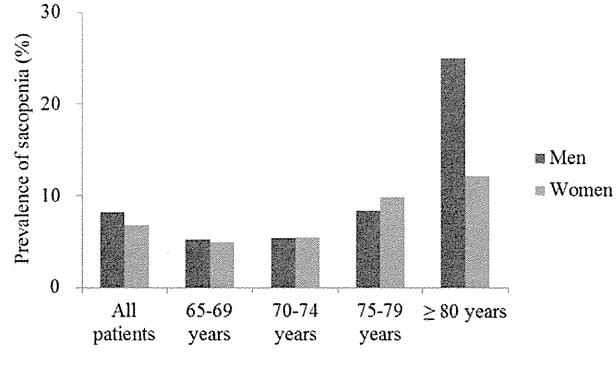

Figure 1 The prevalence of sarcopenia by age category and sex.

Table 1 Comparison of characteristics of those with and without sarcopenia by sex according to the European working group on sarcopenia in older people algorithm

Variables		Men			Women		
		Normal (n = 2,152)	Sarcopenia (n = 191)	P-value	Normal (n = 2,299)	Sarcopenia (n = 169)	P-value
Age	years	71.8 ± 5.2	76.0 ± 7.2	<0.01	71.9 ± 5.5	74.5 ± 7.0	<0.01
BMI	kg/m^2	24.0 ± 2.7	19.9 ± 1.6	<0.01	23.5 ± 3.2	19.0 ± 1.8	<0.01
SMI	kg/m^2	7.8 ± 0.7	6.6 ± 0.4	<0.01	6.6 ± 0.7	5.5 ± 0.3	<0.01
Diagnosis	%						
Hypertension		49.1	34.6	<0.01	45.1	34.3	<0.01
Diabetes mellitus		15.8	17.8	0.46	11.0	4.7	0.01
Stroke		7.1	8.4	0.50	3.8	4.1	0.82
Heart disease		19.2	16.2	0.32	13.9	14.8	0.75
Respiratory disease		12.8	20.9	<0.01	9.1	12.4	0.16
Cancer		11.4	16.2	0.05	8.5	5.3	0.15
Osteoporosis		1.1	6.3	<0.01	19.2	31.4	<0.01
Gait speed	m/s	1.3 ± 0.2	1.1 ± 0.2	<0.01	1.3 ± 0.2	1.2 ± 0.3	<0.01
Grip strength	kg	33.7 ± 5.8	24.5 ± 3.2	<0.01	21.3 ± 4.0	15.8 ± 2.5	<0.01
MMSE	score	25.9 ± 2.7	24.8 ± 3.2	<0.01	26.5 ± 2.8	26.1 ± 3.4	0.13

Values are mean ± SD or %. ASM, appendicular skeletal muscle mass; BMI, body mass index; MMSE, Mini-Mental State Examination; SMI, skeletal muscle index.

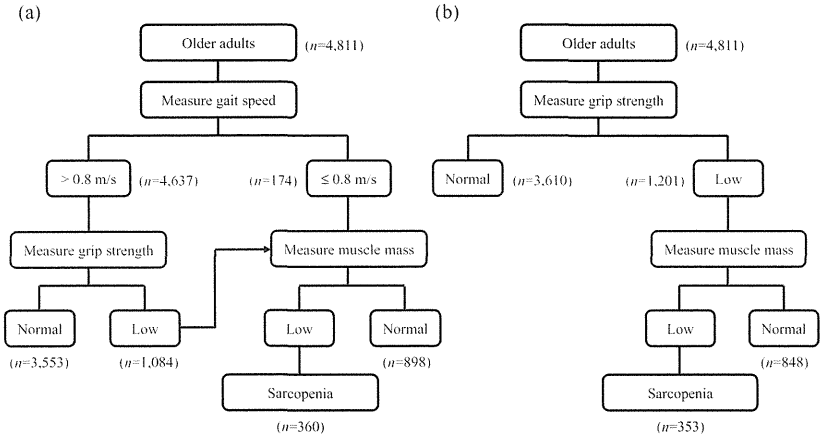

Figure 2 The prevalence of sarcopenia in the community setting determined using two different algorithms. (a) The European working group on sarcopenia in older people-suggested algorithm of sarcopenia. (b) The algorithm based on muscle strength and muscle mass to determine sarcopenia.

EWGSOP and muscle mass and strength algorithms, respectively). The same participants were identified by both algorithms, with the exception of seven people (0.15%) who were classified as having sarcopenia using the EWGSOP-algorithm, but who did not have sarcopenia according to the muscle mass and strength algorithm. Conversely, all of the participants (n = 353) classified with sarcopenia by the muscle mass and strength algorithm were also defined as having sarcopenia using the EWGSOP-algorithm.

Discussion

The EWGSOP recommends that cut-off values for handgrip strength were 30.0 kg in men and 20.0 kg in women.[10] In a sample of Japanese older adults, Tanimoto *et al.* reported the cut-off values for low grip strength were 30.3 kg in men and 19.3 kg in women.[20] However, the EWGSOP recommendations were based on results that included non-Japanese participants. Tanimoto *et al.* recruited regular attendees of welfare centers for the aged or community centers to their study.[20] As a result, the generalizability of their results might be limited, and it may not be appropriate to apply their cut-off values in the present study. The present study, using a similar methodology as several previous studies, applied the lowest quintile of grip strength in a healthy subset of subjects (aged ≥65 years) as the cut-off point. The cut-off values for grip strength determined using this method were slightly lower than those published in previous studies. The validity of the cut-off points used in the present study remains to be determined.