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Original Article

Arterial Stiffness Predicts Cognitive Decline in Japanese Community-dwelling Elderly Subjects: A One-year Follow-up Study

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***Aim*: The purpose of this study was to determine whether arterial stiffness can be used to predict one-year changes in the cognitive function in Japanese community-dwelling elderly subjects.**
***Methods*: A total of 103 Japanese community-dwelling elderly patients joined this study. Information regarding the age, height, weight, gender and past medical history of each participant was obtained. Additionally, arterial stiffness was determined according to the cardio-ankle vascular index (CAVI), and the cognitive function was assessed with the Mini-Mental State Examination (MMSE). One year later, we performed the MMSE in the same subjects. After dividing the cohort according to the 80th percentile of the CAVI (normal and arterial stiffness [AS] groups), we examined whether the degree of cognitive decline, as determined using the pre- and post-MMSE, was significantly different based on the severity of arterial stiffness, adjusted for age, BMI, gender and the pre-MMSE scores.**
***Results*: Of the 103 subjects who participated in the pre-data collection, 74 (38 men and 36 women, 73.4±4.0 years) joined the post-data collection. We found a significant difference in the change in the post-MMSE scores between the normal and AS groups (pre-MMSE: normal group [27.4±2.1] and AS group [26.9±2.4] and post-MMSE: normal group [27.2±2.1] and AS group [25.5±2.3], $F=5.95$, $p=0.02$). For each domain of the MMSE, the changes in MMSE-attention-and-calculation ($F=5.11$, $p=0.03$) and MMSE-language ($F=4.32$, $p=0.04$) were significantly different according to an ANCOVA.**
***Conclusions*: We found that arterial stiffness predicts cognitive decline in Japanese community-dwelling elderly subjects regardless of the initial level of the global cognitive function. This finding indicates the potential use of the degree of arterial stiffness as an indicator for preventing or delaying the onset of dementia in the elderly.**

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Key words: Arterial stiffness, Cognitive impairment, Elderly, Dementia

Introduction

Dementia is a serious issue, especially in community-dwelling elderly subjects[1)]. Thirty-five million people worldwide suffered from dementia in 2012 according to the World Health Organization. Approximately 48% of patients with Alzheimer's disease (AD), the most common form of dementia, are estimated to live in Asia, and this percentage is expected to increase to 59% by 2050[2)]. Elderly people with dementia are typically frail due to their poor mobility and body composition, and the transitional stage between normal aging and AD, called mild cognitive impairment (MCI), results in frailty[3)], depression[4)], lower levels of physical activity[1)] and higher mortality[5)]. Preventing cognitive decline is therefore crucial.

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Of risk factors for cognitive decline, cardiovascular risk factors have received more attention in recent years[6, 7]. High blood pressure[8], dyslipidemia[8], obesity[9] and diabetes mellitus[9] have been proposed to be risk factors for cognitive decline. Among these factors, arterial stiffness is a comparatively easy-to-modify risk factor in community-dwelling elderly subjects. Madden *et al.* reported that three months of aerobic training reduces the degree of multifactorial arterial stiffness without generating any significant improvements in aerobic fitness, weight, BMI, waist-to-hip ratio or blood pressure in community-dwelling older individuals[10]. Additionally, previous studies have demonstrated the effectiveness of antihypertensive agents in improving arterial stiffness in both short- and long-term trials[11]. Community-dwelling elderly can improve their arterial stiffness; therefore, focusing on treating arterial stiffness may be effective for preventing cognitive decline.

Most older adults with MCI live in the community, and more than half of MCI cases progress to dementia within five years[12]. Therefore, a desired goal is the early detection of cognitive decline, especially in the community-dwelling elderly. When evaluating the degree of arterial stiffness in community-dwelling elderly subjects, the most important property is the ease of measurement. Arterial stiffness is one of the most easily measured vascular risk factors in community-dwelling elderly patients due to its non-invasive nature; therefore, it can be used as a predictor of cognitive decline in this population. Previous studies have also shown arterial stiffness to be a predictor of cognitive decline. However, the subjects in these studies were not elderly individuals living in the community[13, 14]. Additionally, other authors have reported that they were unable to validate arterial stiffness as an independent risk factor for cognitive decline, as measured according to the global cognitive function using the Mini-Mental State Examination (MMSE)[15-17]. Yamamoto *et al.* reported a relationship between the cognitive function and arterial stiffness determined according to the CAVI in community dwelling elderly[18], although the mean age was approximately 80 years, which is a bit high considering the mean age of community-dwelling elderly individuals in Japan. It may be more important to focus on healthier and younger older adults when discussing community-dwelling elderly[19]. The efficacy of arterial stiffness as a predictor of cognitive decline, especially in community-dwelling elderly patients, is less well investigated[4].

The purpose of this study therefore was to address whether the degree of arterial stiffness can be used to predict one-year changes in the cognitive function in Japanese community-dwelling elderly subjects. We used the CAVI to assess arterial stiffness, as this parameter was found to significantly correlate with cognitive decline in a cross-sectional study[18, 19].

Methods

Participants

Participants were recruited for this study through local press that requested healthy community-dwelling volunteers 65 years of age or older, and data collection was performed on two occasions: November 2012 (pre-data collection) and November 2013 (post-data collection). Interviews were conducted to exclude participants from both data collections based on the following exclusion criteria: severe cardiac, pulmonary or musculoskeletal disorders; comorbidities associated with a higher risk of falls, such as Parkinson's disease or stroke; and the use of psychotropic drugs. Written informed consent was obtained from each participant in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1995 during both data collection periods. The study protocol was approved by the ethics committee of Kyoto University Graduate School of Medicine.

Measurements — *Pre-data Collection*

Demographic Data

Each patient's age, height, weight, gender, past medical history (cardiovascular disease, hypertension, diabetes mellitus and hyperlipidemia), smoking status (number of cigarettes smoked per day and total number of years smoked) and educational background (elementary school, junior high school, high school, career college or university) were obtained as demographic data. All data were collected at the first data collection time point. We directly asked about each participant's age and gender and measured their height and weight using standardized height and weight scales.

Arterial Stiffness

The degree of arterial stiffness was determined based on the CAVI using the VaSera-1500 device (Fukuda Denshi Co., Ltd., Tokyo, Japan). The details of this procedure have been described previously[20, 21]. After the participants had rested for five minutes in the sitting position, we obtained these measurements as previously described. Higher CAVI values indicate a higher degree of arterial stiffness. The measurements were obtained once, and the mean values of the right

Table 1. Baseline characteristics and post-MMSE scores in the study population

	All ($n=74$)		
	Normal group $n=59$	AS group $n=15$	p
Demographic data			
Age, year	72.8 ± 3.8	76.1 ± 3.6	< 0.01
BMI, kg/m^2	23.2 ± 2.6	23.2 ± 3.2	0.99
Gender, male	28 (47.5%)	10 (66.7%)	0.25
Mean CAVI	8.83 ± 0.61	10.6 ± 0.51	< 0.01
Cognitive function			
Pre-MMSE	27.4 ± 2.1	26.9 ± 2.4	0.40
Post-MMSE	27.2 ± 2.0	25.5 ± 2.3	< 0.01
Pre-MMSE (orientation)	9.6 ± 0.6	9.7 ± 0.5	0.89
Post-MMSE (orientation)	9.7 ± 0.7	9.7 ± 0.5	0.89
Pre-MMSE (registration)	2.9 ± 0.4	3.0 ± 0.0	0.53
Post-MMSE (registration)	2.9 ± 0.3	3.0 ± 0.0	0.49
Pre-MMSE (attention and calculation)	3.2 ± 1.7	2.9 ± 1.8	0.55
Post-MMSE (attention and calculation)	3.4 ± 1.7	2.3 ± 1.5	0.03
Pre-MMSE (recall)	2.6 ± 0.6	2.4 ± 0.8	0.30
Post-MMSE (recall)	2.5 ± 0.6	2.4 ± 0.7	0.69
Pre-MMSE (language)	8.9 ± 0.3	8.9 ± 0.4	0.73
Post-MMSE (language)	8.7 ± 0.5	8.2 ± 1.3	0.15
Comorbidities			
Cardiovascular disease	6 (10.2%)	4 (26.7%)	0.11
Hypertension	23 (39.0%)	8 (53.3%)	0.39
Diabetes mellitus	5 (8.5%)	4 (26.7%)	0.08
Hyperlipidemia	9 (15.3%)	2 (13.3%)	1.00
Brinkman index	0 (0-800)	0 (0-400)	0.63
Educational background			n.s.
Elementary school	0 (0.0%)	1 (6.7%)	
Junior high school	16 (27.1%)	4 (26.7%)	
High school	35 (59.3%)	9 (60.0%)	
Career college	3 (5.1%)	0 (0.0%)	
University	5 (8.5%)	1 (6.7%)	

Mean CAVI = mean value of the right and left CAVI scores. The mean ± SD is shown for age, BMI, mean CAVI and pre- and post MMSE. n (%) is shown for gender, cardiovascular disease, hypertension, diabetes mellitus, hyperlipidemia and educational background. The median (25% quartile-75% quartile) is shown for the Brinkman index. AS: arterial stiffness; n.s.: not significant.

and left CAVI scores for each patient were used for the analysis[19].

Cognitive Function Measurements

The cognitive function was assessed using the Mini-Mental State Examination (MMSE)[22]. The MMSE is a short screening test that consists of the following five areas for detecting cognitive impairment: orientation, registration, attention and calculation, recall and language. The scores range from 0 to 30, with higher scores indicating better cognitive performance. The MMSE was performed at both the pre- and post-data collection time points.

Measurements—*Post-data Collection Cognitive Function Measurements*

One year later, the cognitive function was also assessed using the MMSE[22]. We performed the MMSE using the same inclusion and exclusion criteria as that used at the pre-data collection time point.

Statistical Analysis

The patients were divided into two groups based on the 80th percentile of the CAVI values: the normal

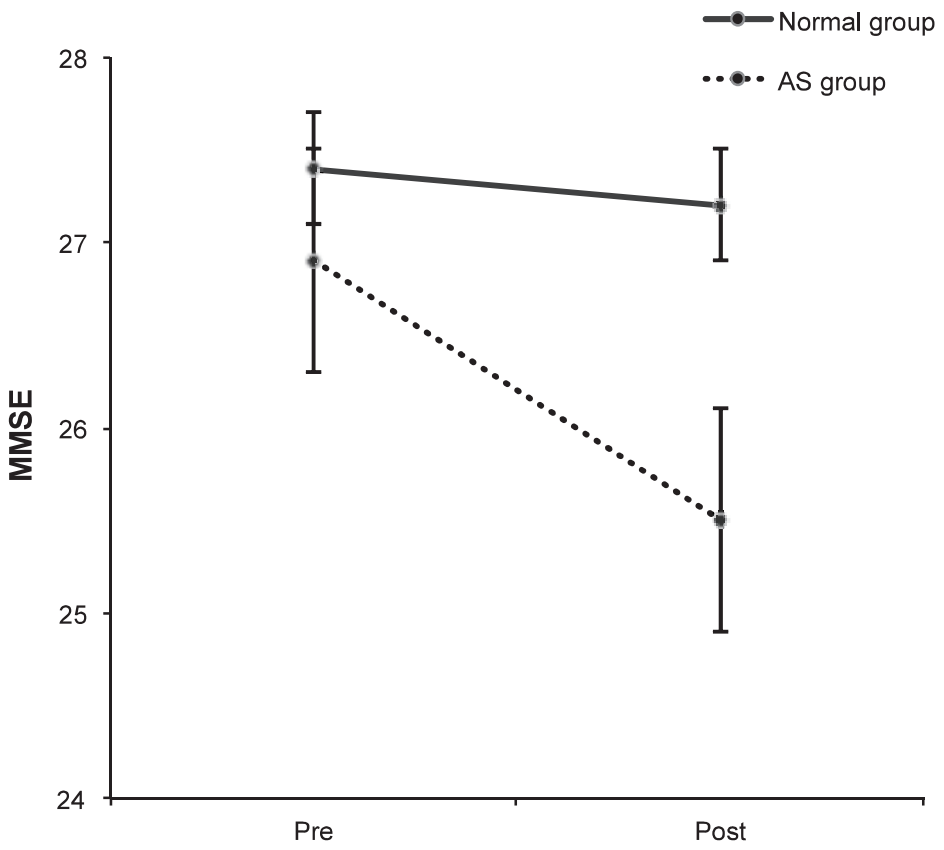

Fig. 1. Two-way analysis of variance showing the differences in the changes in the post-MMSE scores between the normal and AS groups. These findings indicate that the elderly subjects in the AS group experienced greater cognitive decline than those in the control group ($F=5.95$, $p=0.02$).

and arterial stiffness [AS] groups. We analyzed the differences between these two groups using the unpaired *t*-test for age, body mass index (BMI), mean CAVI values on both sides and the pre- and post-MMSE scores (total score and scores for each domain), the χ^2 test for gender, past medical history and educational background and the Mann Whitney *U*-test for the Brinkman index (number of cigarettes smoked per day × total number of years smoked). A repeated measures two-way analysis of covariance (ANCOVA) was used to analyze whether the degree of cognitive decline determined according to the pre- and post-MMSE scores (total score and scores for each domain) differed significantly according to the severity of arterial stiffness, adjusted for age, BMI, gender and the pre-MMSE score. A p value of <0.05 was considered to be statistically significant for all analyses.

Results

In total, 74 individuals (38 men and 36 women, 73.4 ± 4.0 years) participated in both data collection events. Of these individuals, none were excluded. We assigned 59 elderly individuals (28 men and 31 women) to the normal group and 15 (10 men and five women) to the AS group. **Table 1** shows the differences in each variable between the two groups. While there were no significant differences in BMI, gender, pre-MMSE, educational background or past medical history, we found significant differences in age ($p<0.01$) and the mean CAVI values ($p<0.01$). Additionally, the normal group had a significantly higher total post-MMSE scores (normal group: 27.2 ± 2.1, AS group: 25.5 ± 2.3, $p<0.01$) and higher post-MMSE scores for the attention-and-calculation domain (normal group: 3.4 ± 1.7, AS group: 2.3 ± 1.5, $p=0.03$) than the AS group.

The ANCOVA adjusted for age, BMI, gender

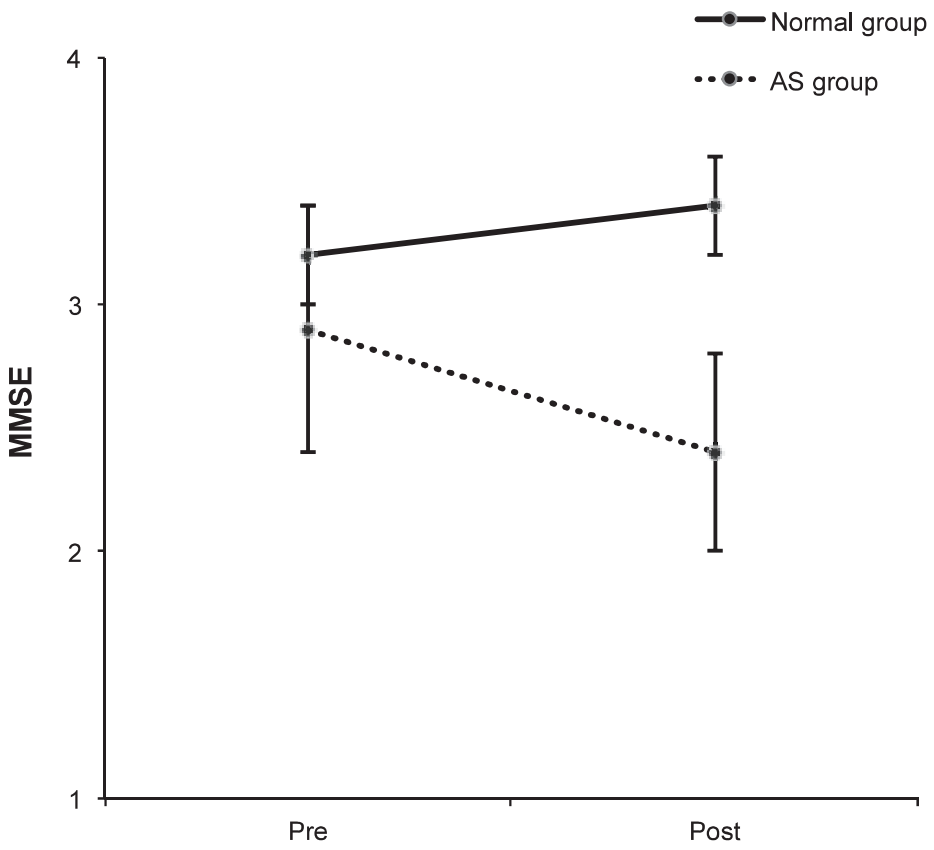

Fig. 2. Two-way analysis of variance showing the differences in the changes in the post-MMSE (attention and calculation) scores between the normal and AS groups. These findings indicate that the elderly subjects in the AS group experienced greater cognitive decline than those in the control group ($F=5.11$, $p=0.03$).

and pre-MMSE showed a significant difference in the changes in the post-MMSE scores between the normal and AS groups ($F=5.95$, $p=0.02$) (**Fig. 1**), indicating that elderly individuals with a higher degree of arterial stiffness may experience greater levels of cognitive decline, even after adjusting for age, BMI, gender and the pre-MMSE score. Additionally, the changes in the MMSE-attention-and-calculation ($F=5.11$, $p=0.03$) (**Fig. 2**) and MMSE-language ($F=4.32$, $p=0.04$) (**Fig. 3**) domains were shown to be significantly different according to the ANCOVA. The other areas did not show any differences between the two groups (orientation; $F=0.27$, $p=0.60$: registration; $F=2.69$, $p=0.11$, recall; $F=0.16$, $p=0.69$).

Discussion

In this study, we analyzed whether the degree of cognitive decline differs significantly according to the severity of arterial stiffness, adjusted for age, BMI, gender and the cognitive function at baseline and at the one-year follow-up. Consequently, we found that arterial stiffness predicts cognitive decline in Japanese community-dwelling elderly subjects, regardless of the initial level of the global cognitive function. Previous studies have demonstrated that arterial stiffness has a predictive effect on cognitive decline in the non-community-dwelling elderly[13-15, 18]; however, few reports have found arterial stiffness to be a predictor of cognitive decline in this group.

There are hypotheses regarding pathways linking arterial stiffness and cognitive decline, wherein augmented pressure pulses penetrate and damage small cerebral vessels in the global brain[23]. Brain lesions, such as ischemic lesions and white matter abnormalities resulting from augmented pressure, are thought to cause cognitive decline, thereby leading to dementia[24]. The augmented pressure caused by arterial stiffness independently predicts cognitive performance[25], and many previously published studies evaluating the

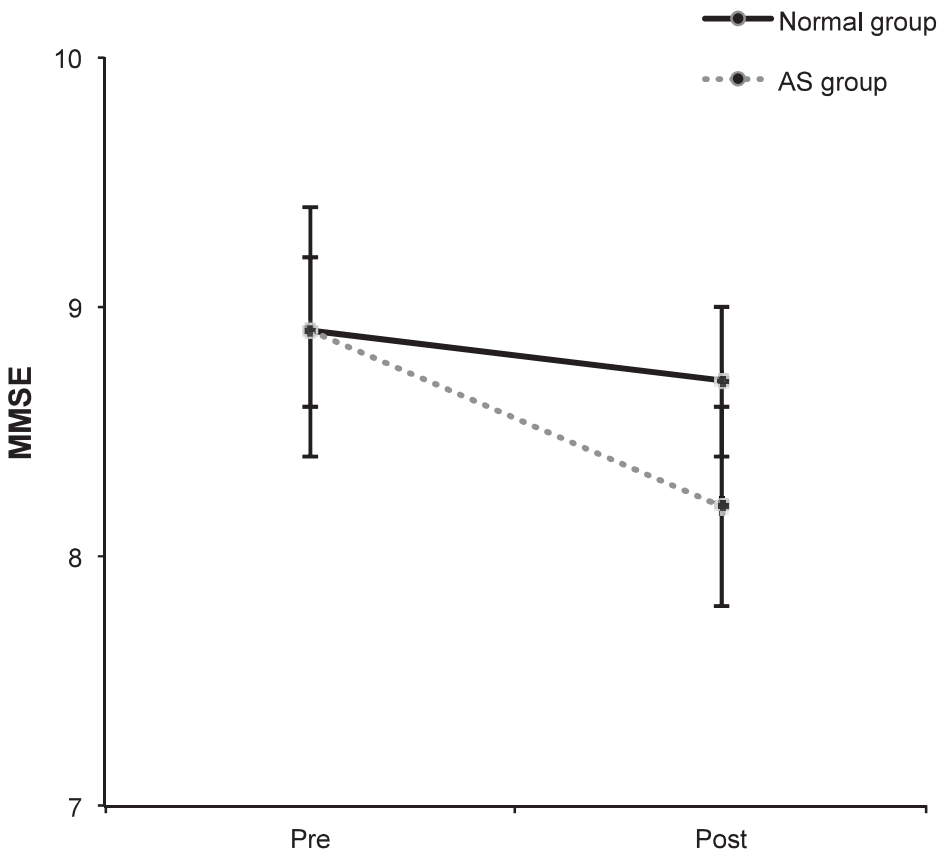

Fig. 3. Two-way analysis of variance showing the differences in the changes in the post-MMSE (language) scores between the normal and AS groups. These findings indicate that the elderly subjects in the AS group experienced greater cognitive decline than those in the control group ($F=4.32$, $p=0.04$).

association between arterial stiffness and the cognitive function have discussed the causal relationship with this phenomenon[14, 17, 18, 23].

Several studies have examined whether the severity of arterial stiffness longitudinally predicts cognitive decline. For example, one study targeting people older than 80 years of age in nursing homes showed results similar to the current findings[13]. The mean baseline MMSE score of these subjects was 23.7 ± 4.9, which is lower than that observed in the current study. Another study, in which the subjects were older patients in the hospital with complaints of memory loss, also reported that arterial stiffness has a strong predictive ability for cognitive decline[14]. Furthermore, Yamamoto *et al.* performed a similar analysis in community-dwelling elderly patients; however, the mean age was higher than that noted in our study[18]. Notably, we found that arterial stiffness predicts cognitive decline in community-dwelling elderly subjects with a comparably preserved cognitive function, even after adjusting for age, gender, BMI and the baseline cognitive function. In addition, we observed the scores for the attention-and-calculation and language domains of the MMSE to be significantly decreased in the AS group. It has been reported that these MMSE domains are not affected by impairment of the hippocampus[26]. Therefore, we assume that the cognitive dysfunction resulting from arterial stiffness is not attributed to dysfunction of the hippocampus. However, other studies have reported that measurements of arterial stiffness do not predict performance for the global cognitive function, as measured according to the MMSE[15-17]. There are various possible reasons for this discrepancy: 1) the mean age of the subjects was 57.1 years and the participants were relatively high functioning (ceiling effect of the MMSE)[15]; 2) many participants dropped out from the follow-up survey and selection bias may have affected the results for the change in the cognitive function[16]; 3) memory tasks that are more demanding for the executive function and attention

may be more sensitive to cerebrovascular alterations due to aging and the MMSE may be too insensitive to accurately detect cognitive changes[17, 27]. As a result, further studies are needed to establish evidence clarifying the association between arterial stiffness and the cognitive function.

The most important clinical implication of our findings is that one of the most easily measured and non-invasive parameters, especially in community-dwelling elderly individuals, arterial stiffness, predicted cognitive decline after one year. These results imply that maintaining the arterial function may prevent or delay the onset of dementia in the community-dwelling elderly. Additionally, it may be possible to identify individuals at risk of dementia by evaluating the degree of arterial stiffness. Interventional and longitudinal studies examining improvements in arterial stiffness with the aim of preventing cognitive decline are required to establish effective strategies for inhibiting the onset of dementia.

This study is associated with several limitations. First, because we were unable to perform neuroimaging assessments, it was not possible to make a specific diagnosis of dementia subtypes. In addition, we only performed MMSE as a cognitive test, and the cognitive function was not fully investigated. There may be asymptomatic brain lesions and specific cognitive domains that exhibit a strong relationship with arterial stiffness. Second, the age at baseline in the AS group was significantly higher than that observed in the normal group. Although we tried to minimize the impact of this difference by adjusting for age, the effect may have been insufficient. Third, the small number of subjects may also have affected the results, and more samples are needed to confirm the results of this study. Finally, many studies have investigated the relationship between arterial stiffness and the cognitive function; therefore, this study may not have adequate novelty. Nevertheless, we regard our findings as providing evidence that strengthens the close relationship between arterial stiffness and cognitive decline.

Conclusions

This study showed that arterial stiffness predicts cognitive decline in Japanese community-dwelling elderly subjects regardless of the initial level of the global cognitive function. These findings indicate the potential of improving arterial stiffness in order to prevent or delay of the onset of dementia in the elderly.

Acknowledgments

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Conflicts of Interest

None.

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Original article

Spot the Difference for Cognitive Decline: A quick memory and attention test for screening cognitive decline

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ABSTRACT

Background: Dementia is currently one of the most common conditions in older adults, and early detection of cognitive decline is crucial for identifying dementia. We developed a new type of short-term memory and attention test that uses a spot-the-difference task: Spot the Difference for Cognitive Decline (SDCD). The purpose of the present study was to examine the accuracy of the SDCD test for the identification of cognitive impairment in community-dwelling older adults.

Methods: The participants were 443 Japanese community-dwelling older adults. The SDCD test uses two scenery pictures. Participants were instructed to memorize the details of the first picture for 30 seconds, after which the first picture was taken away and the second picture was shown. Next, the participants were asked to identify as many differences as possible between the first and second pictures, which were presented sequentially. The number of correct responses comprises the SDCD score (scores: 0–10). The Mini-Mental State Examination and Scenery Picture Memory Test were used to measure the participants' cognitive function. We used receiver-operating characteristic analysis to examine the power of the SDCD test and identify the optimal cutoff value of the SDCD score.

Results: Of the 443 participants, 30 (6.77%) had some cognitive impairment based on the Mini-Mental State Examination scores. Participants without cognitive impairment had higher SDCD scores than those with cognitive impairment ($p < 0.001$). The SDCD scores were significantly associated with the Mini-Mental State Examination ($r = 0.333$) and Scenery Picture Memory Test ($r = 0.402$) results. The receiver-operating characteristic curve used for the identification of cognitive impairment had a comparatively high area under the curve (0.798) for the SDCD score with a cutoff value of 1/2 (with >1 being normal; sensitivity: 70.5%; and specificity: 80.0%).

Conclusion: The present study found that the SDCD test could be an effective clinical tool for the identification of cognitive impairment in older adults.

1. Introduction

Dementia can drastically influence one's daily life and is currently one of the most common conditions in older adults. Dementia affects 5–8% of the population over 65 years of age[1] and up to 30% of the people aged ≥85 years.[2] Currently, the number of people with dementia is increasing. It has been estimated that approximately 48% of the patients with Alzheimer's disease (AD), the most common form of dementia, live in Asia, and this percentage is projected to grow to 59% by 2050.[3] Dementia and AD have been associated with mortality[4]; therefore, prevention and early detection of cognitive decline are crucial.

The presence of cognitive decline increases the risk of progression to mild cognitive impairment (MCI) and AD.[5,6] It is generally agreed that older adults with early AD, compared to healthy older adults, exhibit a greater decline in memory function[7] and working memory[8] than in other major domains of cognitive function._ENREF_7 A central feature of AD is the decline in episodic memory.[9] Visual memory, which is included in episodic memory, is

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an important component of daily life. There are several well-established visual memory tests, such as the Benton Visual Retention Test[10] and the Rey–Osterrieth Complex Figure Test,[11] that can be used to assess nonverbal visual memory. However, these tests are not reflective of situations and activities encountered in daily life, are time consuming, and have complex scoring systems.

Deficits in working memory functions (e.g., attention and executive function) caused by AD are thought to contribute to a range of significant problems such as impairments in performing everyday tasks (e.g., keeping track of conversations, walking while talking, and packing a bag). Thus, the attentional function would appear to be important for the early detection of cognitive decline, as this function decreases with the progression of cognitive decline.[12]

We developed a new short-term visual memory and attention test called the Spot the Difference for Cognitive Decline (SDCD) test. The SDCD test is a brief and simple test that uses pictures of familiar-looking sceneries. Examinees are asked to find the differences between two scenery pictures. This test can be used in clinical or community-based settings with a large population. In a previous study, it was reported that poor visual memory predicts the onset/progression of dementia.[13] The spot-the-difference task has been used as a cognitive test in previous studies,[14–16] although its usefulness for detecting cognitive impairment had not been described. These spot-the-difference tasks have often been used in memory function training for older adults with dementia in many countries, including Japan. However, the effects of this training have not been examined empirically. We hypothesized that the SDCD score would be associated with cognitive function, and this test would be able to identify community-dwelling older adults with cognitive impairment. The purpose of the present study, therefore, was to examine the accuracy of the SDCD test for the identification of cognitive impairment in community-dwelling older adults.

2. Methods

2.1. Participants

Participants for this study were recruited through advertisements in the local newspaper. A total of 443 Japanese people aged ≥65 years (mean age, 73.1 ± 5.3 years) responded. We included only community-dwelling older adults who were able to perform their activities of daily living independently. A screening interview was conducted to exclude participants with severe cardiac, pulmonary, or musculoskeletal disorders, as well as those using medications that affect attention (e.g., psychoactive drugs or drugs prescribed for sleep). Written informed consent was obtained from each participant in accordance with the guidelines of the Kyoto University Graduate School of Medicine, Kyoto, Japan and the Declaration of Helsinki, 1975. The study protocol was approved by the Ethics Committee of the Kyoto University Graduate School of Medicine.

2.2. SDCD test protocol

The SDCD test uses two scenery pictures (Figs. 1 and 2) on A4 size papers. Fig. 1 is called the “first picture” and Fig. 2 the “second picture”. There are 10 differences between the two pictures: the shape of the chimney smoke, shape of the doorknob, height of the fountain, shape of the mountain (seen between the house and the fountain), number of fruits on the tree, direction that the dog on the right is facing, shape of the leftmost flower, shape of the child's mouth, presence of a bird versus a butterfly, and presence of the father's backpack. First, the examinees are instructed to memorize

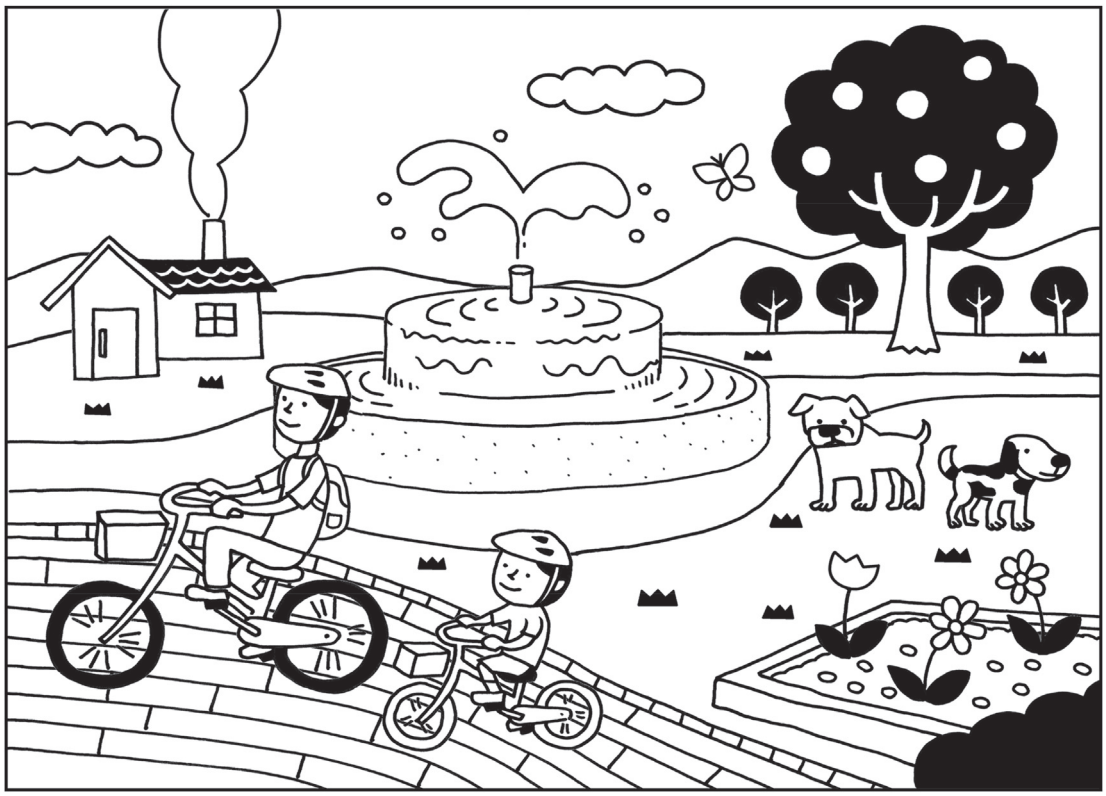

Fig. 1. First picture used in the Spot the Difference for Cognitive Decline test. The examinees were instructed to memorize the details of the picture, which was presented for 30 seconds.

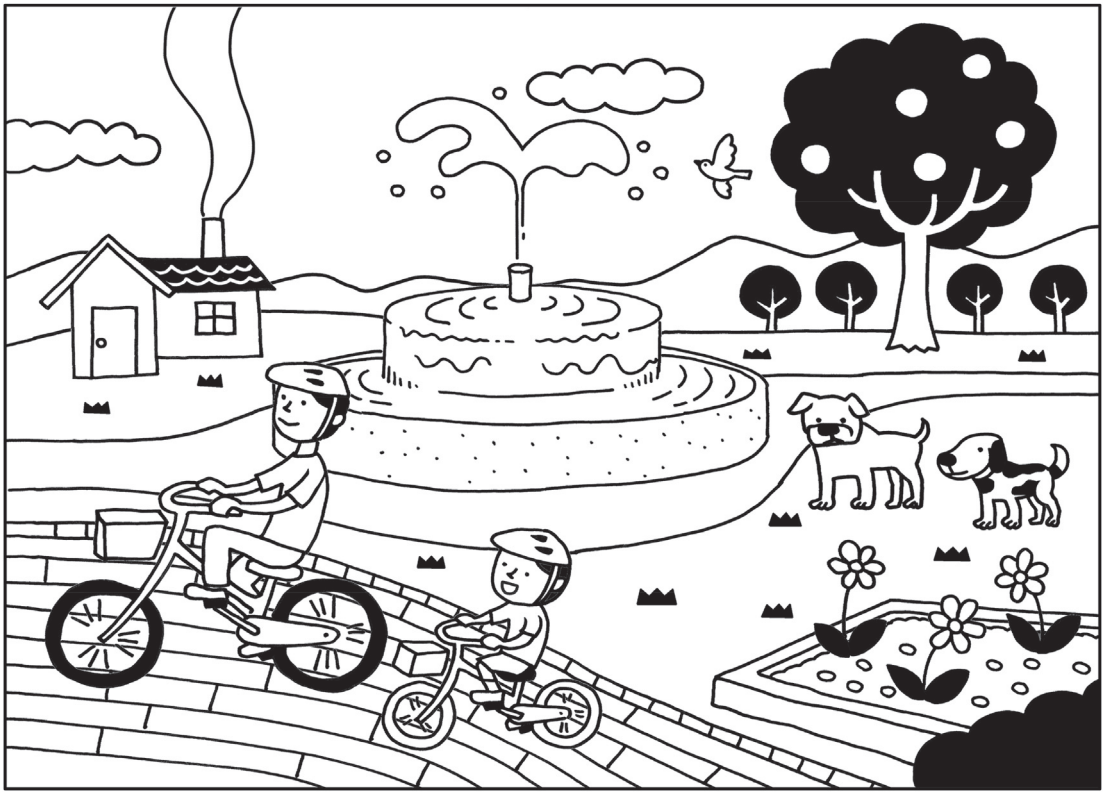

Fig. 2. Second picture in the Spot the Difference for Cognitive Decline test. This picture has 10 differences when compared with the first picture (Fig. 1). After studying the first picture for 30 seconds, the examinees were asked to find as many of the differences between the first and second pictures as they could within 1 minute.

the details of the first picture for 30 seconds. They are also told that there are "some" differences between the first and second pictures. The examiners do not inform the participants that there are 10 differences in total. After showing the first picture, the examiner takes the first picture away and shows the participants the second picture. The examinees are then asked to find the differences in the second picture, within 1 minute and without any hints. The number of the correct answers is then counted to determine the SDCD score. If the examinees' answers are close but not exactly correct (e.g., a flower type or increase in the fruit), these answers are marked as incorrect and not included in the SDCD score. In a sample of 21 participants, the SDCD had a high test–retest reliability [intertrial correlation coefficient (ICC) = 0.801; $p < 0.001$] between the two measurements with a 1-week interval.

2.3. Cognitive function

Participants' cognitive function was measured by two neuropsychological tests: the Mini-Mental State Examination (MMSE)[17] and the Scenery Picture Memory Test (SPMT).[18]

Global cognitive function was assessed using the MMSE, a standard test used in cognitive aging research for assessing mental status. Five areas of cognitive function—orientation, registration, attention and calculation, recall, and language—are tested. It has 11 questions in total and a maximum possible score of 30.

The SPMT is a simple memory test that assesses visual memory combined with verbal responses. This test uses a line drawing of a living room in a house on an A4-size paper, depicting 23 objects that are commonly observed in daily life. The examinee is instructed to look at the picture for 1 minute and remember the items. After this encoding period, participants are given a distractor task (a brief forward digit-span test). Participants are then asked to recall the objects in the picture without a time limit. Recall of the items usually takes approximately 2 minutes. The number of items recalled is the SPMT score. Higher scores indicate a better cognitive function.

2.4. Statistical analysis

We divided the participants into two groups (normal and cognitive impairment groups) based on the cutoff score of the MMSE (23/24). Differences between these two groups were statistically analyzed, using the unpaired t test for continuous variables and the χ^2 test for categorical variables. Differences between the SPMT and SDCD scores were examined using an analysis of variance. When a significant effect was found, the Tukey–Kramer *post hoc* test was used to examine the differences. In addition, the criterion-related validity was determined by evaluating the correlation between the SDCD score and the two neuropsychological tests using Spearman's rank correlation coefficient. Following this, we performed a multiple logistic regression analysis to determine whether the SDCD score was associated with cognitive impairment independently. For this analysis, the two groups (i.e., the normal group and the cognitive impairment group) were the dependent variables, and the SDCD score was the independent variable. We controlled age, sex, body mass index, medications, and the length of education. Furthermore, a receiver-operating characteristic (ROC) analysis was used to examine the power of the SDCD score and determine the optimal cutoff value of the SDCD score as a state variable. The area under the curve, sensitivity, and specificity of the SDCD score were calculated based on the ROC curve. The cutoff value for the SDCD score was determined based on the optimal sensitivity and specificity. Consequently, we performed a univariate logistic regression analysis to determine the correlation between

the SDCD and the five subtests of the MMSE (orientation, registration, attention and calculation, recall, and language). For this analysis, the groups formed on the basis of the cutoff value of the SDCD were the dependent variables and each subtest of the MMSE was the independent variable.

Data were analyzed using SPSS Statistics for Windows, version 20.0 (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered statistically significant.

3. Results

Of the 443 participants, 30 (6.77%) were identified as having cognitive impairment based on an MMSE cutoff score of 23/24. Demographic characteristics of the participants are shown in Table 1. The normal group had a higher SDCD score (2.21 ± 1.38) than the cognitive impairment group (0.77 ± 0.86; $p < 0.001$). The normal group also had a higher SPMT score than the cognitive impairment group ($p < 0.001$). The education level of the normal group was also higher than that of the cognitive impairment group ($p = 0.002$). There were no significant differences in age, sex, body mass index, or the use of medication between the two groups.

The participants were reclassified into five groups according to their SDCD scores; differences in the MMSE and SPMT scores between the groups are shown in Figs. 3 and 4. There were significant differences in the MMSE scores ($F = 15.7$, $p < 0.001$) as well as in the SPMT scores ($F = 22.6$, $p < 0.001$) between the five groups. Results of the *post hoc* tests are shown in Figs. 3 and 4. In addition, the SDCD scores were moderately and positively correlated with the MMSE ($r = 0.333$) and SPMT ($r = 0.402$) scores ($p < 0.001$). These analyses indicated that a higher SDCD score was associated with higher cognitive function. In the logistic regression analysis, the SDCD score was significantly associated with cognitive impairment after adjusting for age, sex, body mass index, medications, and the length of education (odds ratio: 0.388; 95% confidence interval: 0.257–0.584; $p < 0.001$).

The ROC curve for the SDCD scores used for the identification of cognitive impairment was based on the MMSE cutoff score (23/24). The area under the curve was comparatively high for the SDCD scores (0.798, $p < 0.001$), and the cutoff value of the SDCD score was 1/2 (with ≥1 being considered normal) with a 70.5% sensitivity and 80.0% specificity. A univariate logistic regression analysis showed that there were significant correlations between the SDCD scores and the four subtests of the MMSE ($p < 0.05$), except for the registration subtest (refer to Table 2).

Table 1
Characteristics of participants with and without cognitive impairment.[a]

	Normal (n = 413, MMSE ≥ 24, 27.4 ± 2.0)	Cognitive impairment (n = 30, MMSE < 24, 22.4 ± 1.1)	p
Age, y	72.9 ± 5.3	74.4 ± 5.3	0.160
Female	269 (65.3%)	20 (66.7%)	> 0.99
BMI, kg/m^2	22.7 ± 3.1	22.2 ± 2.8	0.384
Number of medications taken, n	2.53 ± 2.59	2.48 ± 2.46	0.237
Education			0.002**
<6 y	3 (0.7%)	0	
6–9 y	98 (23.7%)	17 (56.7%)	
10–12 y	212 (51.3%)	10 (33.3%)	
>12 y	100 (24.2%)	3 (10.0%)	
SDCD	2.21 ± 1.38	0.77 ± 0.86	<0.001**
SPMT	13.8 ± 3.5	10.1 ± 2.8	<0.001**

Data are presented as n (%) or mean ± SD.
* $p < 0.05$.
** $p < 0.01$.
BMI = body mass index; MMSE = Mini-Mental State Examination; SDCD = Spot the Difference for Cognitive Decline; SPMT = Scenery Picture Memory Test.
[a] Normal and cognitive impairment groups were defined according to the MMSE cutoff score of 23/24.

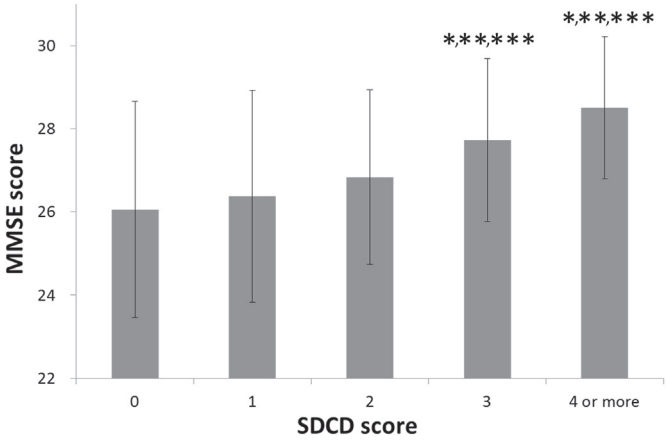

Fig. 3. Comparison of the MMSE scores between the groups formed based on the SDCD scores. There were significant differences in the MMSE scores across the five groups ($F = 15.7$, $p < 0.001$). * Significant difference from Group 0. ** Significant difference from Group 1. *** Significant difference from Group 2. MMSE = Mini-Mental State Examination; SDCD = Spot the Difference for Cognitive Decline.

4. Discussion

We examined a new type of short-term memory and attention test, the SDCD, which used a spot-the-difference task to identify cognitive impairment. In the present study, we showed that the SDCD test is a very quick and reliable screening tool for the identification of cognitive impairment in community-dwelling older adults.

The SDCD test is moderately and positively correlated with global cognitive and memory functions. The SDCD test includes a "memory" phase and a "recall and name the differences" phase. These phases require not only memory functions, but also other cognitive functions, such as attention. Some studies in the past have used similar spot-the-difference tasks as cognitive tests,[14,15] and only one previous study[16] has investigated brain activation in a test

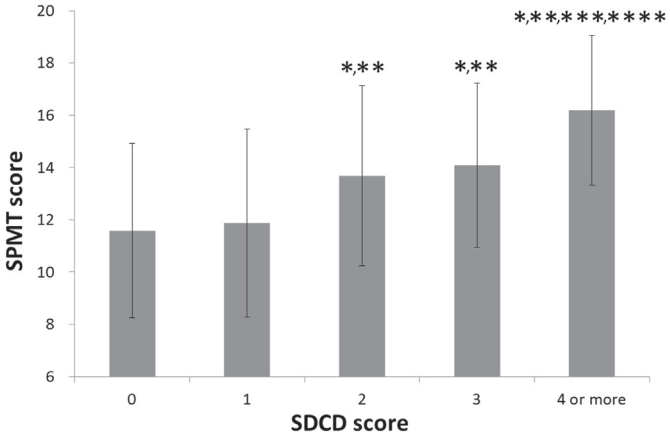

Figure 4. Comparison of the SPMT results between the groups formed based on the SDCD scores. There were significant differences in the MMSE scores across the groups ($F = 22.6$, $p < 0.001$). * Significant difference from Group 0. ** Significant difference from Group 1. *** Significant difference from Group 2. **** Significant difference from Group 3. MMSE = Mini-Mental State Examination; SDCD = Spot the Difference for Cognitive Decline; SPMT = Scenery Picture Memory Test.

Table 2
Correlation between SDCD score and subtests of MMSE.[a]

Subtests (total score)	Subtest score	SDCD score < 2 (n = 146) n (%)	OR (95% CI)
Orientation (10)	≤8	20 (13.7)	Reference
	9	30 (20.5)	0.26 (0.11–0.62)**
	10	96 (65.8)	0.21 (0.10–0.46)**
Registration (3)	≤2	4 (2.7)	Reference
	3	142 (97.3)	0.61 (0.16–2.30)
Attention and calculation (5)	≤2	69 (47.3)	Reference
	3	10 (6.8)	1.10 (0.47–2.59)
	4	18 (12.3)	1.19 (0.61–2.34)
	5	49 (33.6)	0.57 (0.36–0.88)*
Recall (3)	≤1	22 (15.1)	Reference
	2	51 (34.9)	0.21 (0.09–0.50)**
	3	73 (50.0)	0.13 (0.06–0.31)**
Language (9)	≤7	14 (9.6)	Reference
	8	38 (26.0)	0.18 (0.06–0.59)**
	9	94 (64.4)	0.12 (0.04–0.36)**

* $p < 0.05$.
** $p < 0.01$.
CI = confidence interval; MMSE = Mini-Mental State Examination; OR = odds ratio; SDCD = Spot the Difference for Cognitive Decline.
[a] For each univariate logistic regression analysis, SDCD scores <2 or ≥2 were the dependent variables and each subtest of the MMSE was the independent variable.

using a spot-the-difference task. Although the abovementioned test did not include a memory phase (unlike that included in the SDCD test), the results indicated that the brain areas related to visual information and attention was activated while carrying out the task. Our results indicated that the SDCD was associated with most of the subtests of the MMSE. Thus, the SDCD test appears to be associated not only with attention and memory, but also with global cognitive function. We need to minutely assess and investigate other cognitive functions (e.g., executive function and processing speed) and their association with the SDCD test in future studies.

The ROC curve for the SDCD score indicated that the SDCD test identified cognitive impairment with a high degree of accuracy. Previous studies have reported that some picture-based memory tests can reliably detect dementia.[18–20] These studies support the results of the present study. Moreover, the SDCD test is able to detect dementia in less time compared to other tests studied previously. Picture-based memory tests have some advantages over verbal memory tests. First, pictures are remembered better than words, a phenomenon known as the “picture superiority effect”.[21] Previous studies showed that superiority of memory for pictorial material was often applied as a mnemonic aid for older adults.[22,23]_ENREF_17. Second, picture-based memory tests are not limited by the patient's level of education. Some verbal memory tests cannot be used for a population that has a low level of education.[19] Most of the verbal-based screening measures have not been validated in people with low education levels or illiterate individuals,[24,25] and it has been shown in previous studies that a low level of education can result in cognitively unimpaired people screening positive for dementia.[24] Furthermore, the SDCD test takes only approximately 2 minutes to assess short-term memory and attention functioning, in addition to its abovementioned merits. In the present study, the participants took approximately 10 minutes and approximately 5 minutes to complete the MMSE and the SPMT, respectively. The SDCD test appears as an easy game for patients, because of the simplicity of the differences, but it is actually quite a difficult cognitive task. It is possible that this characteristic makes the SDCD test fun for the participants to complete, thereby making its widespread use possible. Thus, we believe that the SDCD test can be used to identify cognitive impairment in older adults in a clinical or community-based setting.

The present study has several limitations. First, although we assessed global cognitive and memory functions with the MMSE and the SPMT, other cognitive functions, such as executive functions and processing speed, were not assessed in this study. We need to assess these cognitive functions and investigate their association with the SDCD test in future studies. Second, participants in the present study were community-dwelling older adults who had not received a diagnosis of dementia or MCI, and we did not confirm the test–retest reliability for older adults with dementia or MCI. In the future, we need to include older adults diagnosed with dementia to ascertain whether the SDCD test can discriminate between normal cognitive function and MCI in older adults.

5. Conclusion

We developed a new type of short-term memory and attention test that uses a spot-the-difference task for the identification of cognitive impairment. The present study indicates that the SDCD test can be an effective clinical tool for the identification of cognitive impairment in older adults.

Conflicts of interest

The authors declare no conflicts of interest.

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資料 9：
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Original Article

Children with flat feet have weaker toe grip strength than those having a normal arch

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Abstract. [Purpose] This study investigated the relationship between toe grip strength and foot posture in children. [Subjects and Methods] A total of 619 children participated in this study. The foot posture of the participants was measured using a foot printer and toe grip strength was measured using a toe grip dynamometer. Children were classified into 3 groups; flatfoot, normal, and high arch, according to Staheli's arch index. The differences in demographic data and toe grip strength among each foot posture group were analyzed by analysis of variance. Additionally, toe grip strength differences were analyzed by analysis of covariance, adjusted to body mass index, age, and gender. [Results] The number of participants classified as flatfoot, normal, and high arch were 110 (17.8%), 468 (75.6%), and 41 (6.6%), respectively. The toe grip strength of flatfoot children was significantly lower than in normal children, as shown by both analysis of variance and analysis of covariance. [Conclusion] A significant difference was detected in toe grip strength between the low arch and normal foot groups. Therefore, it is suggested that training to increase toe grip strength during childhood may prevent the formation of flat feet or help in the development of arch.

Key words: Flatfoot, Toe grip strength, Children

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INTRODUCTION

Foot misalignment (flatfoot and high arch) is one of the common orthopedic issues in pediatric health[1–3)] and it causes many injuries in the foot, knee, and lower back[3–5)]. Almost all children are born with flatfoot and normal foot posture develops during the first decade of life[6, 7)]. However, some children have misaligned feet even after10 years of age. An estimated 19.1% of children, aged 10–13 years, have flatfoot[8)]. The incidence of high-arched foot is reportedly 14.6–25.8%[9, 10)]. If normal foot posture does not develop created during the elementary school period, foot misalignment continues to during adolescence and into adulthood. Therefore, development of normal foot posture during childhood is important.

Flatfoot and high arch are caused by many factors such as neurological disorders, congenital conditions, and structural anomalies[1, 3)]. However, flatfoot and high arch can also be found in otherwise healthy individuals, and in the absence of injury, they can be caused by structural issues such as ligament tension and muscle strength[1, 3)]. Ligament laxity typically improves as bones lengthen with age, and the majority of children develop an arch in the first decade of life[11)]. In early childhood, the intrinsic and extrinsic foot muscles are usually strengthened through walking and running. However, if the intrinsic and extrinsic foot muscles are not used enough in early childhood, they remain weak. Therefore, improving muscle strength in the foot is one method of treating foot misalignment.

Recently it was revealed that toe grip strength is related to foot posture. Toe grip strength is the strength of the toe flexor muscles, such as the flexor hallucis longus and flexor digitorum longus. These muscles are related to the creation of the foot arch. Hashimoto et al.'s study revealed that toe grip strength training can increase the foot arch in adolescents[12)]. Toe grip strength is related to foot posture in adolescents[13)]. However, it is not known if the same relationship between toe grip strength and foot posture is present in children. The authors hypothesized that there was a relationship between toe grip strength and foot posture in children. The demonstration of a relationship between foot posture and toe grip strength would highlight the importance of toe grip strength

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in creation normal foot posture during childhood. Therefore, the authors investigated the relationship between toe grip strength and foot posture in this study.

SUBJECTS AND METHODS

A total of 619 children (boys, n = 311, age = 11.2 ± 0.7 years; girls, n = 308, age = 11.3 ± 0.7 years; age expressed as mean ± SD) participated in this study. Signed consent was obtained from the principals of five elementary schools in Nara Prefecture in Japan for inclusion of their schools in the study. Demographic data were collected from the returned consent forms, as were the inclusion (age 10–12 years) and exclusion (no history of foot surgery or congenital disorders) criteria. The purpose and methods of the current study were explained to the participants and elementary school teachers in detail in a verbal statement and document. The local ethics committee approved the study (H26-6).

Foot posture was measured using a foot printer (Bauerfeind Co. LTD, Germany). A static footprint was obtained as each child stood barefoot on the foot printer, with weight normally distributed between both feet. The dominant foot was identified as that preferred for kicking a ball and we used the posture of the dominant foot in the analysis. Children stood with their feet shoulder width apart and placed their foot at whatever angle they preferred. The width of the foot at the arch and the width of the heel were measured. The arch index for each foot was calculated by dividing the former number by the latter, as described by Staheli et al[14].

Toe grip strength was measured using a T.K.K.3362 toe-grip dynamometer (Takei Scientific Instruments, Niigata, Japan) (Fig. 1). The protocol for measuring toe grip strength was as described in the studies by Uritani et al[15, 16]. Participants sat upright on a chair without leaning on the backrest throughout the toe grip strength measurements. Both of the hips and knees were flexed at about 90° and the ankles were placed in a neutral position and fixed with a strap. The first proximal phalanx was positioned at the grip bar, and the heel stopper was adjusted to fit the heel of each participant. The bar was then gripped with the toes using maximal effort, for about 3 seconds. Toe grip strength of the dominant foot was measured twice. The maximum strength from the two measurements was recorded.

At first, participants were classified into flatfoot, normal, and high arch categories, based on the arch index, as measured by their footprint. An arch index value between 0.44 and 0.89 was defined as a normal foot, an index <0.44 was classified as a high arch, and an index, >0.89 was classified as a low arch[14]. Differences in age, body mass index (BMI), toe grip strength, and gender between the three groups were examined using analysis of variance (ANOVA) and a χ^2 test. Differences in toe grip strength among the 3 groups were examined using analysis of covariance (ANCOVA) adjusted for age, BMI and gender. When a significant effect was found, differences were determined using the Turkey-Kramer post-hoc test for ANOVA, and the Bonferroni post-hoc test for ANCOVA. Statistical analysis were carried out using the SPSS version 20.0 software package (SPSS, Chicago, IL, USA), with a p value < 0.05 accepted as significant.

Fig. 1. T.K.K.3362 toe-grip dynamometer

RESULTS

Table 1 shows the characteristics of the participants. The ANOVA results showed that there was a significant difference in toe grip strength among the 3 groups ($p < 0.01$). The values for toe grip strength were 11.0 ± 3.9 kg in flatfoot, 12.6 ± 4.1 kg in normal, and 11.4 ± 3.6 in high arch (Table 2). The toe grip strength of the low arch group was significantly lower than the normal group ($p < 0.01$) and that there was no significant difference between the high arch group and other groups. In addition, ANCOVA showed a significant difference in toe grip strength among the 3 groups when adjusted for age, BMI, and gender ($F = 5.22$, $p = 0.01$). Post-hoc tests indicated that the toe grip strength of the low arch group was significantly lower than in the normal group ($p < 0.01$).

DISCUSSION

Our study revealed that toe grip strength was related to foot posture in children and that the toe grip strength of the flatfoot group was weaker than that of the normal group. However, there was no significant difference between high arch group and the other groups. In addition, toe grip strength was related to foot posture after adjustment for BMI, age, and gender.

Foot posture of children is related to BMI, age, and gender[17, 18], however in this study toe grip strength was related to foot posture, when measurements were adjusted for these factors. Moreover, muscle strength and physique differ with age and gender as children go through their growth period[19], as does the prevalence of flatfoot[17]. Foot posture in children is flexible, so the foot arch can easily be decreased by the body weight load. Evan found that foot posture was not related to weight in children[20]; nevertheless, many other studies have identified a correlation between BMI and foot posture[17, 18, 21, 22]. Pfeiffer et al.'s study revealed that flatfoot was present in 62% of obese, 51% in overweight, and 42% of young children with normal body weight[17]. In the present study, toe grip strength was related to foot posture adjusted for BMI, age, and gender.

Two possible explanations for the relationship between toe grip strength and foot posture are proposed here. First, toe flexor muscles lift up the navicular and make a medial longitudinal arch. Toe grip strength comes from the toe flexor muscles, such as the flexor hallucis longus and flexor digito-

Table 1. Subject characteristics by foot posture group

	All subjects (N = 619)					
	Flatfoot (n = 110)	SD	Normal (n = 468)	SD	High arch (n = 41)	SD
Age (yrs)	11.1	0.8	11.3	0.7	11.1	0.7
BMI (kg/m^2)	17.9	3.0	17.4	2.6	16.8	2.3
Gender (n boy / %)	66 / 60.0		225 / 48.1		20 / 48.8	

The parameters above were analyzed by ANOVA and χ^2 test, * $p < 0.05$
There were no significant differences between any of these parameters between groups

Table 2. Toe grip strength differences by foot posture group

	All subjects (N = 619)						
	Flatfoot (n = 110)	SD	Normal (n = 468)	SD	High arch (n = 41)	SD	Post-hoc
Toe grip strength (kg) *†	11.0	3.9	12.6	4.1	11.4	3.6	a

[a]significant differences between flatfoot and normal
*analyzed for ANOVA ($p < 0.01$, post-hoc; a)
†adjusted for subject age, BMI and gender (ANACOVA) ($p = 0.01$, post-hoc; a)

rum longus, and these muscles pass under the navicular. The navicular height is the index of the longitudinal medial arch and by definition, flatfoot children have a diminished or absent longitudinal medial arch. Osseous structures, ligaments, tendons, and muscles create navicular height[23, 24], and toe grip strength is one of the factors in creating the foot arch. This is supported by Hashimoto's study, which revealed that toe grip strength training increases the foot arch height in adolescents[12]. Therefore, toe grip strength is related to foot arch, and toe grip strength is different between flatfoot and normal children.

Second, toe flexor muscles are stretched in flatfoot children, so the muscles cannot contract with maximal strength. Muscles contraction strength exhibits a length-tension relationship[25–27], where optimal contraction occurs when the muscle is at the appropriate length and not overly stretched or compressed. In our study, toe grip strength of flatfoot children was lower than that of normal children. When the foot arch is low, toe flexor muscles are stretched. Therefore, toe flexor muscle cannot contract at maximum strength. Conversely, toe flexor muscles are looser in high arch children. However, subjects who had severe high arch due to neurological disorders were excluded from our study, and no significant differences were seen between the high arch group and the other groups. This is the second reason why toe grip strength of low arch feet was low.

The present study revealed that there was a significant difference in toe grip strength between flatfoot and normal children. A recent systematic review of current research demonstrated that there is very limited evidence for the efficacy of nonsurgical interventions in children with flatfoot[28]. Usually, a shoe or insole is used to treat symptomatic flatfoot in children. However, these treatments cannot permanently correct foot alignment[1, 29]. Flatfoot in children is caused by ligament laxity or foot muscle weakness, and ligament laxity is not changeable after foot posture develops. However, muscle strength is changeable, so increasing toe grip strength has the possibility to improve flatfoot. This idea is supported by the present study, which reveals that toe grip strength is related to foot posture in children. Therefore, training to increase toe grip strength during childhood may prevent flatfoot and improve foot posture.

There were several limitations in the present study. First, this study was a cross-sectional design, so the relationship between cause and effect is unknown. Therefore, further research is needed to reveal whether correlated change in grip strength and foot posture can be seen with individuals. Second, foot postures were measured using only a foot printer. The foot is a complex structure, so more detailed measurements of foot posture should be evaluated. Third, foot posture is related to genetics and ethnicity, but these factors were not considered. Despite these limitations, the findings from the present study provide valuable information and illustrate the importance of toe grip strength.

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Research Article Open Access

The Association between Pregnancy-Related Discomforts and Pre-Pregnancy Body Mass Index in Japanese Women

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Abstract

Objective: To determine the association between pregnancy-related discomforts and pre-pregnancy body mass index in a longitudinal study.

Methods: The study included 355 pregnant women (age, 31.1 ± 4.1 years). Participants were divided into three groups according to their pre-pregnancy body mass index: the low body mass index group, normal body mass index group, and high body mass index group. The occurrence of pregnancy-related discomforts during the second and third trimesters was investigated. Binomial logistic regression analysis was used to examine the association between pre-pregnancy body mass index and pregnancy-related discomforts experienced during the last two trimesters.

Results: The occurrence of most pregnancy-related discomforts increased in the third trimester, while that of constipation and shoulder stiffness or headache decreased. Based on logistic regression analysis, pre-pregnancy body mass index was significantly associated with various discomforts. The occurrence of hip joint or pubis pain (odds ratio/95% confidence interval = 2.38/1.14–4.95) during the second trimester, and sleeping difficulty (2.00/1.09–3.67), hand or finger stiffness (3.00/1.36–6.45), leg cramps (2.29/1.32–3.98), low back pain (2.20/1.29–3.75), hip joint or pubis pain (2.14/1.23–3.73), and shoulder stiffness or headache (2.01/1.06–3.82) during the third trimester was significantly higher in the high body mass index group than in the normal body mass index group. The low body mass index group exhibited a significantly a higher occurrence of shoulder stiffness or headache (2.84/1.35–5.96) during the second trimester and constipation (2.28/1.08–4.82) during the third trimester than the normal body mass index group.

Conclusion: The occurrence of discomforts decreased or increased during pregnancy. Furthermore, both pre-pregnancy high and low body mass index represent important risk factors for many pregnancy-related discomforts, compared with a pre-pregnancy normal body mass index.

Keywords: Health promotion; Pregnancy; Pregnancy-related discomforts; Pre-Pregnancy BMI; Prevention

Introduction

Methods

Anatomical, physiological, hormonal, and psychological changes occur in woman during pregnancy [1,2], causing a variety of discomforts such as low back pain, ligament pain, fatigue, and headache [3]. These pregnancy-related discomforts negatively impact mother and child health and affect the quality of life and limit the daily activities of mothers [4,5]. Despite a number of researchers investigating the management of pregnancy-related discomforts [6,7], there are several limitations to the treatments available during pregnancy. For example, non-prescribed medicines are usually unsuitable because of their adverse effects on pregnant women themselves and on the developing fetus [8,9]. Therefore, a longitudinal study is necessary to collect information on the prevalence of discomforts through the stages of pregnancy. Such information will increase the knowledge of the measures that can be taken to protect women from pregnancy-related discomfort and will be essential to prevent their onset.

Before pregnancy, it is important for women to maintain an appropriate body mass index (BMI) to avoid hormone imbalance and its negative impact on fertility [10]. Furthermore, some research indicates that the pre-pregnancy BMI is a predicting factor for conditions such as gestational diabetes, and thus for adverse pregnancy outcomes [11,12]. Pre-pregnancy obesity may also be a modifiable risk factor for intellectual disability in children [13]. On the other hand, women with pre-pregnancy low weight are at an increased risk of intrauterine growth restriction, perineal tears, preterm birth (spontaneous and induced), and low birth weight [14,15]. These results suggest that both pre-pregnancy high and low BMI negatively

affect the progress of the pregnancy. Information about the occurrence of discomforts at each gestational period is necessary for their prevention. Moreover, a normal BMI before pregnancy promotes an uneventful progress through pregnancy. However, to date, very few studies have been conducted on the association between pre-pregnancy BMI and pregnancy-related discomforts. Accordingly, we conducted a longitudinal study aimed to identify pregnancy-related discomforts throughout pregnancy and to identify possible associations between these discomforts and the pre-pregnancy BMI.

Settings

We collected information from 355 women (age, 31.1 ± 4.1 years) at the obstetrics and gynecology clinics in the Aichi Prefecture, Japan, between 2009 and 2013. When the pregnant women visited the clinic for their periodic health examination, the information was collected by the hospital staff such as nurses. The inclusion criteria for the survey were the lack of serious orthopedic disorders, neurological diseases, and high-risk pregnancy. At the first medical examination, we recorded the personal information (age and BMI before pregnancy) of each participant by using a questionnaire.

Questionnaire about Pregnancy-Related Discomforts

The subjects of this study were asked to complete a questionnaire during the second trimester (22.4 ± 2.1 weeks of gestation) and third trimester (33.7 ± 2.1 weeks of gestation). We used the Medical Check Sheet to track pregnancy-related discomforts during gestation. The sheet, developed by the Japan Maternity Fitness Association, is a self-entry questionnaire for the management of physical conditions, to be completed before exercise. Questions were related to the expected date of birth, weeks of gestation, blood pressure, and 10 different pregnancy-related discomforts (i.e., sleeping difficulty, constipation, hand or finger stiffness, swelling, leg cramps, low back pain, hip joint or pubis pain, shoulder stiffness or headache, rib pain, and anorexia or heartburn), reported to commonly occur and to have an adverse effect on pregnancy. If the participants had felt discomfort due to any of the items on the list, those items were checked.

Ethical Considerations

After the purpose of the study had been explained, written informed consent was obtained from each participant in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1975. The protocol was approved by the Ethics Committee of Kyoto University Graduate School of Medicine (protocol approval E-2110).

Statistical Analyses

Participants were divided into three groups (low BMI group, normal BMI group, and high BMI group) according to their pre-pregnancy BMI (<18 kg/m^2, ≥18 kg/m^2, and <22 kg/m^2 or ≥22 kg/m^2, respectively). We statistically calculated the differences in age between these three groups using analysis of variance. Based on the Medical Check Sheet completed during the second and third trimester, we determined the occurrence of each symptom during the second and third trimesters and analyzed this using descriptive statistics. Binomial logistic regression analysis was used to examine the association between each discomfort and the pre-pregnancy BMI for each trimester. We referred to discomforts as the dependent variables, to low and high BMI groups as the independent variables (with the normal BMI group as reference), and to age as the adjustment variable. Data were entered and analyzed using the Statistical Package for the Social Sciences (Windows version 20.0; SPSS Inc., Chicago, IL, USA). For all analyses, $p<0.05$ was considered statistically significant.

Result

Information on 355 women (pre-pregnancy BMI= 20.3±2.1 kg/m^2) who met the inclusion criteria was collected. We assigned 37 women to the low BMI group (BMI= 17.4±0.6 kg/m2), 246 women to the normal BMI group (BMI= 19.8 ± 1.0 kg/m2), and 72 women to the high BMI group (BMI= 23.5±1.8 kg/m^2). There were no significant differences between the three groups (low, normal, and high BMI groups) in age (30.4 ± 4.2 years, 31.2 ± 4.0 years, and 31.2 ± 4.2 years, respectively).

The occurrence of most of the pregnancy-related discomforts analyzed increased from the second to third trimester, in contrast to that of constipation and shoulder stiffness or headache that showed a decrease (Figure 1).

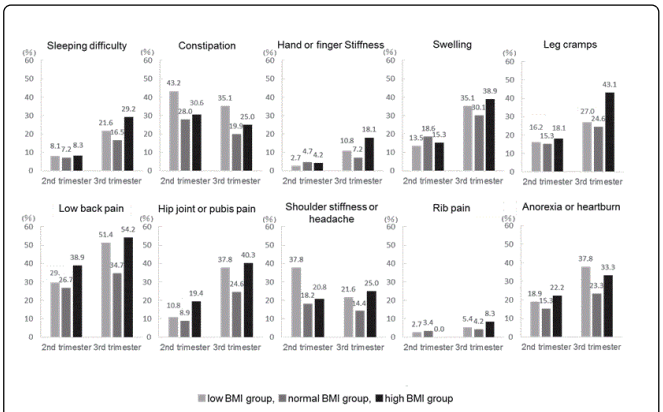

Figure 1: The prevalence of pregnancy-related discomforts during second and third trimester.

Multivariate analysis revealed that pre-pregnancy BMI was significantly associated with some of the discomforts during pregnancy (Table 1). The occurrence of hip joint or pubis pain (odds ratio/95% confidence interval=2.38/1.14–4.95) during the second trimester, and sleeping difficulty (2.00/1.09–3.67), hand or finger stiffness (3.00/1.36–6.45), leg cramps (2.29/1.32–3.98), low back pain (2.20/1.29–3.75), hip joint or pubis pain (2.14/1.23–3.73), and shoulder stiffness or headache (2.01/1.06–3.82) during the third trimester was significantly higher in the high BMI group than in the normal BMI group ($p<0.05$). The occurrence of shoulder stiffness or headache (2.84/1.35–5.96) during the second trimester, and constipation (2.28/1.08–4.82) during the third trimester was significantly higher in the low BMI group than in the normal BMI group ($p < 0.05$). No significant differences were observed in swelling, rib pain, and anorexia or heartburn.

Discussion

We analyzed the changes in the occurrence of pregnancy-related discomforts throughout pregnancy and whether their occurrence was significantly associated with pre-pregnancy BMI. We observed a different trend in the occurrence of the pregnancy-related discomforts

analyzed; in fact, while some of them tended to decrease, others appeared to increase during pregnancy progression. Furthermore, we found that both low and high BMI before pregnancy represent important risk factors for many pregnancy-related discomforts, compared with normal BMI.

		second trimester		second trimester	
Discomforts	**BMI group**	**Odds ratio**	**95%CI**	**Odds ratio**	**95% CI**
sleeping difficulty	**low BMI** **normal BMI** **high BMI**	1.13 1[reference] 1.15	0.32-4.01 0.44-3.02	1.32 1[reference] 2.00*	0.57-3.11 1.09-3.67
constipation	**low BMI** **normal BMI** **high BMI**	1.92 1[reference] 1.13	0.95-3.91 0.64-2.00	2.28* 1[reference] 1.38	1.80-4.82 0.74-2.56
hand or finger stiffness	**low BMI** **normal BMI** **high BMI**	0.6 1[reference] 0.93	0.08-4.81 0.25-3.43	1.61 1[reference] 2.97*	0.74-2.09 1.36-6.45
swelling	**low BMI** **normal BMI** **high BMI**	0.68 1[reference] 0.51	0.25-1084 0.38-1061	1.25 1[reference] 1.45	0.60-2.58 0.84-2.51
leg cramps	**low BMI** **normal BMI** **high BMI**	1 1[reference] 1.14	0..39-2.55 0.57-2.26	1.1 1[reference] 2.29*	0.50-2.40 1.32-3.98
low back pain	**low BMI** **normal BMI** **high BMI**	1.15 1[reference] 1.74	0.54-2.45 1.00-3.01	1.98 1[reference] 2.20*	0.99-3.98 1.29-3.75
hip joint or pubis pain	**low BMI** **normal BMI** **high BMI**	1.27 1[reference] 2.38*	0.41-3.94 1.14-4.95	1.95 1[reference] 2.14	0.94-4.03 1.23-3.73
shoulder stiffness or headache	**low BMI** **normal BMI** **high BMI**	2.84* 1[reference] 1.21	1.35-5.96 0.63-2.33	1.63 1[reference] 2.14	0.69-3.86 1.06-3.82
rib pain	**low BMI** **normal BMI** **high BMI**	0.83 1[reference] 0	0.10-6.86 0	1.32 1[reference] 2.14	0.28-6.31 1.06-3.82 0.75-6.11
anorexia or heartburn	**low BMI** **normal BMI** **high BMI**	1.24 1[reference] 1.56	0.51-3.03 0.81-3.01	1.97 1[reference] 1.62	0.95-4.08 1.06-3.82 0.92-2.87

Table1: The influence of pre-pregnancy BMI on pregnancy related discomforts (logistic regression analysis). **Note:** The analysis for discomforts was adjusted for age. *: $p < 0.05$

The occurrence of most pregnancy-related discomforts increased from the second to third trimester, while the occurrence of constipation and shoulder stiffness or headache decreased. The tendency for the occurrence of the two discomforts of current study was almost equivalent to previous reports. A previous study in the United States showed that the occurrence of constipation decreased (26.3% to 15.7%) from the second to the third trimester [16], and in another cross-sectional study, the occurrence of headache decreased (44.9% to 37.6%) and that of constipation increased (38.6 to 45.2%) from the second to the third trimester [3]. Here, we observed a difference when compared with the previous study of Nazik and Eryilmaz, where the prevalence of constipation decreased in our study but increased in that study. However, it is worth noting that ours is a longitudinal study, and thus, we collected information during each trimester from the same participants, and that found that some discomforts might improve during the course of pregnancy. Therefore, pregnant women should pay attention to constipation and shoulder stiffness or headache during the early stages of pregnancy, especially during the second trimester, and of other discomforts thereafter.

We found significant differences in the occurrence of analyzed discomforts according to pre-pregnancy BMI. The occurrence of hip joint or pubis pain was higher during the second trimester, and the occurrence of sleeping difficulty, hand or finger stiffness, leg cramps, low back pain, hip joint or pubis pain, and shoulder stiffness or headache during the third trimester was higher in the high BMI group than in the normal BMI group. These discomforts are related to changes in the musculoskeletal and cardiovascular systems, common during pregnancy [17-21]. Overweight exposes the musculoskeletal system to excessive loads, resulting in conditions such as low back pain and hand pain (22,23). Overweight might also affect the cardiovascular system [24,25], leading to leg cramps and hand or finger stiffness.

Accordingly, discomforts, especially those related to the musculoskeletal and cardiovascular systems, might occur in the high BMI group. The occurrence of shoulder stiffness or headache during the second trimester, and constipation during the third trimester, was higher in the low BMI group than in the normal BMI group. These discomforts are related to fluctuations in hormones such as estrogen, occurring during pregnancy [26,27], and low weight might determine hormone imbalance, in particular by decreasing the effects of female hormones [28]. Therefore, pre-pregnancy low BMI might hamper the hormonal balance and lead to the observed pregnancy-related discomforts.

In recent years, the occurrence of obesity has increased worldwide [29],while women, especially young adults, attempt to lose weight despite being of normal weight or underweight [30,31]. In this respect, our study showed that both women with high or low pre-pregnancy BMI have a high risk of pregnancy-related discomforts that not only affect their quality of life and limit their daily activities, but might also have a negative impact on their children's health [4,5]. Hence, our findings suggest that young women should maintain an appropriate BMI before getting pregnant, in order to have a good pregnancy progression.

This study has several limitations. First, we could not obtain information on some factors that could affect pregnancy-related discomforts (e.g. living environment, parity, and hormonal fluctuations during pregnancy). These factors may have affected our results. Second, we could not investigate the occurrence of additional discomforts that occur during pregnancy: it is known that more than 30 discomforts might be experienced by pregnant women [3]. In the future, a similar study investigating various pregnancy-related discomforts should be conducted, taking into account the different factors related to the discomforts.

Conclusion

The current study showed that pregnancy-related discomforts have different trends in occurrence from the second to the third trimester. Therefore, pregnant women should pay attention to different discomforts depending on the pregnancy period. Moreover, pre-pregnancy low or high BMI might be a risk factor for pregnancy-related discomforts, regardless of age. These findings indicate that women should maintain an appropriate BMI before pregnancy to prevent potential discomforts during pregnancy.

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資料 10：
JAGS 誌発表論文

CLINICAL INVESTIGATIONS

A 12-Week Physical and Cognitive Exercise Program Can Improve Cognitive Function and Neural Efficiency in Community-Dwelling Older Adults: A Randomized Controlled Trial

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OBJECTIVES: To investigate whether a 12-week physical and cognitive exercise program can improve cognitive function and brain activation efficiency in community-dwelling older adults.

DESIGN: Randomized controlled trial.

SETTING: Kyoto, Japan.

PARTICIPANTS: Community-dwelling older adults (N = 48) were randomized into an exercise group (n = 24) and a control group (n = 24).

INTERVENTION: Exercise group participants received a weekly dual task–based multimodal exercise class in combination with pedometer-based daily walking exercise during the 12-week intervention phase. Control group participants did not receive any intervention and were instructed to spend their time as usual during the intervention phase.

MEASUREMENTS: The outcome measures were global cognitive function, memory function, executive function, and brain activation (measured using functional magnetic resonance imaging) associated with visual short-term memory.

RESULTS: Exercise group participants had significantly greater postintervention improvement in memory and executive functions than the control group ($P < .05$). In addition, after the intervention, less activation was found in several brain regions associated with visual short-term memory, including the prefrontal cortex, in the exercise group ($P < .001$, uncorrected).

CONCLUSION: A 12-week physical and cognitive exercise program can improve the efficiency of brain activation during cognitive tasks in older adults, which is associated with improvements in memory and executive function. **J Am Geriatr Soc 2015.**

Key words: cognitive improvement; physical and cognitive exercise program; fMRI; randomized controlled trial

Dementia, which is common in older adults, affecting 5% to 8% of the population aged 65 and older[1] and up to 30% of people aged 85 and older,[2] can drastically influence daily life; its prevalence is also increasing. Approximately 48% of people with Alzheimer's disease (AD) are estimated to live in Asia, and this percentage is projected to grow to 59% by 2050.[3] Dementia, including AD, is associated with mortality,[4] so ways to prevent dementia onset are urgently needed.

Several meta-analyses have found that physical activity is associated with improvements in cognitive performance in older adults,[5–7] and cognitive activities reduce the risk of dementia.[8] A recent systematic review showed that combined cognitive and exercise training, including dual-task (DT) exercises, which involve concurrent cognitive and motor tasks, can improve cognitive function in older adults with and without cognitive impairment.[9] This review indicated that these interventions were beneficial to various components of cognitive function in older adults with healthy cognition,[10] mild cognitive impairment (MCI),[11] and AD.[12]

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In addition to the effect of multimodal exercise with physical and DT components on cognitive performance, recent functional magnetic resonance imaging (fMRI) studies have provided evidence that physical exercise changes brain activation. Some studies have reported less brain activation during memory-related[13] or conflict tasks,[14] which suggests that such reduced activation improves neural efficiency during cognitive tasks, but few studies have tested whether multimodal exercise affects neural activity, particularly cortical activation. Therefore, the present study used a randomized controlled trial combined with fMRI data from a visual short-term memory task, which requires frontal lobe function,[15] to investigate whether a 12-week multimodal exercise program, including physical and DT components, could improve cognitive function and the efficiency of brain activation in community-dwelling older adults. It was hypothesized that multimodal exercise would lead to less brain activation in the regions associated with visual short-term memory, especially the prefrontal cortex, because of the DT components of the exercise.

METHODS

Participants

Independently community-living individuals aged 60 and older who were willing to participate in group exercise classes for at least 3 months were recruited from the Kyoto City Silver Human Resources Center, Japan. An interview was used to exclude individuals with a history of major psychiatric illness; a serious neurological diagnosis; or severe cardiac, pulmonary, or musculoskeletal disorders according to self-report. Individuals with cognitive impairment (Mini-Mental State Examination (MMSE) score $\leq$23)[16] and those who showed major abnormalities on brain MRI scans, such as cerebral infarction or tumor, were also excluded. The study was conducted in accordance with the guidelines of the Declaration of Helsinki, and the ethics committee of the Kyoto University Graduate School of Medicine reviewed and approved the study protocol. The trial registration number is JMA-IIA00108.

Study Design and Randomization

Randomization via computer-generated random numbers was performed in blocks of four participants, stratified according to MMSE score. Participants were randomly assigned to the exercise intervention group (EG) or the control group (CG). EG participants received 90 minutes of group training sessions once per week for 12 weeks and were assigned a pedometer-based walking exercise. CG participants did not receive any intervention and were instructed to spend their time as usual during the intervention phase.

Required Sample Size

A previous study showed that 2 months of combined cognitive and exercise training can improve working memory in cognitively healthy older adults, with an approximate effect size of 0.9.[10] Considering participants' cognitive status and the intervention program used in this study, a sample size of 21 participants per group would be required to reach a power of 0.8, with an alpha set at 0.05 and beta at 0.2. Assuming a dropout rate of 15%, a final sample size of 24 per group was determined to be required.

Intervention Program

Subjects assigned to the EG received 90 minutes of group training sessions once a week for 12 weeks and pedometer-based walking exercise assignments supervised by physiotherapists.

Exercise classes followed a standardized format that included 15 minutes of stretching and moderate-intensity exercises, 15 minutes of progressive muscle strength training, and 60 minutes of DT exercise that included three DT categories.[17,18] The intensity of these exercises was based on recommendation from the American College of Sports Medicine and the American Heart Association.[19] In the first category, participants were instructed to perform a verbal fluency task during short-, fast-step exercises. In the second category, the supervisor assigned a number to various parts of the body (e.g., 1 = right shoulder, 2 = left shoulder), and participants were instructed to perform seated or standing step exercises at a tempo of 60 to 120 beats per minute according to the tempo of the accompanying music. During these exercises, the supervisor periodically stated a number, at which point participants were to touch the appropriate parts of their own body. In the third category, participants were instructed to perform standing step exercises at the same tempo as the second category exercise and to step in one of four directions indicated verbally by the supervisor (right, forward, back, left). The intensity and difficulty of the three exercises were gradually increased over the 12-week period.

During the 12-week intervention phase, the EG received walking exercises, using a pedometer (Yamax Power Walker EX-300; Yamasa Tokei Keiki Co., Ltd, Tokyo, Japan) to measure daily step counts. Participants were instructed to increase the number of daily steps by 15% each month and to record the number of steps taken by the end of each day on a calendar. At the end of every month, a sheet was given to each participant to collect brief feedback about the month's exercises and to provide reminders to record the exercises. The feedback responses were used to assist in setting the number of daily steps assigned for the next month. Walking exercise intensity was not clearly defined. During the first month, EG participants were instructed to increase their steps by approximately 15% relative to baseline (100% $\rightarrow$ 115%). During the second and third months, they were also instructed to do so relative to the previous month (115% $\rightarrow$ 132.3% $\rightarrow$ 152.1%). That is, their steps would have increased by approximately 50% relative to baseline.

Outcome Measures

All participants underwent several evaluations upon entry into this study (preintervention) and at the end of the study (postintervention). Evaluations included measurements of daily step counts, clinical tests (physical and cognitive function), and MRI scans. Before the study, one of

the authors (SN) trained all staff members on how to obtain the measurements included in the study. Physical therapists administered the physical function tests, and occupational therapists administered the cognitive function tests; therapists were blinded to group allocation.

Measurement of Average Daily Steps

Participants were instructed to wear the pedometer in a clothing pocket on their dominant leg for 14 consecutive days except when bathing, sleeping, or performing water-based activities. The averages of their daily step counts for 14 days were calculated.

Clinical Tests

All participants underwent a 10-m walking test,[20] the Timed Up and Go test (TUG),[21] and the Five Chair to Stand test (5CS)[22] to evaluate physical function. In the 10-m walking test, participants walked at their usual speed over a distance of 10 m. The time was recorded to yield 10-m walking speed. In the TUG, participants were instructed to stand up from a standard chair, walk 3 m and back, and sit down. The task was timed for speed. In the 5CS, participants were asked to stand up and sit down five times as fast as possible; the time was recorded. Each of the three tests was assessed once per participant using a stopwatch.

The MMSE, a standard test in cognitive aging research used to assess mental status, was administered to evaluate global cognitive function.[16] Modified versions of the logical memory subtest from the Wechsler Memory Scale Revised (WMS-R) were used to assess memory.[23] In the logical memory subtest, two short stories are read aloud to for immediate (LM-I; maximum score 50) and delayed (after 30 minutes; (LM-II; maximum score 50) recall. The Trail-Making Test (TMT) was administered as a test of executive function, divided attention, and cognitive flexibility.[24] The test is divided into two parts; Part A tests visual scanning and includes a numbered connect-the-dots task, and Part B measures cognitive flexibility with a more-complex connect-the-dots task that includes alternating letters and numbers. The time required to complete each task was recorded, with longer time indicating worse performance. Data were analyzed using a difference score between Parts A and B, ΔTMT, calculated as the difference between the times taken for each part (Part B–A).[25]

Image Acquisition

Whole-brain imaging was performed using a MRI scanner (3.0-Tesla Magnetom Verio, Siemens, Erlangen, Germany). A T2*-weighted echo planar imaging (EPI) sequence sensitive to blood oxygenation level–dependent contrast with 2,000-ms repetition time (TR), 25-ms echo time (TE), 75° flip angle, 64 × 64 acquisition matrix, 224-mm field of view, 3.5 mm^2 in-plane resolution, and 39 axial slices with a slice thickness of 3.5 mm was used for functional imaging. A high-resolution structural image was also acquired using a T1-weighted magnetization-prepared rapid-acquisition gradient echo pulse sequence (voxel size 1 mm^3). Firm padding was placed around the head of each participant to restrict head motion. The visual stimuli were projected onto a screen, and participant responses were collected using a MRI-compatible response box. The EPI images were acquired during the visual short-term memory task in two consecutive rungs (one for face memory and one for location memory, see below). The first five scans in each run were discarded to compensate for T1 equilibration effects.

fMRI Experimental Protocol

During fMRI scanning, based on a previous study,[26] participants performed the n-back task (n = 1, 0) for the location and face stimuli created.[27] Only 0- and 1-back tasks were used in the present study because 2- or 3-back tasks were thought to be too cognitively demanding for older adults. Because the memory effort for the 1-back task is low, the results of the present study should be interpreted with caution. The visual short-term memory tasks for face and location were conducted in separate fMRI runs. In the 1-back task, participants were required to monitor a series of stimuli (single dot location or faces) and to indicate whether the stimulus was the same as that presented in the previous trial. In the location 0-back task, participants were required to monitor a stimulus and to indicate whether it was located in the center of the screen. In the face 0-back task, participants were required to indicate the sex of a face stimulus. In the rest phase, participants were required to gaze at a fixation cross located in the center of the screen. The location stimuli were made up of a single black dot, which was presented in a randomly designated location. The face stimuli were made up of neutral faces of young Japanese people (university students), with an equal number of male and female faces. The stimulus duration and the interstimulus interval for each task were each 2 seconds. Each of the three conditions (1- and 0-back tasks and rest) was conducted in separate blocks. Each block, which had a duration of 32 seconds (8 trials for 1- and 0-back tasks), was presented four times (a total of 12 blocks), and there were equal numbers of each condition within the block. For the face and location tasks, the order of the 12 blocks was counterbalanced across participants.

Statistical Analysis for Behavioral Data

Baseline characteristics were compared between the EG and CG groups using the Student *t*-test and the chi-square test. The intervention effects on all outcome measures except for brain activation were determined using two-way repeated-measures analyses of variance (ANOVAs) with group (EG, CG) as a between-subject factor and time (pre- and postintervention) as a within-subject factor. Data were entered and analyzed using SPSS Windows version 20.0 (SPSS, Inc., Chicago, IL). For all analyses, $P < .05$ was considered statistically significant.

Image Preprocessing and Statistical Analysis for MRI Data

MRI data were analyzed using Statistical Parametric Mapping 8 (Wellcome Department of Imaging Neuroscience, London, UK). All of the functional images were spatially

realigned to the first functional image to correct for head motion. The resulting volumes were normalized to a standard EPI template based on the Montreal Neurological Institute reference brain (resampled voxel size 2 mm^3). The normalized images were smoothed using an isotropic 8-mm full-width-at-half-maximum Gaussian kernel. A high-pass filter of 1/128 Hz was used to remove low-frequency noise, and a first-order autoregressive model was used to correct temporal autocorrelation.

The fMRI data were analyzed using the blocked design. Activated voxels in each experimental condition were identified using a statistical model containing a boxcar function convolved with a canonical hemodynamic response function. The experimental conditions consisted of a 1-back task, a 0-back task, and rest. In addition to analyzing the face and location conditions, the fMRI data were also analyzed by combining two tasks to maximize the statistical power. Linear contrasts were used to obtain participant-specific estimates for each effect. The brain activation associated with visual short-term memory was analyzed using the contrast of the 1- versus 0-back task. These estimates were then entered into a second-level analysis that treated the participant as a random effect. To identify regions in which brain activation associated with visual short-term memory increased or decreased after the 12-week intervention, brain activation before the intervention was compared with that after intervention in the EG using two-sample *t*-tests. The statistical threshold was set at $P < .001$ (uncorrected for multiple comparisons, cluster size >10 voxels).

The MarsBaR[28] software was also used to extract the signal changes of regions identified in the analysis described above. The signal changes were averaged across all voxels in a given cluster. The group-by-time interactions in the signal changes were determined using two-way repeated-measures ANOVAs using SPSS.

RESULTS

Overall, 70 participants were screened, 52 (74.3%) of whom met the inclusion criteria, agreed to participate, and were enrolled in the study; four of these were removed on the basis of the exclusion criteria, two with a MMSE score less than 24, one with apparent brain damage on structural MRI, and the other with missing fMRI signals, leaving 48 participants to complete the 12-week intervention phase and the postintervention assessment: 24 in the EG and 24 in the CG (Figure 1).

The baseline characteristics of both groups were well matched, and there were no significant differences in any variables between the groups at baseline, with the exception of reaction time in the 0-back tasks (Table 1). Twelve exercise sessions were scheduled during the intervention phase, and all were performed. Median adherence was 91.7% (25th–75th percentile 83.3–100%) in the EG over the 12 weeks. Physiotherapists monitored for adverse events; there were none.

Change in Average Daily Steps

Average daily steps increased in the EG by 54.1% (from 7,266 ± 3,001 to 11,189 ± 5,823) during the study period but not in the CG (from 6,269 ± 1,885 to 5,692 ± 1,654). There was a significant group-by-time interaction ($F = 30.2$, $P < .001$; Table 1). Median adherence for recording the step counts was 100% (25th–75th percentile 99.0–100%) in the EG over the 12 weeks.

Effect of Intervention on Physical and Cognitive Functions

There were significant group-by-time interactions in physical function, with EG participants having greater improvements in walking speed ($F = 9.37$, $P = .004$) and 5CS time ($F = 11.2$, $P = .002$) but not TUG time (Table 1).

There were significant group-by-time interactions in cognitive function, with EG participants having greater improvements in memory (WMS-LM I: $F = 7.44$, $P = .009$; WMS-LM II: $F = 7.80$, $P = .008$) and executive (ΔTMT: $F = 6.05$, $P = .018$) function. There was no group-by-time interaction for MMSE score (Figure 2, Table 1).

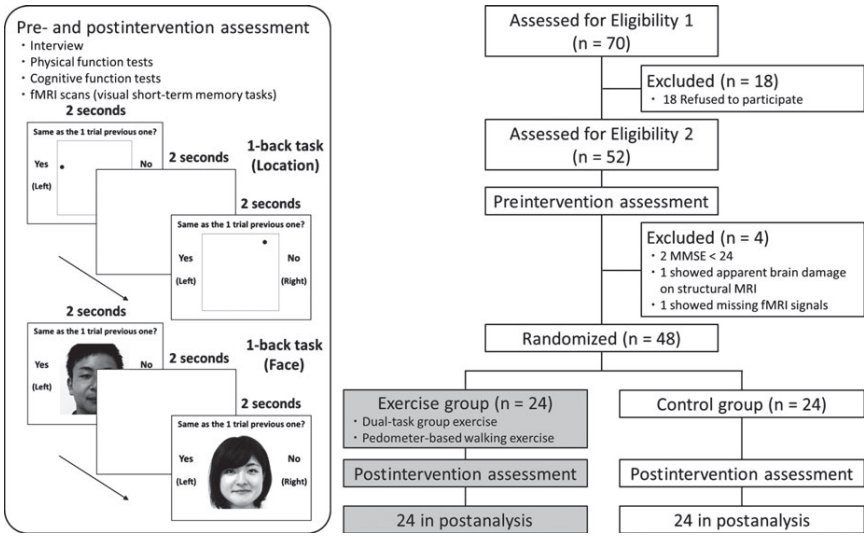

Figure 1. Flowchart of distribution of participants throughout the trial. fMRI = functional magnetic resonance imaging; MMSE = mini mental state examination.

Table 1. Participant Baseline Characteristics and Outcome Measures Before and After the Intervention

Characteristic and Outcome Measure	Exercise Group, n = 24	Control Group, n = 24	Baseline Difference *P*-Value	Group × Time Interaction	
				F-Value	*P*-Value
Age, mean ± SD	73.0 ± 4.8	73.5 ± 5.6	.76		
Female, n (%)	11 (45.8)	11 (45.8)	>.99		
Body mass index, kg/m^2, mean ± SD	21.0 ± 2.4	21.2 ± 2.9	.81		
Education, years, mean ± SD	12.2 ± 2.2	13.0 ± 2.5	.25		
Number of medications taken, mean ± SD	2.08 ± 1.91	2.13 ± 2.2	.94		
Physical function, mean ± SD					
Walking speed, m/s					
Before	1.33 ± 0.20	1.28 ± 0.14	.32		
After	1.40 ± 0.19	1.27 ± 0.13		9.37	.004
Timed Up and Go Test, seconds					
Before	6.79 ± 1.10	6.47 ± 1.23	.34		
After	6.54 ± 1.02	6.32 ± 1.17		0.15	.70
Chair stand test, seconds					
Before	7.46 ± 1.50	7.55 ± 2.06	.87		
After	6.88 ± 1.26	7.85 ± 2.14		11.2	.002
Cognitive function, mean ± SD					
Mini-Mental State Examination range (0–30)					
Before	27.4 ± 1.8	27.9 ± 2.0	.36		
After	28.2 ± 1.6	27.7 ± 2.3		1.90	.17
Wechsler Memory Scale logical memory subtest					
I					
Before	17.3 ± 4.5	20.0 ± 7.7	.14		
After	22.0 ± 5.9	21.3 ± 7.8		7.44	.009
II					
Before	12.8 ± 5.3	14.9 ± 7.9	.28		
After	18.0 ± 6.3	16.3 ± 8.0		7.80	.008
Change in Trail-Making Test, seconds					
Before	43.6 ± 26.1	37.9 ± 20.7	.41		
After	30.4 ± 16.1	41.5 ± 30.7		6.05	.02
Daily steps, mean ± SD					
Before	7,266 ± 3,001	6,269 ± 1,885	.18		
After	11,189 ± 5,823	5,692 ± 1,654		30.2	<.001
Correct responses, mean ± SD					
0-back (face + location), %					
Before	96.9 ± 3.0	97.5 ± 2.0	.42		
After	97.5 ± 3.8	98.7 ± 2.8		0.31	.58
1-back (face + location), %					
Before	90.2 ± 9.8	92.9 ± 5.1	.23		
After	94.3 ± 4.8	95.9 ± 3.3		0.29	.60
0-back (face), %					
Before	97.0 ± 2.5	97.3 ± 3.2	.76	0.16	.69
After	97.4 ± 2.2	97.3 ± 2.8			
1-back (face), %					
Before	87.8 ± 11.4	90.0 ± 7.0	.42	0.44	.51
After	94.3 ± 5.8	94.8 ± 4.5			
0-back (location), %					
Before	96.9 ± 4.2	97.8 ± 2.5	.37	0.05	.83
After	97.5 ± 3.8	98.7 ± 2.8			
1-back (location), %					
Before	92.6 ± 9.8	95.8 ± 4.7	.15	0.04	.84
After	94.2 ± 7.3	97.0 ± 3.4			
Reaction time, mean ± SD					
0-back (face + location), milliseconds					
Before	1,025 ± 109	1,122 ± 132	.009	0.68	.41
After	942 ± 148	1,014 ± 126			
1-back (face + location), milliseconds					
Before	1,181 ± 213	1,224 ± 179	.44	0.25	.62
After	1,118 ± 184	1,148 ± 157			

(Continued)

Table 1 (Contd.)

Characteristic and Outcome Measure	Exercise Group, n = 24	Control Group, n = 24	Baseline Difference *P*-Value	Group × Time Interaction	
				F-Value	*P*-Value
0-back (face), milliseconds					
Before	1,026 ± 93	1,120 ± 140	.009	0.90	.35
After	978 ± 142	1,037 ± 130			
1-back (face), milliseconds					
Before	1,207 ± 235	1,290 ± 211	.21	1.13	.29
After	1,155 ± 187	1,191 ± 175			
0-back (location), milliseconds					
Before	1,028 ± 164	1,125 ± 151	.04	0.16	.69
After	908 ± 166	991 ± 140			
1-back (location), milliseconds					
Before	1,154 ± 220	1,159 ± 189	.93	0.34	.56
After	1,081 ± 203	1,106 ± 163			

SD = standard deviation.

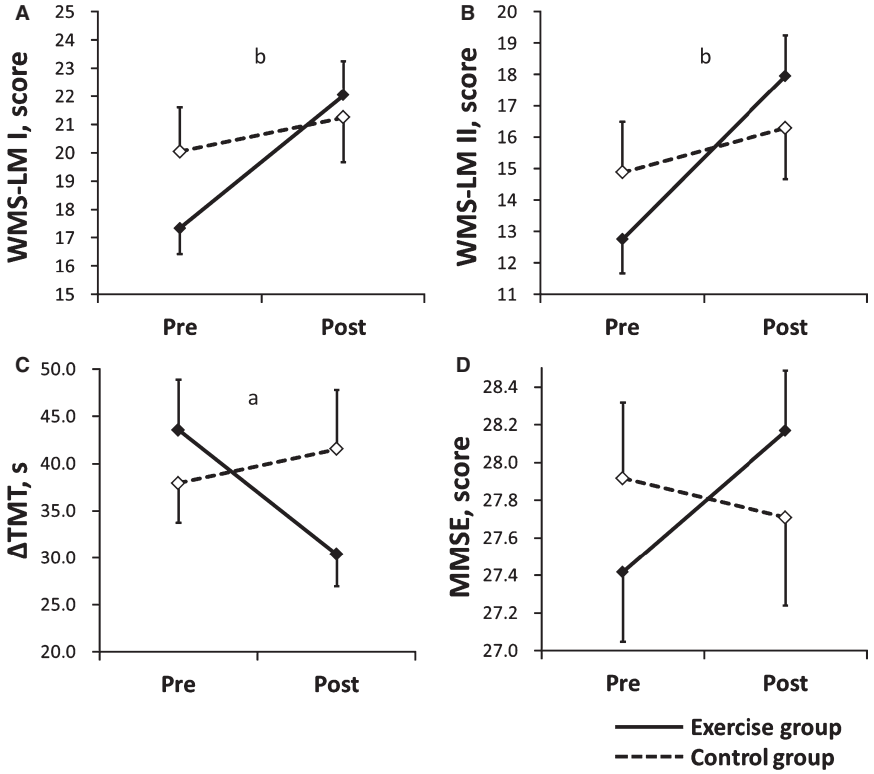

Figure 2. Group-by-time interactions in the cognitive functions before and after the intervention. Group mean differences and standard errors for Wechsler Memory Scale Revised logical memory subtest (WMS-LM) (A) I and (B) II, (C) Trail-Making Test Part A–B (ΔTMT), and (D) Mini-Mental State Examination (MMSE). $P <$ [a].05, [b] .01.

Effect of Intervention on Brain Activation Associated with Visual Short-Term Memory

There was no significant group-by-time interaction for visual short-term memory performance (face, location, face + location) after the intervention phase (Table 1), perhaps because of a ceiling effect.

The fMRI analysis showed that decreased brain activation was associated with each of the face and location tasks in several brain regions in the EG (Table 2). Although these results indicate that the exercise intervention might affect different neural networks (depending on the type of stimuli), these results were not a priori hypothesized, and these results are therefore not further discussed. After the intervention phase in the EG group, it was found that none of the regions showed significantly increased brain activation in association with the face and location tasks.

Table 2. Regions Showing Decreased Activation Associated with Visual Short-Term Memory After the Intervention

Region (Brodmann's Area)	Montreal Neurological Institute Coordinates			*Z*-Value	Cluster Size
	x	*y*	*z*		
1–0 back (face + location)					
Left superior frontal gyrus (9)	−20	48	34	3.84	108
Right thalamus	6	−20	−2	3.52	51
Right superior frontal gyrus (10)	24	60	14	3.46	17
1–0 back (face)					
Right thalamus	2	−16	−4	3.84	35
1–0 back (location)					
Left superior temporal gyrus (22)	−50	10	−8	3.61	29
Left parahippocampal gyrus (36)	−38	−32	−16	3.57	23
Right superior temporal gyrus (38)	42	6	−22	3.42	13

$P < .001$ uncorrected, cluster size >10 voxels.

When combining the data from the two tasks, decreased brain activation was found to be associated with visual short-term memory in several brain regions, including the bilateral prefrontal cortex in the EG after intervention (Figure 3, Table 2), whereas no region showed significantly increased brain activation. The effects observed in the prefrontal cortex did not survive correction for multiple comparisons ($P < .001$ uncorrected, $k > 10$ voxels) and should therefore be interpreted with caution. Nevertheless, the fact that these effects were bilateral and consistent with a strong a priori hypothesis reduces the likelihood that they were due to chance. The region of interest analysis revealed that there were significant group-by-time interactions in the signal changes in the right ($F = 10.8$, $P = .002$) and left ($F = 7.71$, $P = .008$) superior frontal gyri (Figure 3). Although the interaction effect observed in the right superior frontal gyrus aligned with the prediction, greater activation during the 0-back task after the intervention phase drove the interaction in the left superior frontal gyrus. Therefore, the findings in the left superior frontal gyrus prevent us from drawing firm conclusions and should be interpreted cautiously. In the right superior frontal gyrus, the interaction was also observed for the face condition ($F = 7.71$, $P = .008$) but not for the location condition ($F = 0.77$, $P = .38$). In the left superior frontal gyrus, the interactions were also observed for the face ($F = 3.52$, $P = .048$) and location ($F = 3.81$, $P = .047$) conditions. The region of interest analyses to test a group-by-time interaction were performed independently of the whole-brain Statistical Parametric Mapping subtraction analysis (after vs before intervention) for the EG. Thus, the analysis successfully avoided the problems associated with double dipping.[29]

DISCUSSION

A 12-week multimodal exercise program with DT and walking exercises improved memory and executive function and led to decreased brain activation associated with short-term memory. These findings suggest that physical and cognitive exercise may improve the efficiency of brain function and thereby cognitive performance.

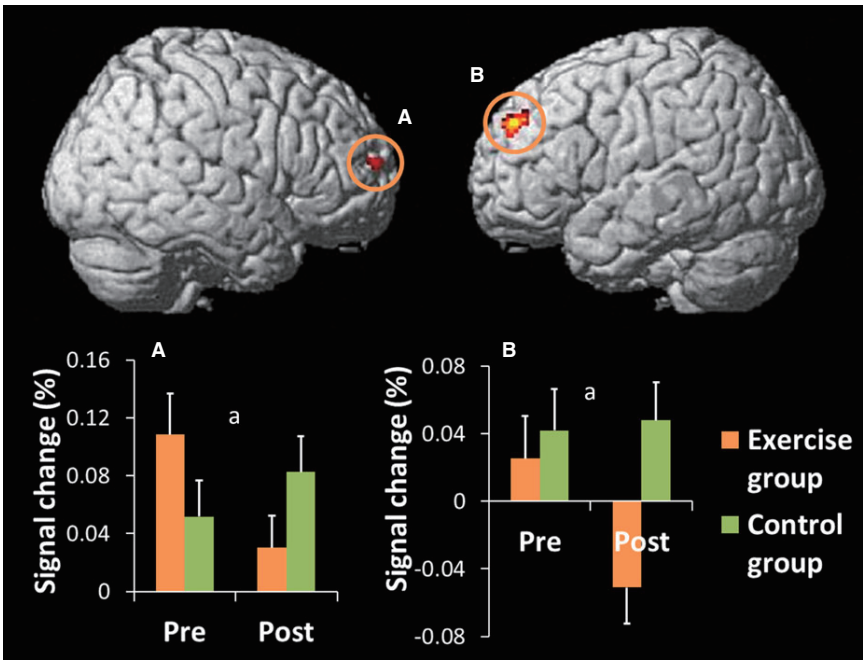

Figure 3. Bilateral prefrontal cortex showing decreased activation associated with visual short-term memory after intervention. The signal changes in these regions showed significant group-by-time interactions. Group mean differences and standard errors are shown. (A) Right and (B) left superior frontal gyrus. $P < {}^{a}.01$.

Participants in the EG had significant improvements in memory and executive function as well as physical performance. Physical activity alone[5–7] and combined cognitive and exercise training[9] can improve cognitive function in older adults. The results of this study support and expand these previous results. The physical and cognitive exercise program was performed for 12 weeks and involved changes in cognitive load using DT stimulation. Of previous studies that used physical and cognitive exercise interventions for 12 or fewer weeks,[10,30,31] only one whose participants exhibited normal cognition[10] showed positive effects on working memory and memory function. Short-term multimodal exercise with DT training could lead to cognitive improvement only in cognitively healthy elderly individuals. In the current study, EG participants performed daily walking exercise in addition to DT training; they also significantly increased their daily steps over the 12 weeks. Furthermore, there were significant correlations between percentage change in daily steps and percentage change in memory function in the EG (WMS-LM II: correlation coefficient = 0.622, $P = .001$). A previous study also indicated that physical activity and behavioral intervention improved memory and global cognitive function in older adults.[32] Because few studies have indicated cognitive improvements induced by short-term aerobic exercise alone,[5–7] the positive results in the present study may be attributed to the addition of walking to everyday life and DT training.

Despite similar pre- and postintervention task performance on the 0- and 1-back task (possibly due to a ceiling effect), it was found (on fMRI) that decreased brain activation was associated with short-term memory in the prefrontal cortex after the intervention, regardless of the type of stimulus. This finding can be interpreted as a marker of improved neural efficiency, given that a smaller amount of energy (prefrontal activity) was needed to perform the same amount of work (n-back task) after the intervention. The logic of neural efficiency (decreased activation at comparable performance levels) has been used in several previous studies in which performance was similar between groups but activation decreased in the experimental group.[33,34] This study hypothesized that multimodal exercise (DT training) would affect the efficiency of neural circuitry during the short-term memory task. It may have been that the higher cognitive loads that the DT exercise required resulted in reduced effort and improved brain activation during the short-term memory task.

Elderly adults with MCI or at risk of dementia tend to have greater brain activation than cognitively healthy elderly adults during interference[35,36] and memory[37] tasks, likely due to more-extensive, stronger cortical recruitment in task-related regions.[38] The compensation-related use of neural circuits hypothesis[39] assumes greater recruitment of neural resources at low levels of cognitive load in older adults than in younger adults, with a loss or reversal in age-related differences in compensatory mechanisms at higher levels of load. A similar difficulty-related reversal would also be observed in cognitively high- and low-risk older adults. The effect of physical exercise or cognitive training on task-related brain activation in cognitively healthy elderly adults has varied according to previous results.[40,41] One study found that DT training led to decreased activation in the bilateral dorsolateral prefrontal cortex and the right ventrolateral prefrontal cortex and increased activation in the left ventrolateral prefrontal cortex.[42] Although the results of the current study support the finding of decreased activation in the bilateral dorsolateral prefrontal cortex, it may be that the exercise training affects the asymmetric change of brain activation depending on the brain regions. Another study also reported that a multimodal intervention led to increased brain activation associated with interference tasks in cognitively high-risk older adults,[43] which may indicate that the effects of the exercise on brain activation differ according to the subject's cognitive level and the type of cognitive task. In the present study, it is likely that the cognitive health of participants and the low cognitive load of the fMRI task after the multimodal exercise were important factors in the decreased brain activation associated with improved cognitive performance. Further studies are necessary to investigate the effect of similar exercise on brain activation in elderly individuals with MCI or AD.

There were several limitations to this study. First, this trial was not double blinded. Second, a follow-up after the intervention was not arranged, so any longitudinal effects of the intervention remain unknown. Third, the control groups were not arranged to have only one component (physical or cognitive exercise) of the multimodal treatment. It is not known whether one or both components were necessary for the observed changes. Fourth, the greater social contact of the EG was not controlled for. Social engagement is known to affect cognitive functioning, and the social engagement in addition to physical activity may have partially affected the EG.

CONCLUSION

A 12-week physical and cognitive exercise program can improve the efficiency of brain activation in older adults; this result is consistent with improvements observed in memory and executive function. Future studies are needed to examine the longitudinal effect of the intervention and whether this program can be used to prevent the onset of dementia.

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Author Contributions: Nishiguchi, Yamada: study concept, participant recruitment, analysis, writing the manuscript. Sekiyama, Abe: study concept and design, participant recruitment, writing the manuscript. Tanigawa,

Kawagoe: acquisition, analysis, interpretation of data. Suzuki, Otsuka, Nakai: acquisition of data. Yoshikawa, Aoyama, Tsuboyama: writing the manuscript. All authors read and approved the final manuscript.

Sponsor's Role: None.

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資料 11：
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Original Study

Mail-Based Intervention for Sarcopenia Prevention Increased Anabolic Hormone and Skeletal Muscle Mass in Community-Dwelling Japanese Older Adults: The INE (Intervention by Nutrition and Exercise) Study

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Keywords:
Sarcopenia
frailty
walking
nutrition
older adults

A B S T R A C T

Objective: The aim of the Intervention by Nutrition and Exercise (INE) study was to investigate the effects of a mail-based intervention for sarcopenia prevention on muscle mass and anabolic hormones in community-dwelling older adults.
Design: A cluster-randomized controlled trial.
Setting and Participants: This trial recruited community-dwelling adults aged 65 years and older in Japan. The 227 participants were cluster randomized into a walking and nutrition (W/N) group (n = 79), a walking (W) group (n = 71), and a control (C) group (n = 77). We analyzed the physical and biochemical measurements in this substudy.
Intervention: Six months of mail-based intervention (a pedometer-based walking program and nutritional supplementation).
Measurements: The skeletal muscle mass index (SMI) using the bioelectrical impedance data acquisition system, biochemical measurements, such as those of insulinlike growth factor (IGF-1), dehydroepiandrosterone sulfate (DHEA-S), and 25-hydroxy vitamin D (25[OH]D), as well as frailty, were assessed by the Cardiovascular Health Study criteria.
Results: Participants in the W/N and W groups had significantly greater improvements in SMI, IGF-1, and 25(OH)D ($P < .05$) than those in the C group. Participants in the W/N group had significantly greater improvements in DHEA-S ($P < .05$) than in the other groups. These effects were more pronounced in frail, older adults.
Conclusion: These results suggest that the mail-based walking intervention of the remote monitoring type for sarcopenia prevention can increase anabolic hormone levels and SMI in community-dwelling older adults, particularly in those who are frail.

Sarcopenia is the age-dependent loss of skeletal muscle mass.[1] In 2014, the Asian Working Group for Sarcopenia recommended using the presence of both low muscle function and low muscle mass to diagnose sarcopenia.[2] Several epidemiologic studies have shown that sarcopenia is highly prevalent and a serious problem in older adults.[3,4] In addition, frailty is strongly associated with sarcopenia. Frailty is also highly prevalent with advanced age and is considered to be characterized by an impaired state of health with mortality.[5]

The mechanism underlying sarcopenia and frailty remains unclear. However, it may be related to the age-related loss of skeletal muscle mass due to multifactorial processes, such as a sedentary life, malnutrition, and changes in hormone levels.[6] Additionally, the age-dependent decrease in anabolic hormones, such as sex hormones and growth hormones, can result in increased skeletal muscle

The authors declare no conflicts of interest.

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breakdown.[7,8] By contrast, age-dependent increases in inflammatory cytokines, such as tumor necrosis factor alpha and interleukin-6 (IL-6), may lead to skeletal muscle mass loss.[9]

A previous study reported that physical exercise can effectively increase anabolic hormone levels, such as those of testosterone and insulinlike growth factor (IGF-1). Several studies have also shown that testosterone is increased by resistance training.[10,11] Moreover, the dehydroepiandrosterone (DHEA) and IGF-1 levels showed a good correlation.[12]

The American College of Sports Medicine (ACSM) Position Stands indicate that usual walking for older adults corresponds approximately to high-intensity exercise for younger people.[13] Additionally, older adults exhibited greater activation of leg muscles for usual walking than young adults.[14] Furthermore, the ACSM reports that exercise with 40% to 50% of 1 repetition maximum for inactive older adults can improve muscle strength.[15] Therefore, it is possible that continuous walking can improve the muscle function in older adults. Indeed, body composition may be improved by light-to-moderate-intensity exercise, such as walking, in older adults.[16] The pedometer-based walking program in older adults also showed a significant increase in physical activity and physical function.[17,18]

The combination of physical exercise and nutritional supplementation is more effective in improving body composition and physical function than physical exercise by itself. Resistance training and amino acid supplementation, protein, β-hydroxy β-methylbutyric acid, or vitamin D together can improve muscle mass.[19–23] In addition, a more recent study showed that resistance training with a protein-enriched diet can effectively increase lean tissue mass and reduce IL-6 in older women.[24]

However, sarcopenia is highly prevalent in community-dwelling older adults (approximately 10%–20%), and there are several limitations in group-intervention programs. Therefore, we have developed the mail-based walking intervention for sarcopenia prevention (pedometer-based walking program and nutritional supplementation). Many older adults can participate in the intervention program at the same time in this program because it is a remote monitoring type. The aim of the Intervention by Nutrition and Exercise (INE) study was to investigate the effects of a mail-based intervention for sarcopenia prevention on muscle mass and anabolic hormones in community-dwelling older adults. This intervention of a remote monitoring type is the combination of a stepwise approach to increase physical activity and nutritional supplementation. In addition, we examined the relationship between frailty and trainability for this intervention program.

Methods

Participants

Ine-cho is a small town located in the northern part of Kyoto prefecture. The population and aging rate in Ine-cho are 2185 and 42%, respectively. Participants were recruited by an advertisement in the local press and in a poster. The following criteria were used to screen the participants in an initial interview: aged 65 years and older, community-dwelling, and able to walk independently (or with a cane). The exclusion criteria were severe cardiac, pulmonary, diabetes, or kidney disease or musculoskeletal disorders; comorbidities associated with a greater risk of falls, such as Parkinson disease and stroke; severe cognitive impairment (Mini-Cog <3)[25]; and the use of psychotropic drugs or regular supplementation of amino acids and vitamin D in the last 12 months. Written informed consent was obtained from each participant in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 2000. The trial registration number is JMA-IIA00122.

Cluster Randomization

We used a 3-arm, cluster-randomized, controlled trial, and autonomous communities were randomly assigned to the walking and nutrition (W/N) group, walking (W) group, and control (C) group. Eleven autonomous communities were randomly allocated to each group and 79, 71, and 77 participants were enrolled in the W/N group, W group, and C group, respectively.

Intervention

Exercise program

Participants randomized to the W/N group and W group received pedometer-based walking programs for 6 months. A valid, accurate, and reliable pedometer, the Yamasa EX-300 (Yamasa Tokei Keiki, Ltd, Tokyo, Japan), was used to measure free-living step counts.[26]

We used a stepwise approach to increase physical activity in which the participants were instructed to increase the number of daily steps by 10% each month. In addition, the participants walked with an ankle weight (0.5 kg) at their own discretion. Written activity logs were averaged monthly to determine whether the participants were achieving their step goal. The intervention consisted of motivation for walking followed by goal setting, self-monitoring, and feedback. Participants were asked to record the step counts taken at the end of each day. A sheet for brief feedback and setting the number of daily steps was mailed to all of the participants to evaluate the recorded calendar monthly (Fig. 1).

Nutritional supplementation

Protein and a vitamin D supplement were provided every day for the participants in the W/N group for 6 months. Protein and the vitamin D supplement (200 kcal, 10.0 g of protein with branched chain amino acids 12.5 μg of vitamin D, and 300 mg of calcium [Resource PemPal Active; Nestle Japan Ltd, Tokyo, Japan]) were provided for the participants. Participants recorded the dietary supplementation and meal size per day on a calendar. The nutritional supplement was mailed to all participants monthly. Therefore, both the exercise and nutritional programs were remotely monitored by the researcher.

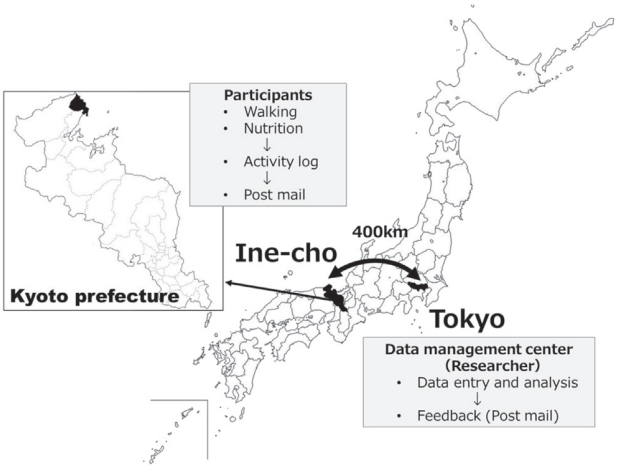

Fig. 1. Schematic representation of mail-based intervention of the remote monitoring type for sarcopenia prevention. Participants of the W/N and W groups were instructed to increase the number of daily steps by 10% each month. Protein and the vitamin D supplement were provided every day for the participants in the W/N group. Participants were asked to record the date on the calendar and steps taken at the end of each day. A sheet for brief feedback and setting the number of daily steps was mailed to all participants to evaluate the recorded calendar monthly.

Outcome Measures

Skeletal muscle mass index

A bioelectrical impedance data acquisition system (Inbody 430; Biospace Co, Ltd, Seoul, Korea) was used to determine bioelectrical impedance. This system uses electrical current at different frequencies (5, 50, and 250 kHz) to directly measure the amount of extracellular and intracellular water in the body. Participants stood on 2 metallic electrodes and held metallic grip electrodes. Using segmental body composition and muscle mass, a value for the appendicular skeletal muscle mass was determined and used for further analysis. Muscle mass was converted into the skeletal muscle mass index (SMI) by dividing by the muscle weight by height squared (kg/m^2).

Biochemical measurements

For all participants, the following 3 biomarkers were obtained: IGF-1, DHEA-S, and 25-hydroxy vitamin D (25[OH]D). Blood samples were drawn in the morning before physical exercise. The collected serum was stored at −80°C until the analysis. IGF-1 (ng/mL) was measured by immunoradiometric assay. Intra- and interassay coefficients of variance were 2.35% and 3.90%, respectively. DHEA-S (μg/dL) was measured by chemiluminescence enzyme immunoassay. Intra- and interassay coefficients of variance were 6.20% and 7.71%, respectively. Radioimmunoassay was used to measure 25(OH)D levels (ng/mL). Intra- and interassay coefficients of variance were 6.66% and 10.82%, respectively. All of the assays were performed in the same laboratory.

Definition of frailty

We defined frailty by the Cardiovascular Health Study criteria[27] with minor modifications by Shimada et al.[28]

We assessed weight loss by asking the single "yes or no" question, "Have you lost 5% or more of your body weight in the past 2 years?" Weakness was defined as a handgrip strength less than 26 kg in men and less than 18 kg in women. In the handgrip strength test, participants used a handheld dynamometer with the arm by the side of the body. The participant squeezed the dynamometer with the dominant hand using maximum isometric effort. No other body movement was allowed. The handgrip strength score was defined as the better performance of 2 trials. We assessed exhaustion by asking the single "yes or no" question, "Do you feel full of energy?" Slowness was defined as a usual walking speed less than 1.0 m/s identified in participants with a low physical performance. In the walking speed test, participants were asked to walk 11 m at a comfortable pace. A stopwatch was used to record the time required to reach the 5-m point (marked in the course). The time recorded in the 2 trials was averaged to obtain the data for the present analyses. We assessed low physical activity by the following 2 questions: "Do you engage in moderate levels of physical exercise or sports aimed at health?" and "Do you engage in low levels of physical exercise aimed at health?" Low physical activity was defined if the responses to these 2 questions were "no."

Required sample size

Several previous studies[19–23] showed that the effect size for physical exercise with nutritional supplementation on the skeletal muscle mass was approximately 0.65. Therefore, we designed the effect size of the current study to detect 0.65. With a significance level of 0.017 (0.05/3), a power of 80%, and an effect size of 0.65, 69 participants were needed in 3 groups. Accounting for a potential 10% attrition rate, a total of 228 participants were targeted for this study, a number that was sufficiently large to detect statistically significant differences.

Statistical Analysis

One-way analysis of variance (ANOVA) and post hoc test were used to test any differences in baseline measures between groups, and χ^2 test was performed on categorical variables. Bonferroni-adjusted t test was used to assess which group differed significantly from the others.

The effect of each intervention on outcome measurements was analyzed using a mixed 3 × 2 (group (W/N, W, and C group) × time (pretraining, posttraining) ANOVA. In addition, analysis of covariance (ANCOVA) with the baseline value as a covariate was used to determine the effect of the intervention on each outcome measure. ANOVA was used to test any differences in percentage changes of outcome measurements between the groups. Bonferroni-adjusted t test was used to assess which group differed significantly from the others.

For stratified analysis according to the level of frailty, we divided the cohort into 2 groups: nonfrail and frail. We compared the trainability in frailty-stratified and unstratified analyses for each outcome measure.

The data were managed and analyzed using SPSS (Statistical Package for the Social Sciences, Windows version 21.0; SPSS, Inc, Chicago, IL). A P value less than .05 was considered to indicate statistical significance for all analyses.

Results

Overall, 248 people were screened, and 227 (91.5%) who met the inclusion criteria for the trial and agreed to participate were enrolled (Figure 2). Most of the participants who were excluded had diabetes mellitus or severe musculoskeletal disorders. Twenty-one older adults who were eligible for the study withdrew from their participation after screening. Of 227 individuals selected for the study, 222 (97.8%) completed the 6-month follow-up, 77 in the W/N group (97.5%), 70 in the W group (98.6%), and 75 in the C group (97.4%). The baseline characteristics in the W/N, W, and C groups were comparable and well matched (Table 1). The median relative adherence was 80% (25th–75th percentile, 67%–92%) with nutritional supplementation; however, all of the participants completed the step count record during this study. No fall incident or health problems, including cardiovascular or musculoskeletal complications, occurred during the study period. A minor problem observed in both intervention groups was muscle aches in the first intervention month. This was easily managed by adjusting the intervention, and the muscle aches decreased over the course during the intervention. In both the W/N and W groups, the average daily steps were increased by 35.7% (from 4471 ± 2370 to 6067 ± 2967) and 42.1% (from 3795 ± 1913 to 5394 ± 2197), respectively ($P < .01$).

Significant time effects were found for IGF-1, DHEA-S, and 25(OH)D ($P < .05$) (Table 2). The pre- and postintervention group statistics and Group × Time interactions are shown in Table 2. Significant differences were observed among the 3 groups for SMI, IGF-1, and 25(OH)D with significant Group × Time interactions using ANOVA. Similarly, significant differences were observed among the 3 groups for SMI and 25(OH)D with significant Group × Time interactions using ANCOVA. Participants in the W/N and W groups had significantly greater improvement in SMI, IGF-1, and 25(OH)D ($P < .05$), but not in the C group (Table 2). Participants in the W/N group had significantly greater improvements in DHEA-S ($P < .05$) but not in the other 2 groups (Table 2).

We next analyzed nonfrail older adults. In this group, we also found significant time effects for IGF-1, DHEA-S, and 25(OH)D ($P < .05$) (Table 2). Significant differences were observed among the 3 groups for IGF-1 and 25(OH)D with significant Group × Time interactions. Participants in the W/N and W groups had significantly greater improvements in IGF-1 and 25(OH)D ($P < .05$) but not in the C group (Table 2).

We also performed subgroup analysis in frail older adults. In this subgroup, we found significant time effects for IGF-1 and 25(OH)D

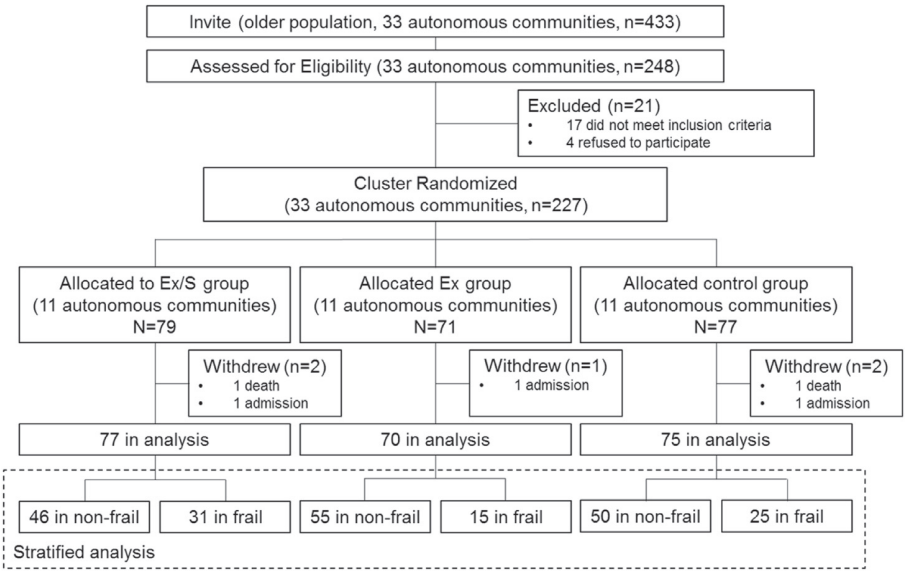

Fig. 2. A flowchart showing the distribution of participants throughout the trial.

($P < .05$) (Table 2). Significant differences were observed among the 3 groups for SMI, IGF-1, DHEA-S, and 25(OH)D with significant Group × Time interactions. Participants in the W/N and W groups had significantly greater improvements in SMI ($P < .05$) but not in the C group (Table 3). Participants in the W/N group had significantly greater improvements in IGF-1 and 25(OH)D ($P < .05$) but not in the others (Table 3).

Discussion

The 6-month mail-based walking intervention along with nutritional supplementation is an effective means to prevent sarcopenia in community-dwelling older adults. We have shown that participants in the W/N and W groups, but not in the C group, showed a significant increase in SMI, IGF-1, and 25(OH)D. The W/N group showed the largest increase in DHEA-S among the 3 groups. These results were more pronounced in frail older adults. These results suggested that the combination of walking exercise and nutritional supplementation may be beneficial for community-dwelling older adults to prevent and treat sarcopenia. In particular, this intervention program was useful for the muscle mass increase in frail older adults.

In this 6-month mail-based intervention for community-dwelling older adults, we have shown that the average daily steps were successfully increased by 35.7% and 42.1% in the W/N and W groups, respectively. We showed that the pedometer-based behavioral change program was very effective for the improvement of average daily steps. Goal setting and self-monitoring of behavior are crucial for behavioral change. In this study, pedometers and a record sheet

Table 1
Baseline Characteristics of the Study Participants in Each Group

	Walking + Nutrition		Walking		Control		F Value	*P* Value
	Mean	SD	Mean	SD	Mean	SD		
Overall	n = 77		n = 70		n = 75			
Age	76.3	5.9	75.8	5.2	75.7	6.5	0.38	.687
Height	153.5	8.4	152.8	8.3	155.1	9.3	2.67	.071
Weight	52.6	8.8	53.2	9.3	55.8	9.9	**4.49**	**.012****a*
BMI	22.3	3.2	22.7	3.2	23.1	2.8	2.08	.127
Women, n %	50	64.9%	48	68.6%	44	58.7%		.452
Nonfrail	n = 46		n = 55		n = 50			
Age	75.2	5.6	75.9	5.1	75.3	6.8	0.32	.724
Height	154.4	8.8	152.0	8.7	155.0	9.4	2.58	.078
Weight	53.6	8.9	52.9	9.5	55.3	9.3	1.52	.220
BMI	22.5	2.9	22.8	3.2	22.9	2.4	0.50	.609
Women, n %	31	67.4%	40	72.7%	29	58.0%		.452
Frail	n = 31		n = 15		n = 25			
Age	78.1	5.7	75.7	5.8	76.4	6.2	1.63	.199
Height	152.2	7.8	155.3	6.2	154.7	9.1	1.52	.222
Weight	51.3	8.6	54.5	8.7	55.7	10.1	2.94	.056
BMI	22.1	3.6	22.6	3.1	23.2	3.2	1.31	.272
Women, n %	19	61.3%	8	53.3%	15	60.0%		.452

BMI, body mass index.
**P* < .01.
a, W/N group versus C group.

Table 2
SMI and Serum Biomarkers Before and After the Intervention in the Overall, Frail, and Nonfrail Groups

	Pre		Post		2-Way ANOVA				2-Way ANCOVA	
					Time Effect		Time × Group Interaction		Time × Group Interaction	
	Mean	SD	Mean	SD	F Value	*P* Value	F Value	*P* Value	F Value	*P* Value
Overall										
SMI										
Walking + Nutrition	6.5	0.9	6.4	0.9	0.21	.65	**7.75**	**<.001****	**5.98**	**.015***
Walking	6.5	0.9	6.4	0.9						
Control	6.6	0.9	6.7	1.0						
IGF-1										
Walking + Nutrition	77.1	24.3	95.4	32.7	**105.73**	**<.001****	**9.16**	**<.001****	3.13	.078
Walking	71.6	26.7	83.6	29.1						
Control	86.7	29.4	92.7	26.8						
DHEA-S										
Walking + Nutrition	72.8	47.4	80.8	45.3	**24.54**	**<.001****	1.80	.168	1.32	.271
Walking	62.2	47.3	71.7	50.5						
Control	89.9	55.2	93.1	60.3						
25(OH)D										
Walking + Nutrition	31.0	10.3	41.0	12.4	**58.35**	**<.001****	**17.89**	**<.001****	**18.33**	**<.001****
Walking	30.1	9.8	36.7	7.1						
Control	33.5	11.8	33.3	9.8						
Nonfrail										
SMI										
Walking + Nutrition	6.4	0.9	6.5	0.9	0.82	.367	2.60	.078	2.39	.095
Walking	6.3	0.8	6.4	0.8						
Control	6.7	0.9	6.7	0.9						
IGF-1										
Walking + Nutrition	80.6	23.2	96.3	27.8	**75.59**	**<.001****	**5.30**	**.006***	**3.60**	**.030***
Walking	70.2	27.0	82.8	29.4						
Control	94.0	30.5	99.4	26.8						
DHEA-S										
Walking + Nutrition	79.2	48.3	68.7	48.7	**24.10**	**<.001****	0.33	.720	0.26	.774
Walking	65.0	47.0	56.0	42.8						
Control	100.6	64.2	93.7	58.4						
25(OH)D										
Walking + Nutrition	30.9	11.1	41.2	12.9	**43.47**	**<.001****	**11.09**	**<.001****	**10.45**	**<.001****
Walking	30.2	9.8	36.8	7.0						
Control	34.6	13.5	34.8	10.1						
Frail										
SMI										
Walking + Nutrition	6.3	0.9	6.5	0.9	0.10	.755	**5.15**	**.008****	**4.39**	**.016***
Walking	6.8	1.0	6.9	1.2						
Control	6.7	1.1	6.4	0.9						
IGF-1										
Walking + Nutrition	71.5	25.4	94.1	40.0	**22.09**	**<.001****	**4.56**	**.015****	**4.48**	**.016***
Walking	75.3	27.0	84.3	29.7						
Control	75.7	26.1	81.1	25.1						
DHEA-S										
Walking + Nutrition	79.7	45.2	83.6	40.4	2.92	.093	**3.60**	**.034***	**3.76**	**.030***
Walking	86.2	57.3	97.8	57.1						
Control	84.6	51.9	80.6	53.9						
25(OH)D										
Walking + Nutrition	31.2	9.2	40.6	11.7	**11.38**	**<.001****	**6.39**	**<.001****	**6.83**	**.002****
Walking	29.2	10.5	36.1	8.0						
Control	32.6	7.9	30.8	8.7						

*$P < .05$; **$P < .01$.

were primarily used as motivational tools, and our behavioral support seemed to have mainly affected the behavioral change toward increasing physical activity.

The W/N group showed a significant increase in the serum DHEA-S and IGF-1 levels. The W group showed a significant increase in the serum IGF-1 levels only, and a tendency for higher serum DHEA-S levels after intervention. The age-dependent decrease in anabolic hormones, such as DHEA and IGF-1, may lead to a loss of skeletal muscle mass.[7,8] However, a recent study suggested that physical activity is associated with the serum IGF-1 level, and physical activity training can effectively increase the serum IGF-1 level in premenopausal women.[29] Several studies have shown that an exercise training program greatly increases the serum DHEA levels in older adults.[10,11] In addition, the serum IGF-1 and DHEA can be maintained at a high level by long-term training in older adults.[30] The current trial shows that physical activity was increased in the W/N and W groups. Therefore, the W/N and W groups, but not the C group, showed a great increase in the IGF-1 and DHEA-S levels.

The W/N group showed the largest increase in 25(OH)D and SMI among the 3 groups. Several studies have suggested that a low 25(OH) D concentration is associated with lower muscle strength, reduced physical performance, and increased disability.[31–33] It has been shown that vitamin D supplementation may enhance muscle strength in frail older adults with vitamin D deficiency.[34] However, older adults have a high risk of inadequate protein intake,[35] and their

Table 3
Percentage Changes of Outcome Measurements in the Overall, Frail, and Nonfrail Groups

	Walking + Nutrition		Walking		Control		F Value	*P* Value
	Mean	SD	Mean	SD	Mean	SD		
Overall	n = 77		n = 70		n = 75			
Change of SMI	1.88	6.53	1.01	4.56	−1.85	6.90	**7.66**	**<.001**** *a*, *b*
Change of IGF-1	25.4	23.7	20.7	25.2	9.6	18.4	**8.03**	**<.001**** *a*, *b*
Change of DHEA-S	22.6	58.3	18.4	25.8	5.4	22.0	**3.26**	**.041*** *a*
Change of 25(OH)D	42.0	60.7	31.8	45.5	3.0	24.6	**12.50**	**<.001**** *a*, *b*
Nonfrail	n = 46		n = 55		n = 50			
Change of SMI	1.02	5.58	1.11	4.24	−0.86	5.72	2.32	.102
Change of IGF-1	21.4	20.3	22.5	25.5	8.6	17.1	**5.35**	**.006**** *a*, *b*
Change of DHEA-S	26.6	65.5	18.1	25.7	8.4	17.8	1.96	.145
Change of 25(OH)D	39.9	44.1	32.0	47.1	6.1	27.8	**7.35**	**<.001**** *a*, *b*
Frail	n = 31		n = 15		n = 25			
Change of SMI	3.16	7.66	0.64	5.76	−3.87	8.78	**5.63**	**.005**** *a*, *b*
Change of IGF-1	31.8	27.6	14.5	24.8	9.4	19.8	**4.70**	**.013**** *a*
Change of DHEA-S	15.9	44.2	19.7	27.3	−0.8	28.9	1.67	.197
Change of 25(OH)D	45.2	81.4	33.6	42.6	−5.6	16.5	**4.55**	**.015*** *a*

*$P < .05$; **$P < .01$.
a, W/N group versus C group; *b*, W group versus C group.

synthetic response to protein intake may be blunted.[36] Several studies have found a positive association between protein intake and muscle mass.[37,38] In fact, protein supplementation has been shown to augment the muscle strengthening effect of resistance exercise.[39,40] Therefore, the Society for Sarcopenia, Cahexia, and Wasting Disease (SSCWD) recently recommended the combination of exercise with protein and/or vitamin D supplementation for reducing the age-related skeletal muscle decline.[41] The results of the current study also supported the SSCWD recommendation, and the nutritional supplementation provided added benefits to those with walking exercise for increasing muscle mass.

The important point is that the effectiveness of this intervention was more pronounced in frail older adults. Recent frailty-related studies show that the frailty status is associated with muscle mass decline in older adults,[42] and regular physical activity may mitigate frailty in frail older adults.[43] Thus, it is possible that the intensity of our intervention was appropriate for frail older adults, but was low for nonfrail older adults. ACSM's recommendation is 40% to 50% of 1 repetition maximum for beginner or sedentary older adults, but the habitually exercising older adult requires 60% to 70% of 1 repetition maximum.[15]

Several limitations of the present study need to be mentioned. First, the intake of dietary food was not recorded. The nutritional supplement may have changed participants' dietary intake. Second, no follow-up after completion of the trial was conducted. Because there is a lack of evidence regarding the long-term effect of nutritional supplementation on sarcopenia treatment, this issue also needs to be addressed in future studies. Follow-up and cost-effective analyses are needed to confirm the present results and evaluate the most effective program for the prevention of sarcopenia and frailty.

In conclusion, the current study suggests that mail-based walking intervention of the remote monitoring type for sarcopenia prevention can increase anabolic hormone levels and SMI in community-dwelling older adults, particularly in frail older adults. This program is very simple and may be useful as a large population approach for the prevention of sarcopenia and frailty.

Acknowledgments

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資料 12：
J Strength Cond Res 誌発表論文

Functional Movement Screen for Predicting Running Injuries in 18- to 24-Year-Old Competitive Male Runners

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[1]*Department of Physical Therapy, Human Health Sciences, Graduate School of Medicine, Kyoto University, Kyoto, Japan; and* [2]*Japan Society for the Promotion of Science, Tokyo, Japan*

Abstract

Hotta, T, Nishiguchi, S, Fukutani, N, Tashiro, Y, Adachi, D, Morino, S, Shirooka, H, Nozaki, Y, Hirata, H, Yamaguchi, M, and Aoyama, T. Functional movement screen for predicting running injuries in 18- to 24-year-old competitive male runners. *J Strength Cond Res* 29(10): 2808–2815, 2015–The purpose of this study was to investigate whether the functional movement screen (FMS) could predict running injuries in competitive runners. Eighty-four competitive male runners (average age = 20.0 ± 1.1 years) participated. Each subject performed the FMS, which consisted of 7 movement tests (each score range: 0–3, total score range: 0–21), during the preseason. The incidence of running injuries (time lost because of injury ≤ 4 weeks) was investigated through a follow-up survey during the 6-month season. Mann-Whitney *U*-tests were used to investigate which movement tests were significantly associated with running injuries. The receiver-operator characteristic (ROC) analysis was used to determine the cutoff. The mean FMS composite score was 14.1 ± 2.3. The ROC analysis determined the cutoff at 14/15 (sensitivity = 0.73, specificity = 0.54), suggesting that the composite score had a low predictability for running injuries. However, the total scores (0–6) from the deep squat (DS) and active straight leg raise (ASLR) tests (DS and ASLR), which were significant with the *U*-test, had relatively high predictability at the cutoff of 3/4 (sensitivity = 0.73, specificity = 0.74). Furthermore, the multivariate logistic regression analysis revealed that the DS and ASLR scores of ≤3 significantly influenced the incidence of running injuries after adjusting for subjects' characteristics (odds ratio = 9.7, 95% confidence interval = 2.1–44.4). Thus, the current study identified the DS and ASLR score as a more effective method than the composite score to screen the risk of running injuries in competitive male runners.

Key Words distance runner, screening, dynamic assessment, risk factor

Introduction

The functional movement screen (FMS) is a screening tool for injury risk that assesses the movement patterns of individuals and evaluates mobility and stability comprehensively. The FMS consists of 7 component tests; each scored based on the movement patterns within the kinetic chain, asymmetries between the sides, and compensatory movements. The validity of the FMS as a predictor of injury risk has been confirmed in several studies (5,10,11,17). The study by Kiesel et al. (10) examined the relationship between the FMS and serious injury in professional football players. They revealed that professional football players with an FMS score of ≤14 were at a greater risk of serious injury than those with higher scores (10). Other studies reported similar findings in other groups, such as officer candidates (11,17) and female collegiate athletes (5).

Recently, 2 studies investigated normative values of FMS scores for runners. Loudon et al. (12) reported the normative value for running athletes and Agresta et al. (1) reported the value for healthy runners (the mean FMS composite scores were 13.1 ± 1.8 and 15.4 ± 2.4, respectively). Additionally, Agresta et al. (1) investigated the association between FMS scores and injury history. However, no prospective cohort studies have investigated the association between the FMS and running injuries. Running injuries are a serious problem for most runners, especially for competitive runners (8). Unfortunately, some runners are forced to retire from running because of serious running injuries. Previous studies reported some risk factors for running injuries, such as inadequate flexibility (24), muscle weakness and imbalance (16), and deficits in neuromuscular coordination (19). Cook et al. (6,7) stated that these factors also caused poor movement

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patterns, which were reflected in the lower score of the FMS. Thus, runners with low FMS scores might have certain risk factors for running injury and become more prone to injury. In addition, although Parchmann and McBride (18) reported that the FMS was not significantly associated with sprinting, Chapman et al. (4) revealed that a high FMS score had a positive effect on performance in elite track and field athletes in the long view. Because athletes with a higher FMS score rarely suffered from injury, they could practice continuously and improve their performance. Therefore, we hypothesized that the FMS could predict running injuries.

The receiver-operator characteristic (ROC) curve is a plot of the sensitivity vs. 1 − specificity of a screening test; this analysis is useful in determining the cutoff where the sensitivity and specificity are maximized. In previous studies, the ROC curve was used to determine the validity of the FMS as a predictor of injury risk (3,10,17). In addition, a cutoff value allows determining more easily whether a runner has a potential injury risk simply based on the FMS scores. Therefore, the aim of the current study was to determine the cutoff value and to investigate if the FMS score during preseason could be used to predict running injuries in young competitive runners during season.

Methods

Experimental Approach to the Problem

This study, using a prospective cohort design, investigated whether preseason FMS scores could predict serious running injuries during the season in 18- to 24-year-old competitive male runners. Figure 1 illustrates the process of this study in the form of a flow chart. The subjects performed the FMS at their college during preseason, February 2014. To minimize the influence of fatigue on performance, the FMS tests were conducted during the daytime on the day after a non-training day according to each team's schedule. No warm-up was included. The testing days added up to 7 days in total. After the FMS test, follow-up surveys were distributed to the subjects to investigate the incidence of running injuries during the 6-month season. The follow-up surveys were conducted twice at the end of May and August 2014 to reduce a recall bias. Statistical analyses were conducted using the data of the returned surveys. The ROC analysis determined the cutoff, and the logistic regression analysis determined if the FMS could be used for the prediction of running injuries.

Subjects

A total of 84 competitive male runners volunteered to participate in the study (mean age = 20.0 ± 1.1 years, range = 18–24 years, height = 171.6 ± 4.5 cm, weight = 57.5 ± 4.3 kg). For inclusion, subjects had to be competitive male runners belonging to collegiate track and field teams, were injury free at the time of FMS test in preseason, whose events were middle or long distance, and whose running experience exceeded 1 year. The purpose and methods of this study were explained to the subjects in detail in a verbal statement, and written informed consent was obtained from the subjects. The current study did not include athletes under the age of 18 years; thus, parental or guardian consent was not needed. This study was approved by the Institutional Review Board of Kyoto University (Approval No. E2023).

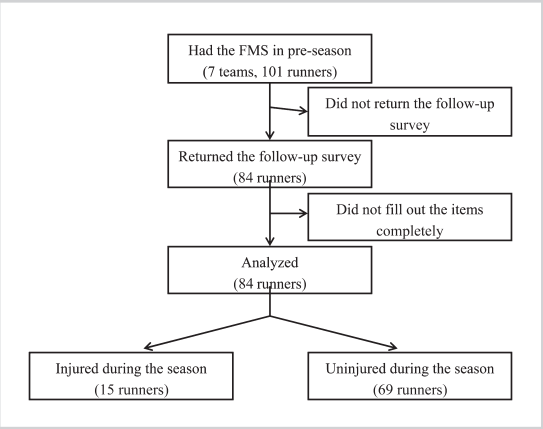

Figure 1. Flow chart illustrating the process of the study.

Procedures

Before the study, the physical therapists collecting data were instructed on the FMS evaluation method by an FMS specialist. The FMS scoring criteria were used as described by Cook et al. (6,7), and they discussed standardization of the testing.

On testing day, all subjects were questioned about their characteristics, such as age, height, weight, running experience, training sessions per week, weekly mileage, personal best time in their primary event in 2013, and injury history, by questionnaire. To allow comparison between different events, performances were normalized to a percentage of collegiate Japanese record performances (as of March 31, 2013) (4). To assess injury history, we asked the following question: "Have you ever suffered from musculoskeletal injury that was so severe that it required medical attention?" (5). Subsequently, all subjects were briefed on the FMS and were given a demonstration of the movements. After the demonstration, all subjects performed the FMS, which consisted of 7 movement tests to comprehensively assess mobility, stability, and coordination. The 7 tests were the deep squat (DS), hurdle step (HS), in-line lunge (ILL), shoulder mobility (SM), active straight leg raise (ASLR), trunk stability push-up (TSPU), and rotary stability (RS) tests. All tests were scored using standardized scoring criteria (6,7). Each movement test was scored on a 4-point scale (0–3), and the maximal FMS score that could be achieved was 21. A score of 3 was awarded for perfect form, a score of 2 was given for completing the test with compensations, a score of 1 was awarded for not completing the test accurately, and a score of 0 was given

Table 1. Interrater reliability for the functional movement screen composite score.*

Bland-Altman plot									
Intraclass correlation coefficient (2, 1)	95% CI	Fixed bias		Proportional bias					
		95% CI	Presence/ absence	Test for no correlation		Presence/ absence	*SEM*	MDC_{95}	SEP
0.98	0.93–1.00	−0.83 to 0.43	Absence	$r = -0.44$	$p = 0.90$	Absence	0.31	0.87	0.44

*CI = confidence interval; MDC = minimum difference to be considered real; SEP = standard error of prediction.

if the subjects felt any pain during the test. Each test was performed 3 times, and the highest score was used. Of the 7 tests that comprise the FMS, 5 tests (HS, ILL, SM, ASLR, and RS) were performed and scored separately for the right and left sides of the body. For these bilaterally assessed tests, the lower score was used.

After the FMS test, follow-up surveys were distributed to all subjects through each team's manager to investigate the incidence of running injuries during the 6-month season. If information was missing in the questionnaires, we asked the subjects to answer the omitted questions by contacting them through the team's managers. For the current study, the definition of running injury was a musculoskeletal injury that met the following criteria: (1) the injury occurred as a result of participating in a practice or race in track and field (trauma injuries, such as sprains, were excluded) and (2) the injury was sufficiently severe to prevent participation for at least 4 weeks; this definition was based on that used in previous studies (10,17).

Reliability

Similar to a previous study (12), interrater reliability was assessed in a subgroup of 10 subjects by 2 physical therapists. Interrater reliability was calculated for the FMS composite score using the intraclass correlation coefficient (ICC, model 2, 1). On the basis of the reliability coefficients, the standard error of measurement ($SEM = SD \times \sqrt{1-ICC}$), the minimum difference to be considered real ($MDC = SEM \times 1.96 \times \sqrt{2}$), and the standard error of prediction ($SEP = SD \times \sqrt{1-ICC^2}$) were calculated (23). The Bland-Altman analysis was performed to determine whether systematic error was present. The weighted kappa statistic was used to establish the interrater reliability for each movement test of the FMS.

Statistical Analyses

We divided the subjects into 2 groups with and without running injuries according to the follow-up survey. Comparisons between the 2 groups were made using Student's *t*-tests (for parametric continuous variables), Mann-Whitney *U*-tests (for nonparametric continuous variables), or χ^2 tests (for categorical variables). The short version of the FMS was calculated from the movement tests that were significant

Table 2. Interrater reliability for each functional movement screen component test.

Test	Kappa	Strength of agreement
Deep squat	1.000	Excellent
Hurdle step	1.000	Excellent
In-line lunge	1.000	Excellent
Shoulder mobility	1.000	Excellent
Active straight leg raise	0.831	Substantial
Trunk stability push-up	0.836	Substantial
Rotary stability	1.000	Excellent

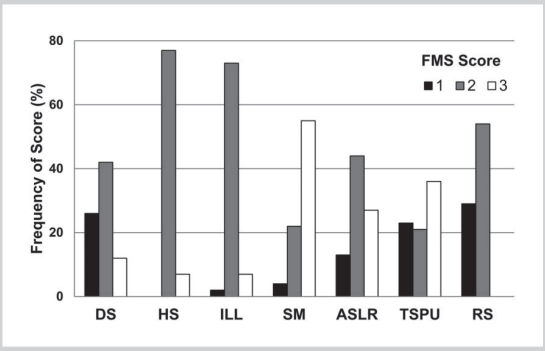

Figure 2. Distribution of scores for each functional movement screen (FMS) component test.

Table 3. Comparison of runners with and without running injuries during the season.*

Variable	Serious running injury		p
	Without ($n = 69$)	With ($n = 15$)	
Characteristics			
Age (y)†	20.1 ± 1.2	19.6 ± 0.9	0.15
Height (cm)	171.3 ± 4.3	172.7 ± 5.6	0.29
Weight (kg)	57.3 ± 4.2	58.4 ± 5.0	0.39
Running experience (y)†	6.9 ± 2.2	6.7 ± 2.4	0.64
Weekly training sessions ($d \cdot wk^{-1}$)‡	5.9 ± 0.6	5.9 ± 0.6	0.85
Weekly mileage ($km \cdot wk^{-1}$)†	80.9 ± 53.8	98.4 ± 57.3	0.26
Performance (%)	87.6 ± 4.1	88.7 ± 3.6	0.34
Injury history, *n* (%)§	34 (49.3)	8 (53.3)	1.00
FMS			
FMS total score†	14.4 ± 2.2	13.3 ± 2.7	0.10
Deep squat‡	1.8 ± 0.7	1.3 ± 0.7	0.01‖
Hurdles step‡	2.1 ± 0.3	2.0 ± 0.0	0.20
In-line lunge‡	2.0 ± 0.4	1.9 ± 0.7	0.26
Shoulder mobility‡	2.6 ± 0.8	2.5 ± 0.6	0.36
Active straight leg raise‡	2.3 ± 0.6	1.6 ± 0.5	<0.01¶
Trunk stability push-up‡	2.0 ± 1.0	2.5 ± 0.8	0.06
Rotary stability‡	1.6 ± 0.5	1.6 ± 0.6	0.97

*FMS = functional movement screen.
†Continuous data are expressed as the mean ± *SD* (tested by the student's *t*-tests).
‡Nonparametric data are expressed as the mean ± *SD* (tested by the Mann-Whitney *U*-tests).
§Categorical data are expressed as numbers (percentages) (tested by the χ^2 test).
‖$p \leq 0.05$.
¶$p < 0.01$.

according to the *U*-tests. The ROC curve was calculated by pairing the FMS score with running injury to determine the cutoff on the FMS that maximized sensitivity and specificity according to previous studies (3,5,10,17). In this context, the FMS can be thought of as a screening test that determines if a runner is at risk for a running injury. An ROC curve is a plot of the sensitivity (true positive) vs. 1 − specificity (false positive) of a screening test. The area under the curve (AUC) was calculated based on the ROC curve. The optimal cutoff was determined based on the Youden index, which consists of the following formula: Youden index = (sensitivity + specificity) − 1 (2). Maximizing this index allows finding the optimal cutoff value. Once the cutoff value was identified, a 2 × 2 contingency table was created dichotomizing those with and without injury and those above and below the cutoff on the FMS. To determine whether a runner, whose FMS score was below the cutoff, had potential injury risk during season, the multivariate logistic analysis was adjusted for each subject's characteristics, including age, height, weight, running experience, training sessions per week, weekly mileage, performance level, and injury history. A value of $p \leq 0.05$ was considered to be statistically significant for all analyses. All data were analyzed using the Statistical Package for the Social Sciences version 20.0 (SPSS, Inc., Chicago, IL, USA).

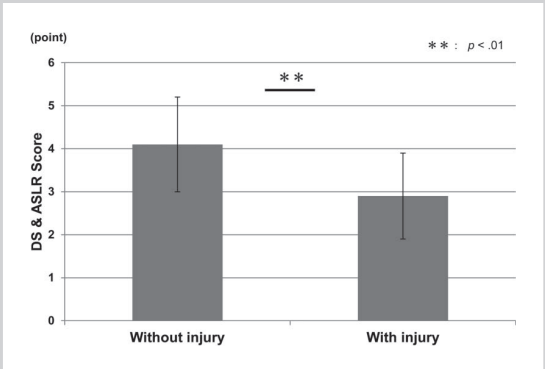

Figure 3. Comparison of the deep squat and active straight leg raise (DS and ASLR) scores between groups with and without injury.

Results

In preseason, 101 runners from 7 teams participated in the FMS, of which 84 returned for the follow-up surveys (response rate was 83.2%).

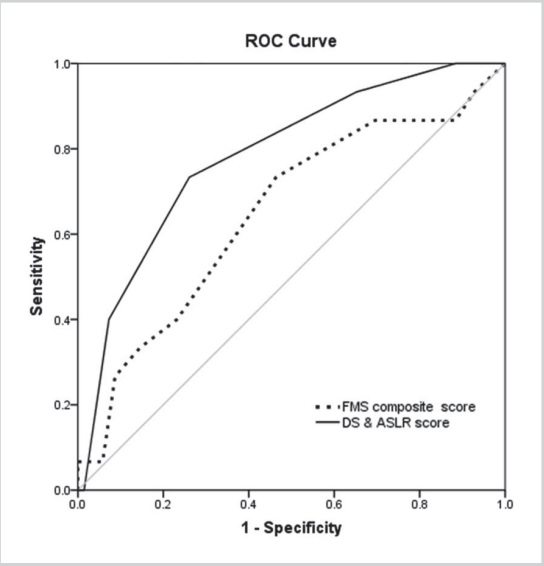

Figure 4. Receiver-operator characteristic (ROC) curves for functional movement screen (FMS) composite and deep squat and active straight leg raise (DS and ASLR) score.

Reliability

Interrater reliability for the FMS composite score is shown in Table 1. The ICC (2, 1) was 0.98 (95% confidence interval [CI] = 0.93–1.00), demonstrating excellent reliability, and the Bland-Altman analysis revealed that there was no systematic error present (both fixed bias and proportional bias). Interrater reliability (weighted kappa) for each component movement test is presented in Table 2 and shows that the majority of the FMS tests demonstrated a substantial to excellent agreement. These results were in accordance with the previous studies (9,15,21) and confirmed the reliability of the procedure in the current study.

Functional Movement Screen Score Distribution

The mean FMS composite score was 14.2 ± 2.3 with a range of 7–18. Of the 84 subjects, 43 (51.2%) scored ≤14 on the FMS composite score, indicating that they had a high injury risk according to Kiesel et al. (10). Among all the subjects, 4 reported pain in the DS and TSPU tests, 3 reported pain in the SM test, 2 reported pain in the ILL test, and 1 in the HS and RS tests, which resulted in a score of 0 for these tests.

The distribution of scores for each component movement test is presented in Figure 2. The SM test was the movement with the highest frequency of a score of 3 (65.5%). Conversely, the RS was the movement with the highest frequency of a score of 1 (34.5%); no subject achieved a score of 3 on this test. The DS, HS, ILL, and ASLR tests had the highest frequency of a score of 2 on each test.

Table 4. 2 × 2 contingency table: functional movement screen (FMS) composite score × running injuries.

	Running injuries	
	Without	With
FMS composite score ≤ 14	32	11
FMS composite score ≥ 15	37	4

Table 5. 2 × 2 contingency table: DS and ASLR score × running injuries.*

	Running injuries	
	Without	With
DS and ASLR score ≤ 3	18	11
DS and ASLR score ≥ 4	51	4

*DS = deep squat; ASLR = active straight leg raise.

Functional Movement Screen Score and Injuries

Among the 84 subjects, 15 (17.9%) experienced running injuries during the season. The comparisons between groups with and without running injuries are presented in Table 3. The mean FMS composite scores were 13.3 ± 2.7 and 14.4 ± 2.2 for subjects with and without any injury, respectively. Although there was a trend for the injury group to have a lower score, this difference was not significant ($p = 0.07$). Of the 7 tests, the scores on the DS and ASLR tests were significant with the *U*-test. Using the composite score of the 2 tests, we calculated a short version of the FMS, which was named "DS and ASLR" (score range: 0–6). Figure 3 shows the significant difference in the DS and ASLR score between the injured and the noninjured groups, whose scores were 2.9 ± 1.0 and 4.1 ± 1.1, respectively ($p < 0.01$).

The ROC curves for the FMS composite and DS and ASLR scores are presented in Figure 4. The cutoff of the FMS composite score was determined to be 14/15, which was consistent with a previous study (10). However, the ROC curve had a relatively low AUC (AUC = 0.65, $p = 0.08$), and at this point, the sensitivity was 0.73 and the specificity was 0.46. Subjects were dichotomized into groups with FMS composite scores ≤14 and ≥15, which are presented in Table 4. Conversely, the ROC curve for the DS and ASLR score had a relatively high AUC (AUC = 0.79, $p = 0.01$), and it determined the cutoff to be 3/4 with a sensitivity of 0.73 and a specificity of 0.74 (Figure 4). Subjects were again dichotomized into groups with DS and ASLR scores

Table 6. Influence of the FMS on running injury.*

	Univariate			Multivariate†		
	OR	95% CI	*p*	OR	95% CI	*p*
FMS composite score ≤ 14	3.2	0.9–11.0	0.07	3.0	0.8–11.6	0.10
DS and ASLR score ≤ 3	7.8	2.2–27.6	<0.01‡	9.7	2.1–44.4	<0.01‡

*FMS = functional movement screen; OR = odds ratio; CI = confidence interval; DS = deep squat; ASLR = active straight leg raise.
†Adjusted for age, height, weight, running experience, weekly training sessions, weekly mileage, performance, and injury history.
‡$p < 0.01$.

≤3 and ≥4, which are presented in Table 5. Among the subjects with a score of ≤3, 11 out of 29 had been injured during the season (injury rate: 37.9%), whereas among the subjects with a score of ≥4, 4 out of 55 (injury rate: 7.3%) had been injured. The logistic regression analysis revealed similar results presented in Table 6. A score of ≤14 of the composite FMS did not significantly influence the incidence of running injuries (odds ratio [OR] = 3.0, 95% CI = 0.8–11.6, $p = 0.10$). However, the same analysis revealed that a runner with a DS and ASLR score of ≤3 was significantly more likely to become injured even when adjusting for each subject's characteristics (OR = 9.7, 95% CI = 2.1–44.4, $p < 0.01$).

Discussion

The purpose of the current study was to investigate whether the FMS could predict running injuries in competitive male runners. The study revealed that the cutoff on the FMS was 14/15, which was in accordance with a previous study (10), but the composite score of ≤14 had low predictability for running injuries. In contrast, the current study also revealed that a DS and ASLR score of ≤3 during preseason was a more useful approach for predicting running injuries during season in 18- to 24-year-old competitive male runners. This is the first study to investigate the validity of the FMS as a predictor for running injuries and to establish the short version of the FMS (DS and ASLR) for screening running injuries.

The mean FMS composite score for the 18- to 24-year-old competitive male runners in the current study was 14.1 ± 2.3, which is similar to the results of college basketball, volleyball, and soccer athletes in the studies by Warren et al. (22) and Chorba et al. (5) (mean scores were 14.3 ± 2.5 and 14.3 ± 1.7, respectively). However, Loudon et al. (12) reported a mean score of 15.0 ± 2.4 for male running athletes, whereas Agresta et al. (1) reported a mean score of 13.1 ± 1.7 for healthy male runners. Although their findings slightly differ from ours, the runners in the current study had a comparable average performance as other runners. Additionally, our scores were relatively lower than the mean composite scores for professional football players (10) and officer candidates (17) (mean scores were 16.9 ± 3.0 and 16.6 ± 1.7, respectively). These differences are expected to occur because distance running mainly requires cardiorespiratory endurance and does not involve as much stability and power as required by football players or officer candidates.

Considering each movement test of the FMS, Figure 2 shows that the subjects performed the best on the SM test, which required mobility of the shoulder and scapula and thoracic spine extension. Because runners need to swing their arms frequently during running, SM is needed to minimize the burden from arm swing. However, the subjects performed the worst in the RS test, which requires multiplane trunk stability during a combined upper and lower extremity motion. This result was similar to the results of previous studies (1,17,20); there were only a few subjects who scored 3 on the RS test. Thus, these findings suggest that the RS test may be one of the more difficult tests of the FMS.

The ROC analysis revealed that sensitivity and specificity were 0.73 and 0.74, respectively. Subsequently, the multivariate logistic regression analysis revealed that subjects with a score of ≤3 on the DS and ASLR were approximately 10 times more likely to have running injuries than those with a score ≥4 after adjusting for each subject's characteristics. The relatively strong predictability of running injuries according to the DS and ASLR score was attributed to the following reasons. First, the DS test by itself had a strong predictability of injuries, which was in accordance with the result of the study by Butler et al. (3). The DS test assesses bilateral symmetrical mobility, especially mobility of hips, ankles, and thoracic spine, and coordination in the close kinetic chain. Renström (19) reported that poor flexibility and deficit in neuromuscular coordination can cause running injuries. Additionally, excessive pronation and knee-in during testing, which were the causes that decreased the score on the DS test (6), were also reported to be risk factors for injury (14). Second, the ASLR test was also found to be related to running injuries; it assesses active hamstring and gastric-soleus flexibility while maintaining a stable pelvis. This finding agreed with the study by Yagi et al. (24), who

also reported that limited SLR ability increased the injury risk in high school runners. Additionally, Lysholm and Wiklander (13) reported that flexibility of the hamstrings was a risk factor for injury. Consequently, deficits in the DS and ASLR tests are likely to induce asymmetric or compensatory movement patterns and thus result in running injuries. Thus, the FMS contains both helpful and less helpful movement tests for predicting injury risk in competitive male runners. The HS test assesses stepping ability, which requires mobility and stability of the legs and also coordination. The ILL test requires mobility and stability in the split stance and also coordination. Although these 2 tests seem to be relevant for running, they were not significantly associated with incidence of running injury because most subjects received a score of 2 (91.7% for HS, 86.9% for ILL). Because of their ceiling effects, these 2 tests were ineffective in screening injury risk. As a result, the FMS composite score had low predictability. For the SM, TSPU, and RS tests, there is no solid evidence that SM and core stability influence the incidence of running injuries.

There were several limitations in the study. The first is the definition of injury as a running injury (lost training time ≥ 4 weeks). Although the current study revealed that the DS and ASLR could predict serious running injuries, it is unclear if it could successfully screen the risk of nonserious running injuries (lost training time < 4 weeks). A second limitation was the mode of collecting injury data by a self-report questionnaire because of the absence of athletic trainers in all teams. As a result, relevant details, such as type of injury, were not collected. A third limitation was that the study was carried out among 18- to 24-year-old competitive male runners in Japan. It is unclear whether the results can be extrapolated to other running populations, such as female, older, or recreational runners. Therefore, further study is required to ensure the external validity of the DS and ASLR score for other runners.

Practical Applications

First, the study provided reliable normative data for FMS scores among 18- to 24-year-old competitive male runners. These data can be used as reference values for strength and conditioning by professional coaches when they need to assess the injury risk of similar groups using the FMS.

Additionally, the study revealed that a score of ≥ 4 or ≤ 3 of the DS and ASLR was more useful for predicting running injuries than the FMS composite score in the 18- to 24-year-old competitive male runners. This finding is meaningful for the strength and conditioning professional who supports a similar group of athletes. First, injury risks can be screened easily by using the DS and ASLR as it only takes approximately 5 minutes. This is an advantage because time is often limited and rather spent on training. Second, it allows the strength and conditioning professional to prevent serious problems in younger runners that could result in retiring from running because of injuries. Timely prediction of injury risks allows initiating strategies for preventing injury. For example, performing hamstring and gastric-soleus stretches are effective in improving scores on the ASLR (7). As to the DS test, the strength and conditioning professional or physical therapist should assess which deficit is limiting influence on this test before conducting corrective exercises. This is because the DS test is affected by many variables, such as the mobility of the hip, ankle, thoracic spine, and shoulder, the stability of the hip, and coordination (7). The current study suggests that, by improving scores on the DS and ASLR in preseason, the incidence of running injuries in 18- to 24-year-old competitive male runners could be reduced.

Acknowledgments

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