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ORIGINAL ARTICLE

Prevalence of knee pain, lumbar pain and its coexistence in Japanese men and women: The Longitudinal Cohorts of Motor System Organ (LOCOMO) study

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Abstract The Longitudinal Cohorts of Motor System Organ (LOCOMO) study was initiated in 2008 through a grant from the Ministry of Health, Labour, and Welfare of Japan to integrate information from several cohorts established for the prevention of musculoskeletal diseases. We integrated the information of 12,019 participants (3,959 men and 8,060 women) in the cohorts comprising nine communities located in Tokyo (two regions: Tokyo-1 and Tokyo-2), Wakayama [two regions: Wakayama-1 (mountainous region) and Wakayama-2 (seaside region)], Hiroshima, Niigata, Mie, Akita, and Gunma prefectures. The baseline examination of the LOCOMO study consisted of an interviewer-administered questionnaire, anthropometric measurements, medical information recording, X-ray radiography, and bone mineral density measurement. The prevalence of knee pain was 32.7 % (men 27.9 %; women 35.1 %) and that of lumbar pain was 37.7 % (men 34.2 %; women 39.4 %). Among the 9,046 individuals who were surveyed on both knee pain and lumbar pain at the baseline examination in each cohort, we noted that the prevalence of both knee pain and lumbar pain was 12.2 % (men 10.9 %; women 12.8 %). Logistic regression analysis showed that higher age, female sex, higher body mass index (BMI), living in a rural area, and the presence of lumbar pain significantly influenced the presence of knee pain. Similarly, higher age, female sex, higher BMI, living in a rural area, and the presence of knee pain significantly influenced the presence of lumbar pain. Thus, by using the data of the

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LOCOMO study, we clarified the prevalence of knee pain and lumbar pain, their coexistence, and their associated factors.

Keywords Nation-wide population-based cohort study · Epidemiology · Prevalence · Knee pain · Lumbar pain

Introduction

Musculoskeletal diseases, including osteoarthritis (OA) and osteoporosis (OP), are major public health problems among the elderly; these diseases can affect activities of daily living (ADL) and quality of life (QOL), and can lead to increased morbidity and mortality. According to the recent National Livelihood Survey by the Ministry of Health, Labour, and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities and subsequently require support for ADL, whereas falls and osteoporotic fractures are ranked fifth [1]. Studies have reported increased mortality after osteoporotic fractures at the hip and other sites [2]. An estimated 47,000,000 individuals (21,000,000 men and 26,000,000 women) aged ≥40 years will eventually be affected by either OA or OP [3].

Considering that the population of Japan is aging rapidly, a comprehensive and evidence-based prevention strategy for musculoskeletal diseases is urgently needed. However, only a few prospective, longitudinal studies designed to develop such a strategy have been conducted. Therefore, little information is available regarding the incidence of disability and the prevalence and incidence of musculoskeletal disorders, including knee pain, and lumbar pain, and their associated factors in Japan. The absence of such epidemiological data hampers the rational design of clinical and public health approaches for the diagnosis, evaluation, and prevention of musculoskeletal diseases.

Several cohorts have focused on the prevention of OP, knee OA (KOA), lumbar spondylosis (LS) or disability caused by musculoskeletal diseases. However, since the prevalence of the musculoskeletal diseases has been reported to be high [3], the extent of the population at risk after excluding those who had the target disease at the baseline seems to be small. To identify epidemiological indices, especially the incidence of musculoskeletal diseases and/or disability, a large number of subjects is required. In addition, to determine the regional differences in epidemiological indices, we need a survey of cohorts across Japan.

The Longitudinal Cohorts of Motor System Organ (LOCOMO) study was initiated in 2008 by the members of the committee for 'the prevention of knee and back pain and bone fractures in a large cohort of regionally representative residents from across Japan,' through a grant from the Ministry of Health, Labour, and Welfare of Japan (Director, Noriko Yoshimura). This study aimed to integrate the information of several cohorts established for the prevention of musculoskeletal diseases from 2000 onwards, and to initiate a follow-up examination using the unified questionnaire from 2006 onwards in Japan.

In the present paper, by using the integrated information at the baseline of the LOCOMO study, we tried to confirm the prevalence of clinical symptoms of musculoskeletal diseases, such as knee pain and lumbar pain and their characteristics.

Materials and methods

Participants

Participants in the cohorts were residents of nine communities located in Tokyo (two regions: Tokyo-1, principle investigators (PIs): Shigeyuki Muraki, Toru Akune, Noriko Yoshimura, Kozo Nakamura; Tokyo-2, PIs: Yoko Shimizu, Hideyo Yoshida, Takao Suzuki), Wakayama [two regions: Wakayama-1 (mountainous region) and Wakayama-2 (seaside region); PIs: Noriko Yoshimura, Munehito Yoshida], Hiroshima (PI: Saeko Fujiwara), Niigata (PI: Go Omori), Mie (PI: Akihiro Sudo), Akita (PI: Hideyo Yoshida), and Gunma (PI: Yuji Nishiwaki) prefectures [4]. Figure 1 shows the location of each cohort in Japan, and Fig. 2 provides the timeline of the LOCOMO study. Residents of the nine regions were recruited from resident registration lists in the relevant region. Data for the 12,019 participants were collected and registered as an integrated cohort. Numbers of participants in the LOCOMO study classified by regions of each cohort are shown in Table 1. The smallest cohort consisted of 826 individuals in Wakayama-2, and the largest consisted of 2,613 individuals in Hiroshima.

All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo (nos. 1264 and 1326), the Tokyo Metropolitan Institute of Gerontology (no. 5), Wakayama (no. 373), The Radiation Effects Research Foundation (RP03-89), Niigata University (no. 446), Mie University (no. 837 and no. 139), Keio University (no. 16–20), and National Center for Geriatrics and Gerontology (no. 249). Safety of the participants was ensured during the examination and during all other study procedures.

Data collection

The baseline examination of the LOCOMO study consisted of the following: an interviewer-administered questionnaire,

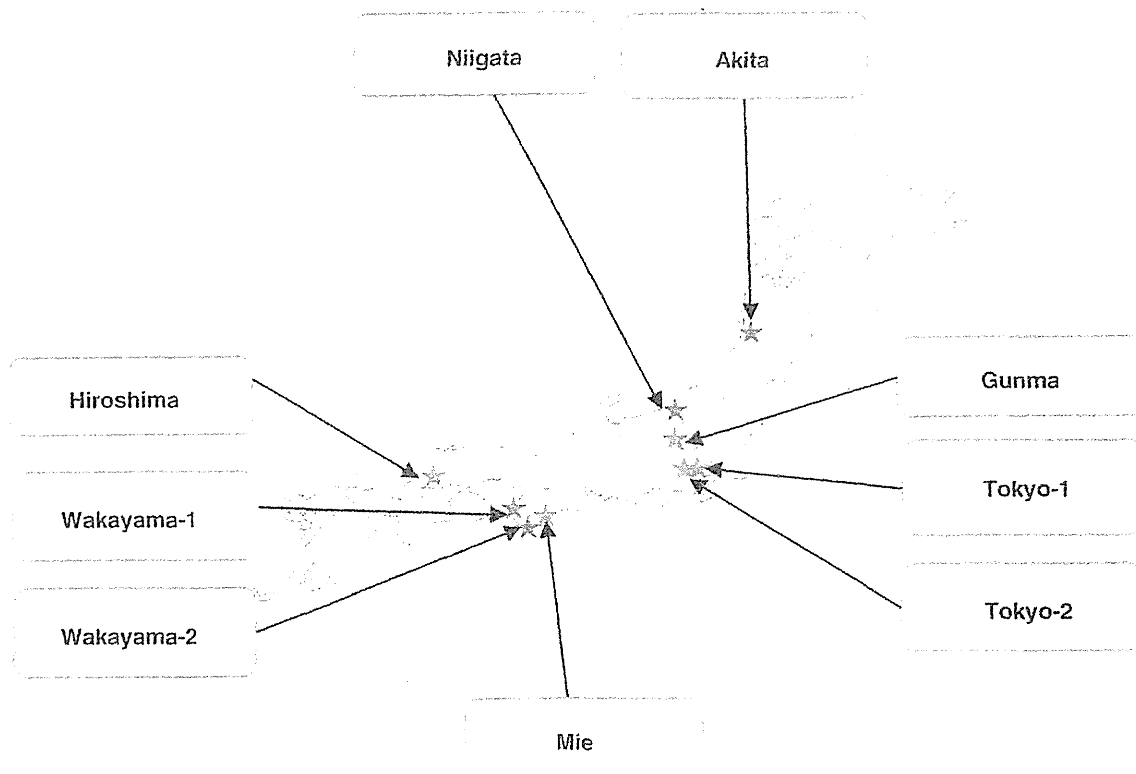

Fig. 1 Locations of the nine different regions from which the study cohorts were derived

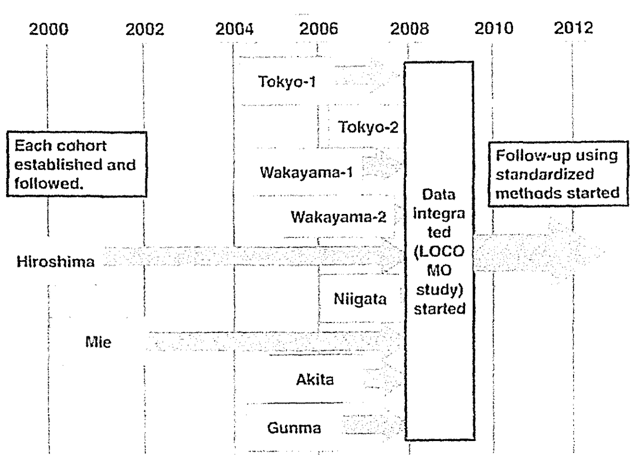

Fig. 2 Timeline of the LOCOMO study

Table 1 Numbers of participants in the LOCOMO study classified by regions of each cohort

Regions of each cohort	Start year	Total	Men	Women
Tokyo-1	2005	1,350	465	885
Tokyo-2	2008	1,453	59	1,394
Wakayama-1 (mountainous)	2005	864	319	545
Wakayama-2 (seaside)	2006	826	277	549
Hiroshima	2000	2,613	794	1,819
Niigata	2007	1,474	628	846
Mie	2001	1,175	423	752
Akita	2006	852	366	486
Gunma	2005	1,412	628	784
Total		12,019	3,959	8,060

anthropometric measurements, medical information recording, radiography, and bone mineral density (BMD) measurement.

Interviewer-administered questionnaire

A questionnaire was prepared by modifying the questionnaire used in the Osteoporotic Fractures in Men Study (MrOS) [5], and some new items were added to the modified questionnaire. Knee symptoms were evaluated using the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) [6]. Health-related QOL was evaluated using the European QOL-5 dimensions instrument (EuroQOL EQ5D) [7] and the Medical Outcomes Study 8-item Short Form (SF-8) [8]. The study staff recorded all the medications administered and their doses.

Anthropometric measurements

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

Medical information

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

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

Radiography and radiographic assessment

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

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

BMD measurement

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

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

Statistical analysis

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

Results

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

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

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

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

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

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

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

Values are represented as mean (standard deviation)

BMI body mass index

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

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

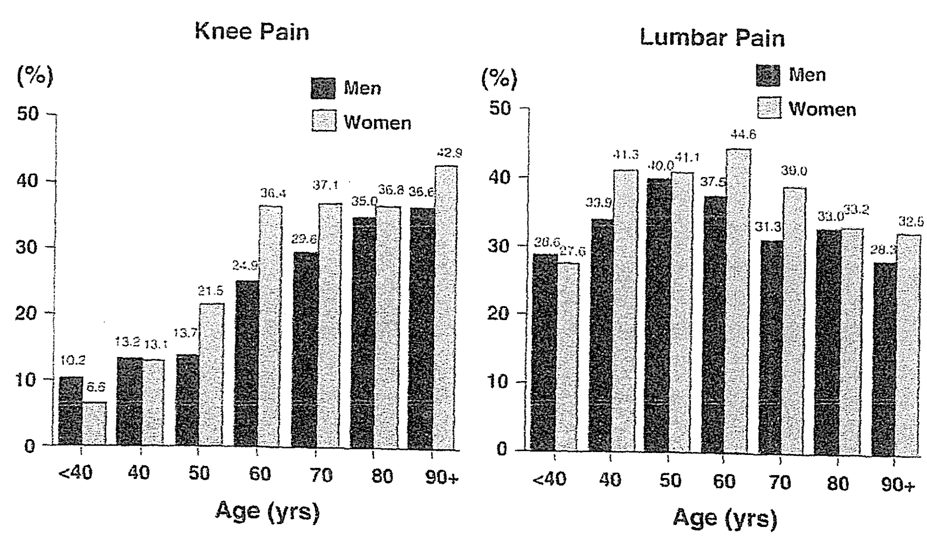

Fig. 3 Prevalence of knee pain and lumbar pain according to age and gender

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

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

BMI body mass index
* $p < 0.05$, *** $p < 0.001$

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

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

Discussion

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

With regard to musculoskeletal pain, several population-based epidemiological studies have demonstrated that chronic pain is a highly prevalent condition. Soni et al. [14] reported that the prevalence rates of self-reported knee pain using the baseline data in 1,003 participants from the Chingford Women's Study were 22.97 % in the left knee and 24.80 % in the right knee. The definition of the presence of the knee pain (based on the following two questions: 'Have you had any knee pain in either knee in the last month?' and 'How many days of pain have you experienced in the last month?') was similar but not identical to our definition used in the LOCOMO study, and the subjects' age was younger in the Chinford study than in the LOCOMO study. Therefore, we could not compare the prevalence between the Chinford and LOCOMO studies directly. However, at a glance, the prevalence seems to be higher in the Japanese population. This may be due to the fact that the prevalence of KOA (KL grades ≥2) was higher in the Japanese population than that in the Caucasian population [15]. Verhaak et al. [16] reviewed epidemiological studies on chronic benign pain among adults, including subjects aged between 18 and 75 years, and reported that the prevalence ranged between 2 and 40 % of the population. Coggon et al. did not perform a population-based study, but instead conducted a cross-sectional survey comparing the prevalence of disabling low back pain and disabling wrist/hand pain among groups of workers carrying out similar physical activities in different cultural environments in 18 countries including Japan. They reported that the 1-month prevalence of disabling low back pain in nurses ranged from 9.6 to 42.6 %, and that of disabling wrist/hand pain in office workers ranged from 2.2 to 31.6 % [17]. We could not compare our results to those of Coggon's results directly because of the difference in the characteristics of the targeted population. However, previous reviews and reports demonstrated that the prevalence of the chronic pain varied in the population surveyed, and therefore, estimating the prevalence and number of patients in pain would require a study that comprises various regions with a large number of subjects. Our LOCOMO study contains 12,019 participants from the cohorts consisting of nine communities in different locations in Japan. Therefore, we believe that our estimation of the prevalence of knee pain and lumbar pain is appropriate, and the number of patients was sufficient.

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

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

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

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

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

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ORIGINAL ARTICLE

Effects of knee extensor muscle strength on the incidence of osteopenia and osteoporosis after 6 years

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Abstract The association of knee extensor muscle strength with bone mineral density (BMD) has been reported in cross-sectional epidemiological studies, but it remains unclear whether or not this is the case with longitudinal change. Thus, we investigated whether or not the knee extension strength can predict the incidence of osteopenia or osteoporosis after 6 years, then compared the difference between sexes. Subjects were 1255 community-dwelling Japanese men and menopaused women, aged 40–81 years. BMD of lumbar spine and femoral neck was assessed by dual-energy X-ray absorptiometry twice at 6-year intervals. Subjects were divided into three groups, normal, osteopenia, and osteoporosis, depending on their young adult mean BMD % value. In the cross-sectional analysis the correlations between the knee extension strength and BMD of the two regions were examined, using Pearson's correlation coefficient. Longitudinal analyses were then conducted to determine the odds ratio, controlled for age and BMI, given that those who were normal in the initial stage developed osteopenia or osteoporosis after 6 years, for every 1 SD decrease in knee extension strength, as well as those who first had normal or osteopenia and then developed osteoporosis. Cross-sectional analysis showed a statistically significant relation between knee extensor muscle strength and BMD at both the lumbar spine ($p = 0.02$) and the femoral neck ($p < 0.0001$) only in men. The longitudinal analysis showed the significant effect of muscle strength on the loss of femoral neck BMD from normal to osteopenia or osteoporosis both in men (OR 1.84, 95 % CI 1.36–2.48, $p < 0.0001$) and in women (OR 1.29, 95 % CI 1.002–1.65, $p < 0.05$), as well as on the loss of spinal BMD from normal or osteopenia to osteoporosis only in men (OR 2.97, 95 % CI 1.07–8.23, $p < 0.05$). The results suggest the importance of knee extension strength to maintain the bone health of the proximal femur and spine in aging particularly in men.

Keywords Longitudinal epidemiological study · Knee extensor strength · Bone mineral density · Femoral neck · Lumbar spine

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Introduction

Bone mineral density (BMD) is the greatest determinant of bone strength [1], so the loss of bone mass leads to the increased risk of fracture at that site. Several factors are known to affect the BMD or future bone loss, such as body weight [2, 3], age [2], nutrition [4], smoking [5, 6], physical exercise [7–11], physical training [12] or physical activity [6, 13, 14] and body composition like muscle mass [14–20]. Muscle strength is also known to associate with BMD [2, 6, 12, 13, 18, 19, 21–29]. Their association seems to be site-specific [26, 27] as well as systemic [13]. However, not many epidemiological studies have been carried out on a large scale regarding the influence of leg strength on the longitudinal BMD changes; particularly those investigating the gender difference are rare. The purpose of our study is to clarify whether or not the knee extension strength can predict the incidence of osteopenia or osteoporosis after 6 years in the two regions of lumbar spine and femoral neck, and to compare the difference in sexes, utilizing a large cohort of local inhabitants.

Materials and methods

Subjects

The subjects were selected among people who participated in both the 2nd and 5th waves of the National Institute for Longevity Sciences Longitudinal Study of Aging (NILS-LSA). Details of the NILS-LSA are described elsewhere [30], but a brief description follows. This biannual examination to check the physical and mental condition so as to clarify the aging mechanism of ordinary Japanese people is conducted by the National Center for Geriatrics and Gerontology (NCGG), located in central Japan. The NILS is a research section of NCGG. The participants are chosen randomly among residents of Obu City and Higashiura-cho, in Aichi Prefecture in Japan.

For this study, data were analyzed from 763 men (57.3 ± 10.2, mean ± SD) and 476 women (62.0 ± 8.3, mean ± SD). In order to avoid the effect of menopause, we excluded the premenopausal women in the 2nd stage. Their age ranged from 40 to 81 (from 40 to 81 for men, and 41 to 80 years for women) at initial time (2nd wave). The 2nd and 5th waves were from April 2000 to May 2002, and July 2006 to July 2008, respectively, so the interval between the 2nd and 5th waves was 6 years. The number of participants who had a BMD examination in the 2nd wave were 1101 men and 732 women. So the response rates were 69.3 % (763 out of 1101) in men, and 65.0 % (476 out of 732) in women.

The reasons for non-response were various; such as moving out, health related problems, becoming the residents in the nursing homes, death, etc.

Measurements of bone mineral density

Bone mineral densities were measured using Hologic QDR4500, both at the initial time and after 6 years. Mean follow-up interval was 6.24 years ± 0.33. Data on the lumbar spine (L2–4) and the right side of the femoral neck were used for the analysis. For the state of bone density in terms of osteoporotic conditions, we adopted the classification widely used in Japan, as recommended by the Japanese Society for Bone and Mineral Research. Those who had equal or more than 80 % young adult mean (the YAM value of BMD), between 20 and 40-year-old, were classified as "normal," those who had equal or more than 70 and less than 80 % YAM as "osteopenia," and those with less than 70 % YAM as "osteoporosis." In the 2nd wave, numbers of subjects classified as normal, osteopenia and osteoporosis in lumbar spine were 633, 98, and 30, respectively, in men and 280, 134, and 78, respectively, in women, while in the 5th wave those classified as normal, osteopenia and osteoporosis in lumbar spine were 591, 121, and 51 in men, and 226, 176, and 90 in women, respectively. As for the femoral neck lesion, numbers of subjects classified as normal, osteopenia and osteoporosis in the 2nd wave were 680, 69, and 14, respectively, in men, and 352, 106, and 34, respectively, in women, while in the 5th wave those classified as normal, osteopenia and osteoporosis were 591, 121, and 51 in men, and 226, 176, and 90 in women, respectively.

Measurements of knee extension strength

Isometric knee extension strength was measured in the upright sitting position with knee and hip flexed 90°, as is often adopted in the usual epidemiological studies [31]. For more accuracy than by a handheld-dynamometer, we used a measurement device (Fig. 1) built by Takei Kiki Co., Niigata, Japan. This company has the responsibility for the verification and maintenance of this device every year. Measurements of knee extension strength were repeated three times, and the maximum values were used. Values measured for the right knee at the initial time wave were used for the analysis.

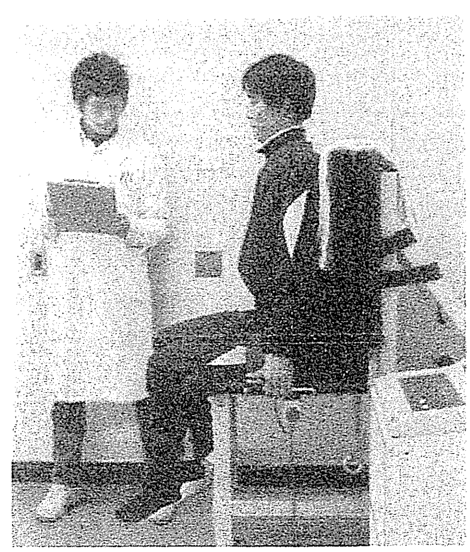

Fig. 1 Isometric knee extension strength was measured in the upright sitting position with knee and hip flexed 90°, using the fixed machine

Statistical analysis

All analyses were conducted using SAS Ver. 9.13 (SAS Institute, Cary, NC, USA). Unpaired Student *t* tests were used to compare characteristics between men and women, and also for the knee extension strength of those who had BMD examinations both at the 2nd and 5th wave and those who did so only at the 2nd. Paired *t* tests were used to compare the BMDs of the subjects at the 2nd and 5th wave.

In the cross-sectional analysis, the correlation between the knee extension strength and BMD at the lumbar spine and femoral neck were tested using Pearson's correlation coefficient controlled for age, square of age, and BMI. Men and women were calculated separately. Trend analysis was made for the change in knee extension strength, according to the age stratum, using a general linear model. As for the longitudinal analysis, multiple logistic regression analyses were conducted. We defined the statistical risk of those who had normal BMD in the initial time (greater than or equal to YMA 80 %) and would become osteopenic or osteoporotic BMD (less than 80 %) after 6 years as the "osteopenia risk." Also, we defined the statistical risk of those who had normal or osteopenic BMD (greater than or equal to YMA 70 %) in the initial time and would develop osteoporosis (BMD less than 70 %) after 6 years as the "osteoporosis risk." "Osteopenia risk and osteoporosis risk" were determined by calculating the odds ratio as a 1 SD decrease in the knee extension strength. Each analysis was conducted controlled for age and BMI.

Results

Characteristics of the subjects were shown in Table 1

Cross-sectional examination; the correlations between knee extension strength and bone mineral densities in the initial time.

Significant correlations between knee extension strength and bone mineral densities were found in men at both lumbar spine and femoral neck, and the adjusted Pearson's correlation coefficients were 0.08 and 0.16, respectively (Table 2). Correlation was rather weak at the lumbar spine. On the other hand, in women the correlation between knee extension strength and bone mineral densities was not significant either in the lumbar spine or in the femoral neck (Table 2).

Longitudinal examination; the associations between the knee extension strength in the initial time and the BMDs after 6 years.

Among 632 men in the group with normal lumbar spine in the initial time, 34 evidenced osteopenia and no men became osteoporotic in 6 years. Among 98 men of the osteopenic group in the initial time, 7 became osteoporotic in 6 years. In the meantime, 48 out of 280 women in the group with normal lumbar spine initially became osteopenic, and 4 women became osteoporotic in 6 years, while 38 out of 134 in the osteopenic group became osteoporotic. As for femoral neck BMD, among 680 men of the normal group in the initial time, 83 showed osteopenia and 7 men became osteoporotic in 6 years. Among 69 in the osteopenic group initially, 30 became osteoporotic in 6 years. In the meantime 116 out of 352 women in the normal group became osteoporotic, and 14 women became osteoporotic in 6 years, while 44 out of 106 in the osteopenic group became osteoporotic.

As for the association between the knee extension strength in the initial time and the BMD at the lumbar spine after 6 years, only the "osteoporosis risk" in men was significant (Table 3), its odds ratio being 2.97 (95 % CI

Table 1 Characteristics of subjects

	Men (n = 763)	Women (n = 476)	p
Age (years)	57.3 ± 10.2	62.0 ± 8.3	<0.0001
Height (cm)	166.0 ± 6.0	151.6 ± 5.6	<0.0001
Weight (kg)	63.6 ± 8.8	52.2 ± 7.5	<0.0001
BMI (kg/m^2)	23.1 ± 2.7	22.7 ± 3.0	0.0192
Knee extension strength	43.0 ± 10.7	25.9 ± 8.3	<0.0001
BMD at initial time			
Lumbar spine (L2–4) (g/cm^2)	0.984 ± 0.151	0.844 ± 0.143	<0.0001
Femoral neck (g/cm^2)	0.767 ± 0.108	0.667 ± 0.101	<0.0001
BMD after 6 years			
Lumbar spine (L2–4) (g/cm^2)	0.994 ± 0.170	0.817 ± 0.138	<0.0001
Femoral neck (g/cm^2)	0.726 ± 0.111	0.611 ± 0.100	<0.0001

Values are mean ± SD

* $p < 0.0001$

Table 2 Correlation analyses using Pearson's correlation coefficient of knee extensor strength and BMD

	Coefficient	(95 % CI)	p
At lumbar spine			
Men	0.081	(0.011 to 0.152)	0.024
Women	0.015	(−0.075 to 0.105)	0.739
At femoral neck			
Men	0.157	(0.087 to 0.226)	<0.0001
Women	0.022	(−0.068 to 0.112)	0.630

Correlation analyses were made between the knee extensor strength and bone mineral density using Pearson's correlation coefficient controlled for age, square of age, and BMI

Table 3 Association of knee extension strength and BMD change at the lumbar spine

	OR	(95 % CI)	p
Osteopenia risk			
Men ($n = 633$)	1.32	(0.86–2.02)	0.21
Women ($n = 265$)	0.78	(0.56–1.09)	0.143
Osteoporosis risk			
Men ($n = 731$)	2.97	(1.07–8.23)	0.036
Women ($n = 399$)	1.08	(0.74–1.55)	0.70

All analyses were conducted controlled for age and BMI

OR odds ratio as 1 strength decreases (SD)

Table 4 Association of knee extension strength and BMD change at the femoral neck

	OR	(95 % CI)	p
Osteopenia risk			
Men ($n = 681$)	1.84	(1.36–2.48)	<0.0001
Women ($n = 336$)	1.29	(1.002–1.65)	0.048
Osteoporosis risk			
Men ($n = 750$)	1.50	(0.93–2.42)	0.09
Women ($n = 442$)	1.25	(0.91–1.72)	0.18

All analyses were conducted controlled for age and BMI

OR odds ratio as 1 strength decreases (SD)

1.07–8.23). As for the BMD of the femoral neck, however, a significant effect of knee extension strength was observed in the "osteopenia risk" in both men and women. Their odds ratios were 1.84 (95 % CI 1.36–2.48), and 1.29 (95 % CI 1.002–1.65), respectively. On the other hand there was no significant difference in the "osteoporosis risk" of the femoral neck in both men and women (Table 4).

Discussion

Utilizing a large cohort of local inhabitants, we examined the effects of knee extensor muscle strength on the bone mineral densities in the longitudinal changes, as well as in the cross-sectional studies. In the cross-sectional studies, significant correlations were found in men at both lumbar spine and femoral neck, but not in women. Although we excluded pre-menopausal women in order to avoid the menopausal effect on bone mineral densities, women's bone may be more influenced by something other than the muscle force compared to men; for example, by estrogen decline [32], and also much weaker knee extensor strength in women than in men [33]. Thus, there may not be enough effect on the bone.

We have also examined the effect of knee extension strength on the longitudinal bone loss of the lumbar spine and femoral neck, checking between normal and osteopenia, as well as between osteopenia and osteoporosis. At the femoral neck, the decrease in knee extension strength had a significant effect on whether osteopenia developed or not; however, it failed to show an effect on whether or not it became osteoporosis. This was the case with both sexes. From these results, exercise for strengthening the legs seemed to be good not only for locomotive ability or prevention from falls but also for protecting against bone loss at the proximal femur in the future, particularly when bone was in healthy condition. Quadriceps femoris are the only knee extensor muscle and they originate from both above and below the hip joint. Thus, during knee extension behavior force should be applied to the proximal part of the femur, making it stronger. In the advanced stage of bone loss, however, this effect may not be strong enough.

In the meantime, as for the lumbar spine, the decrease in knee extension strength had a significant effect on whether osteoporosis developed only in men, but not in women. Since this is not site-specific, it may reflect physical activity and the systemic effect on the bone metabolism. The decline of muscle strength in men was more prominent in aging than in women [33], and might affect physical activity more.

As for the relation of muscle strength on longitudinal BMD change, Iki and colleagues [26] demonstrated a site-specific relation of the back in women; trunk muscle strength was related with BMD loss in the lumbar spine during a 4-year period. Since they did not investigate BMD in the hip lesion, they had no results about the site-specific association of muscle strength and bone loss in the lower extremities. In that study, they failed to demonstrate any relation between lumbar BMD and knee extensors, and flexors as well in women, which is consistent with our results at 6 years.

In a study over longer time intervals, Sirola et al. [28] investigated the loss of BMD in the lumbar spine and femoral neck BMD over 10 years. Although the study showed a good relation with grip strength change at both sites, the knee extensor or trunk muscles were not examined, so no mention was made in the site-specific connection.

There are some limitations in this study. First, our response rates were 69.3 % (763 out of 1101) in men, and 65.0 % (476 out of 732) in women. Thus, there may be some difference between the responder (who participated in both the 2nd and 5th wave) and non-responder (who participated only in the 2nd wave). Actually non responders were about 7-year-older than responders. Moreover, knee extension strength was also stronger in the responder, but when we controlled with sex and age, the difference was minimum (only 0.3 kg). Another limitation is that we excluded premenopausal women in order to eliminate the effect of estrogen on bone, which made for a significant age difference between sexes. Our study focused on the relation between knee extensor muscle strength and longitudinal bone loss. However, some factors may influence BMD, like nutrition [4], physical activity [6, 13, 14] or exercise status [7–10]. These might be confounding factors, which should be the next target for investigation.

The strong point of our study is that our samples were randomly selected from people in the local community with very little bias in the selection process. NILS-LSA is one of the few major epidemiological studies for investigating the aging mechanism that is designed to select the subject in a completely random manner, so as to avoid bias when conducting epidemiologic study in many ways.

In summary, we investigated whether or not knee extension strength can predict the incidence of osteopenia or osteoporosis after 6 years, utilizing a large-scale cohort of subjects randomly selected from the local community. We showed the clear effect of muscle strength on BMD loss in the early stage in the femoral neck both in men and women, but not in the lumbar spine. The effect proved to differ by gender; it affected men in the late stage of bone loss in lumbar spine, but not in women. This suggests the importance of knee extension strength to maintain the bone health of the proximal femur and lumbar spine in aging particularly in men.

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Conflict of interest The authors declare that no conflict of interest, with any company and/or other organization, exists pertaining to the article mentioned below regarding the content, conclusion, and significance of the research as well as opinions on them.

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Cereal Intake Increases and Dairy Products Decrease Risk of Cognitive Decline among Elderly Female Japanese

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Abstract

BACKGROUND: If cognitive decline can be prevented through changes in daily diet with no medical intervention, it will be highly significant for dementia prevention.
OBJECTIVES: This longitudinal study examined the associations of different food intakes on cognitive decline among Japanese subjects.
DESIGN: Prospective cohort study.
SETTING: The National Institute for Longevity Sciences - Longitudinal Study of Aging, a community-based study.
PARTICIPANTS: Participants included 298 males and 272 females aged 60 to 81 years at baseline who participated in the follow-up study (third to seventh wave) at least one time.
MEASUREMENTS: Cognitive function was assessed with the Mini-Mental State Examination (MMSE) in all study waves. Nutritional intake was assessed using a 3-day dietary record in the second wave. Cumulative data among participants with an MMSE >27 in the second wave were analyzed using a generalized estimating equation. Multivariate adjusted odds ratios (OR) and 95% confidence intervals (CI) for an MMSE score ≤27 in each study wave according to a 1 standard deviation (SD) increase of each food intake at baseline were estimated, after adjusting for age, follow-up time, MMSE score at baseline, education, body mass index, annual household income, current smoking status, energy intake, and history of diseases.
RESULTS: In men, after adjusting for age, and follow-up period, MMSE score at baseline, the adjusted OR for a decline in MMSE score was 1.20 (95% CI, 1.02-1.42; p=0.032) with a 1-SD increase in cereal intake. After adjusting for education and other confounding variables, the OR for a decrease in MMSE score did not reach statistical significance for this variable. In women, multivariate adjusted OR for MMSE decline was 1.43 (95% CI, 1.15-1.77; p=0.001) with a 1-SD increase in cereal intake and 0.80 (95% CI, 0.65-0.98; p=0.034) with a 1-SD increase in milk and dairy product intake.
CONCLUSIONS: This study indicates that a 1-SD (108 g/day) decrease in cereal intake and a 1-SD (128 g/day) increase in milk and dairy product intake may have an influence of cognitive decline in community-dwelling Japanese women aged 60 years and older. Further studies are needed in order to explore the potential causal relationship.

Key words: Cereal, milk and dairy products, diet, Japanese, elderly.

Introduction

Dementia, including Alzheimer's disease, is one of the most serious geriatric diseases because it interferes with a person's daily routines and social life. With the aging of the population, there is a growing concern that the number of dementia cases will increase in Japan (1). However, because there are no treatment strategies for dementia to date, there is a pressing need to establish prevention strategies. Many factors such as medical history, lifestyle habits, and psychological and genetic factors are thought to be associated with the onset of dementia (2). Concurrently, reports that indicate a possible link between dietary factors and cognitive function are beginning to emerge. Food consumption is vital for human life, and is an essential factor for health maintenance and health promotion throughout life. From a public health perspective, if cognitive decline can be prevented through changes in daily diet with no medical intervention, it will be highly significant for dementia prevention.

High intake of vegetables (3), fish (4), and dairy products (5) are thought to play a protective role against age-related cognitive decline or Alzheimer's disease. However, these reports were based on studies conducted in Western countries. Japanese cuisine is based on a combination of staple foods, typically rice or noodles (6), and Japanese consume higher levels of fish, salt, and soy products compared with the Western diet, which includes high intake of meat and dairy products (7). For example, the main sources of protein among Japanese subjects in the 2008 National Health and Nutrition Survey in Japan were fish (22%), meat (18%), and beans (7%) (8). Thus, it is important to determine whether there is a specific dietary factor that would help reduce the risk of cognitive decline among Japanese. Recently, dietary patterns characterized by a high intake of soybeans, vegetables, algae, and milk and dairy products and a low intake of rice were reported to be associated with reduced risk of dementia during a median of 15 years of follow-up in the general Japanese population (9). However, that

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study defined dietary patterns based on a food frequency questionnaire; thus, the effect of each dietary factor and the amounts eaten on the risk of dementia were not clear. No other longitudinal studies in Japan have reported the association between dietary factors and cognitive decline.

The present longitudinal study was carried out in elderly community-dwelling Japanese subjects to clarify the effectiveness of different food intakes calculated by dietary records on cognitive decline.

Methods

Participants

Data for this survey were collected as part of the National Institute for Longevity Sciences - Longitudinal Study of Aging (NILS-LSA). In this project, the normal aging process has been assessed over time using detailed questionnaires and medical checkups, anthropometric measurements, physical fitness tests, and nutritional examinations. Participants in the NILS-LSA included randomly selected age- and sex-stratified individuals from the pool of non-institutionalized residents in the NILS neighborhood areas of Obu City and Higashiura Town in Aichi Prefecture. The first wave of the NILS-LSA was conducted from November 1997 to April 2000 and comprised 2,267 participants (1,139 men, 1,128 women; age range, 40-79 years). Details of the NILS-LSA study have been reported elsewhere (10). Subjects have been followed up every 2 years from the first wave, second wave (April 2000 - May 2002), third wave (May 2002 - May 2004), fourth wave (June 2004 - July 2006), fifth wave (July 2006 - July 2008), sixth wave (July 2008 - July 2010), and seventh wave (July 2010 - July 2012). When participants could not be followed up (e.g., they transferred to another area, dropped out for personal reasons, or died), new age- and sex-matched subjects were randomly recruited. All waves included nearly 1,200 men and 1,200 women. In this study, we selected participants who participated in the second wave (n=2,259; age range, 40-81 years) and also participated in more than one study wave from the third to seventh wave, as variables could be followed up at least one time from the second wave.

Exclusion criteria were as follows: 1) those who were <60 years in the second wave (n=1,114), because cognitive function tested by the Mini-Mental State Examination (MMSE) was assessed only among participants aged 60 or older; 2) those who had an MMSE score ≤27 in the second wave (n=414); 3) those who did not complete nutritional assessments in the second wave (n=40); and 4) those who did not complete the self-reported questionnaire (n=30). In addition, 91 men and women did not participate in more than one study wave from the third to seventh wave. Thus, a total of 570 Japanese (298 men, 272 women) who were between 60 and 81 years in the second wave of the NILS-LSA were available for analysis. Each wave was conducted for 2 years; the total length of the second through seventh waves was 10 years. However, the mean interval and participation times between the second and seventh wave for each participant was 8.1 years and 3.9 times, respectively (Table 1).

The study protocol was approved by the Committee of Ethics of Human Research of the National Center for Geriatrics and Gerontology. Written informed consent was obtained from all subjects.

Assessment of cognitive function

Cognitive function was assessed by the Japanese version of the MMSE through interviews with a trained psychologist or clinical psychotherapist through the second and seventh waves (11, 12). The MMSE is widely used as a brief screening test for dementia, and scores range from 0 to 30 points, with a higher score indicating better cognitive function. The MMSE includes questions on orientation of time and place, registration, attention and calculation, recall, language, and visual construction. A cut-off score of ≤23 is traditionally used to represent "suggestive cognitive impairment" (11, 12). Because only 4 to 12 individuals in each study wave had an MMSE ≤23, the number of cases was too small to analyze. However, our sample was relatively highly educated, and 58.4% of men and 39.3% of women graduated from 2- or 4-year colleges. A cut-off score ≤26 (sensitivity, 0.69; specificity, 0.91) or ≤27 (sensitivity, 0.78; specificity, 0.78) has been suggested for samples of highly educated individuals (13). Thus, we used a cut-off score of ≤27 in the main analyses. Among participants in this study with an MMSE >27 in the second wave (n=570), 134 in the third wave, 133 in the fourth wave, 137 in the fifth wave, 124 in the sixth wave, and 124 in the seventh wave had an MMSE score ≤27 and were classified as showing cognitive decline.

Nutritional assessments

Nutritional intake was assessed using a 3-day dietary record after participation in the second wave survey. The dietary record was completed over 3 continuous days (both weekdays and 1 weekend day) (14), and most subjects completed it at home and returned records within 1 month. Food was weighed separately on a scale (1-kg kitchen scales; Sekisui Jushi, Tokyo, Japan) before being cooked or portion sizes were estimated. Subjects used a disposable camera (27 shots; Fuji Film, Tokyo, Japan) to take photos of meals before and after eating. Dietitians used these photos to complete missing data and telephoned subjects to resolve any discrepancies or obtain further information when necessary. Averages for

3-day food and nutrient intakes were calculated according to the Standard Tables of Foods Composition in Japan 2010 and other sources (14).

Other measurements

Medical history of heart disease, hypertension, hyperlipidemia, and diabetes (past and current), education (≤9, 10-12, or ≥13 years of school), annual household income (11 point scale, 1; <¥1,500,000, 11; ≥¥ 20,000,000) and smoking status (yes/no) were collected using self-reported questionnaires. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. These measurements were assessed in the second wave. Follow-up time (year) was calculated by the length of time (days) that has elapsed since the day each subjects participated in the second wave.

Statistical analysis

All statistical analyses were conducted using Statistical Analysis System (SAS) software version 9.3 (SAS Institute, Cary, NC, USA). Comparisons between baseline characteristics and food intake of subjects according to the MMSE score at the follow-up study were performed by independent t-test (continuous variables) and chi-square tests (categories), respectively.

Cumulative data were analyzed using a generalized estimating equation (GEE), which takes into account the dependency of repeated observations within participants; this is an important feature that is necessary for longitudinal analyses. An additional advantage of GEE is that participants are included regardless of missing values. Thus, participants who were lost to follow-up after early wave examination were also included in the analyses. GEE models were fitted using the GENMOD procedure of SAS. The GENMOD procedure fits generalized linear models. The correlation structure was specified to be compound symmetry.

GEE analyses were performed to estimate the odds ratio (OR) and 95% confidence interval (CI) for an MMSE score ≤27 in each study wave according to a 1-SD increase of each food intake at baseline, adjusted for the following variables. The confounding variables were 1) model 1, age (year, continuous), and follow-up time (year, continuous); 2) model 2, model 1, and MMSE score at baseline (continuous); and 3) model 3, model 2, education (≤9, 10-12, ≥13 years), BMI (kg/m^2), annual household income (11 point scale, continuous), current smoking status (yes or no), energy intake (kcal/day), and history of heart disease, hypertension, hyperlipidemia, and diabetes (yes or no). Probability levels less than 0.05 were considered significant.

Results

Number of subjects, follow-up time, and period in this study are shown in Table 1. About 31.3% of men (356/1137 cases) and 27.8% of women (296/1065 cases) had an MMSE score ≤27. Table 2 shows baseline characteristics and food intake of included subjects and excluded subjects by sex. Compared with included subjects, excluded subjects in the analyses had significantly lower MMSE scores, were less likely to be educated, and had lower body mass index in women.

Table 3 shows the longitudinal relationships between baseline food intake and OR (95% CI) for MMSE scores ≤27 10 years later. The cumulative data were analyzed with GEE. In men, after adjusting for age, follow-up period, and MMSE score at baseline, the adjusted OR for a decline in MMSE score was 1.20 (95% CI, 1.02-1.42;

Table 1. Number of subjects, follow-up time, and period in this study

	Men				Women			
			MMSE score ≤27				MMSE score ≤27	
	n	%	n	%	n	%	n	%
Second wave*	298	100.0	-	-	272	100.0	-	-
Third wave	288	96.6	77	26.7	260	95.6	57	21.9
Fourth wave	254	85.2	60	23.6	243	89.3	73	30.0
Fifth wave	225	75.5	77	34.2	219	80.5	60	27.4
Sixth wave	197	66.1	70	35.5	186	68.4	54	29.0
Seventh wave	173	58.1	72	41.6	157	57.7	52	33.1
Cumulative number	1,137	-	356	31.3	1,065	-	296	27.8
	Mean±SD				Mean±SD			
Follow-up year	8.0 ±3.0				8.2 ±2.8			
Follow-up participation times	3.8 ±0.5				3.9 ±0.4			

* Second wave is the baseline in this study. Abbreviations: MMSE=Mini-Mental State Examination

Table 2. Baseline characteristics and food intake of subjects by sex

	Men (total n=583)			Women (total n=562)		
	Subjects available for analyses	Subjects excluded From the analyses*	p value	Subjects available for analyses	Subjects excluded From the analyses	p value
Number of subjects	298	285		272	290	
Age(mean± SD, years)	67.7±5.6	71.1±5.6	0.915	68.0±5.3	71.3±5.7	0.235
MMSE score(mean± SD)	29.0±0.8	26.6±1.9	<.0001	29.1±0.8	26.7±2.2	<.0001
Body mass index (mean± SD, kg/m^2)	22.9±2.7	22.7±3.0	0.085	22.7±2.9	23.3±3.6	0.0003
Alcohol (mean ± SD, ml/day)	13.9±18.2	12.3±16.8	0.201	2.3±6.1	1.8±4.1	<.0001
Household annual income score (mean ± SD, 1-11 scale)	5.7±2.6	5.4±2.7	0.721	5.0±2.8	4.8±2.8	0.889
Education (n, %)						
≤9 years	84 , 28.2%	127 , 44.6%	<.0001	102 , 37.5%	162 , 55.9%	<.0001
10-12 years	40 , 13.4%	48 , 16.8%		63 , 23.2%	71 , 24.5%	
≥13 years	174 , 58.4%	110 , 38.6%		107 , 39.3%	57 , 19.7%	
Smoking status (n, %)						
Current	84 , 28.2%	88 , 30.9%	0.477	14 , 5.1%	3 , 1.0%	0.005
Former/never	214 , 71.8%	197 , 69.1%		258 , 94.9%	285 , 98.3%	
Clinical history (n, %)						
Heart disease	26 , 8.7%	31 , 10.9%	0.344	24 , 8.8 %	24 , 8.3 %	0.876
Stroke	22 , 7.4%	28 , 9.8%	0.281	9 , 3.3%	7 , 2.4%	0.542
Hypertension	102 , 34.2%	112 , 39.3%	0.182	99 , 36.4%	126 , 43.4%	0.071
Hyperlipidemia	47 , 15.8%	36 , 12.6%	0.310	78 , 28.7%	85 , 29.3%	0.786
Diabetes	37 , 12.4%	44 , 15.4%	0.284	14 , 5.1%	27 ,9.3%	0.053
Energy (mean ± SD, kcal/day)	2266.4±373.5	2157.1±386.7	0.565	1849.5±326.3	1789.3±345.0	0.367
Cereals (mean ± SD, g/day)	516.8±145.6	535.4±144.7	0.928	394.4±108.4	405.2±109.6	0.861
Potatoes (mean ± SD, g/day)	51.6±42.4	45.9±37.2	0.032	47.1±37.5	46.5±36.0	0.510
Beans (mean ± SD, g/day)	78.9±54.8	70.6±54.3	0.865	70.3±46.9	66.2±48.9	0.494
Green yellow vegetables (mean ± SD, g/day)	132.2±74.4	117.8±74.0	0.925	133.8±71.7	115.4±72.3	0.890
Non-green yellow vegetables (mean ± SD, g/day)	203.5±87.8	187.6±91.8	0.456	184.9±77.6	177.2±77.2	0.931
Fruits (mean ± SD, g/day)	173.3±142.7	145.5±127.9	0.073	178.6±127.0	171.3±132.1	0.529
Fish and shellfish (mean ± SD, g/day)	113.6±55.8	106.0±49.1	0.038	87.3±44.3	82.5±40.0	0.097
Meats (mean ± SD, g/day)	60.6±35.6	52.3±34.6	0.648	47.4±28.7	46.1±29.7	0.598
Eggs (mean ± SD, g/day)	50.2±27.2	48.7±30.8	0.037	42.9±23.9	41.5±26.8	0.068
Milk and dairy products (mean ± SD, g/day)	163.3±134.0	153.6±130.4	0.661	166.3±128.1	158.5±128.5	0.964
Sweets (mean ± SD, g/day)	33.5±37.4	27.7±33.9	0.105	44.6±39.5	38.6±39.4	0.967

*Subjects excluded from the analyses included those who were older than 60 years or scored ≤27 in the second wave and those who did not participate in the follow-up survey or had any missing values. The number of excluded subjects according to the characteristics listed ranged from 249-285 in men and 253-290 in women. P value for continuous variables, independent t-test was used; for categorical variables, chi-square test or Fisher's exact probability test was used. Abbreviations: MMSE=Mini-Mental State Examination.

Table 3. Longitudinal relationships between baseline food intake and odds ratios (95% CI) for MMSE scores≤27 10 years later. Cumulative data were analyzed with generalized estimation equations

			Men (total n=1,137)			Women (total n=1,065)		
			1 SD	Odds ratio (95%CI)	p value	1 SD	Odds ratio (95%CI)	p value
Energy intake	1 SD kcal/day increase	Model 3	374	1.09 (0.90 - 1.31)	0.378	326	0.90 (0.72 - 1.12)	0.343
Cereals	1 SD g/day increase	Model 1	146	1.18 (1.00 - 1.40)	0.056	108	1.38 (1.13 - 1.68)	0.002
		Model 2		1.20 (1.02 - 1.42)	0.032		1.29 (1.05 - 1.57)	0.013
		Model 3		1.18 (0.97 - 1.43)	0.103		1.43 (1.15 - 1.77)	0.001
Potatoes	1 SD g/day increase	Model 1	42	0.97 (0.82 - 1.15)	0.747	37	1.06 (0.86 - 1.30)	0.611
		Model 2		0.95 (0.81 - 1.11)	0.528		1.09 (0.89 - 1.34)	0.389
		Model 3		0.97 (0.83 - 1.13)	0.707		1.11 (0.88 - 1.40)	0.365
Beans	1 SD g/day increase	Model 1	55	0.93 (0.78 - 1.11)	0.429	47	0.80 (0.65 - 0.98)	.0.035
		Model 2		0.93 (0.78 - 1.11)	0.417		0.82 (0.67 - 1.00)	0.053
		Model 3		0.96 (0.79 - 1.15)	0.649		0.84 (0.68 - 1.03)	0.094
Green yellow vegetables	1 SD g/day increase	Model 1	74	0.83 (0.69 - 0.99)	0.041	72	0.95 (0.76 - 1.18)	0.626
		Model 2		0.84 (0.69 - 1.03)	0.087		1.00 (0.80 - 1.25)	0.993
		Model 3		0.86 (0.71 - 1.05)	0.144		1.07 (0.84 - 1.37)	0.563
Non-green yellow vegetables	1 SD g/day increase	Model 1	88	0.92 (0.78 - 1.09)	0.347	78	0.86 (0.70 -1.06)	0.152
		Model 2		0.90 (0.77 - 1.06)	0.202		0.83 (0.67 - 1.02)	0.075
		Model 3		0.91 (0.77 - 1.07)	0.247		0.87 (0.70 - 1.08)	0.206
Fruits	1 SD g/day increase	Model 1	143	0.96 (0.82 - 1.13)	0.634	127	0.98 (0.79 - 1.22)	0.866
		Model 2		0.92 (0.79 - 1.07)	0.271		1.06 (0.85 - 1.32)	0.623
		Model 3		0.92 (0.78 - 1.07)	0.265		1.15 (0.90 - 1.46)	0.266
Fish and shellfish	1 SD g/day increase	Model 1	56	0.98 (0.82 - 1.17)	0.824	44	1.06 (0.86 - 1.30)	0.605
		Model 2		1.02 (0.86 - 1.21)	0.795		1.09 (0.89 - 1.33)	0.400
		Model 3		1.00 (0.85 - 1.19)	0.956		1.18 (0.94 - 1.47)	0.149
Meats	1 SD g/day increase	Model 1	36	0.95 (0.80 - 1.13)	0.576	29	0.88 (0.70 -1.09)	0.244
		Model 2		0.99 (0.83 - 1.18)	0.908		0.83 (0.65 - 1.04)	0.109
		Model 3		1.01 (0.84 - 1.21)	0.931		0.83 (0.66 - 1.06)	0.138
Eggs	1 SD g/day increase	Model 1	27	0.93 (0.78 - 1.10)	0.395	24	1.16 (0.93 - 1.45)	0.194
		Model 2		0.89 (0.75 - 1.04)	0.137		1.13 (0.89 - 1.42)	0.313
		Model 3		0.88 (0.75 - 1.05)	0.151		1.16 (0.93 - 1.46)	0.195
Milk and dairy products	1 SD g/day increase	Model 1	134	0.99 (0.85 - 1.17)	0.939	128	0.78 (0.65 -0.92)	0.004
		Model 2		0.95 (0.81 - 1.11)	0.516		0.77 (0.63 - 0.93)	0.007
		Model 3		0.95 (0.81 - 1.11)	0.533		0.80 (0.65 - 0.98)	0.034
Sweets	1 SD kcal/day increase	Model 1	37	0.96 (0.81 - 1.13)	0.622	39	1.00 (0.82 - 1.22)	0.982
		Model 2		0.94 (0.79 - 1.10)	0.428		0.96 (0.79 - 1.17)	0.694
		Model 3		0.93 (0.79 - 1.10)	0.412		1.01 (0.81 - 1.26)	0.934

Model 1: Adjusted for age (year) and follow-up time (year). Model 2: Adjusted for Model 1 + MMSE score at baseline. Model 3: Adjusted for Model 2 + education (≤9, 10-12, ≥13 years), body mass index (kg/m²), household annual income (1-11 score), current smoking status (yes or no), energy intake (kcal/day), and history of heart disease, hypertension, hyperlipidemia, and diabetes (yes or no).Abbreviations: MMSE=Mini-Mental State Examination.