Table 4
Association between LBP and radiographic changes at each level in the lumbar region

	L1–L2		L2–L3		L3–L4		L4–L5		L5–S1	
	Proportion of participants with LBP (%)	OR (95% CI)	Proportion of participants with LBP (%)	OR (95% CI)	Proportion of participants with LBP (%)	OR (95% CI)	Proportion of participants with LBP (%)	OR (95% CI)	Proportion of participants with LBP (%)	OR (95% CI)
None	225/593 (37.9)	1	153/416 (36.8)	1	121/347 (34.9)	1	74/228 (32.5)	1	99/284 (34.9)	1
DD alone	76/193 (39.4)	1.0 (0.7–1.4)	138/322 (42.9)	1.19 (0.9–1.6)	161/400 (40.3)	1.17 (0.9–1.6)	184/449 (41.0)	1.36 (0.9–1.9)	176/440 (40.0)	1.14 (0.8–1.6)
ESC alone	11/27 (40.7)	1.06 (0.5–2.3)	9/23 (39.1)	0.96 (0.4–2.3)	3/10 (30.0)	0.74 (0.2–2.7)	3/16 (18.8)	0.50 (0.1–1.6)	6/15 (40.0)	1.24 (0.4–3.6)
SN alone	19/46 (41.3)	1.07 (0.6–2.0)	15/40 (37.5)	1.03 (0.5–2.0)	10/22 (45.5)	1.58 (0.6–3.8)	5/14 (35.7)	1.18 (0.3–3.5)	1/1 (100)	—
DD and ESC	16/36 (44.4)	1.20 (0.6–2.4)	33/69 (47.8)	1.37 (0.8–2.3)	55/93 (59.1)	2.43 (1.5–4.0)*	81/164 (49.4)	1.82 (1.2–2.8)†	96/201 (47.8)	1.60 (1.1–2.3)*
DD and SN	31/61 (50.8)	1.47 (0.8–2.6)	32/73 (43.8)	1.14 (0.7–1.9)	24/70 (34.3)	0.84 (0.5–1.5)	16/52 (30.8)	0.84 (0.4–1.6)	3/15 (20.0)	0.45 (0.1–1.5)
SN and ESC	2/3 (66.7)	2.48 (0.2–53.8)	0/6 (0)	—	2/2 (100)	—	1/2 (50.0)	2.04 (0.08–52.5)	0/0 (0)	—
DD, ESC, and SN	13/16 (81.3)	6.00 (1.9–26.6)‡	13/26 (50.0)	1.49 (0.7–3.4)	17/31 (54.8)	2.07 (0.9–4.5)	29/50 (58.0)	2.56 (1.4–4.9)‡	12/19 (63.2)	2.85 (1.1–2.3)*

CI, confidential interval; DD, disc degeneration; ESC, end plate signal change; LBP, low back pain; OR, odds ratio; SN, Schmorl node.
Note: Proportion of participants with LBP means the number of participants with LBP/the number of participants with each radiographic change. Multivariate logistic regression analysis of radiographic change was associated with LBP after adjustment for age, body mass index, and sex.
* p<.05.
† p<.01.
‡ p<.005.

demonstrating ESC [35]. Therefore, pain may originate from damaged end plates in patients with ESC.

Another possibility is that ESC is a proxy for discogenic pain, as ESC is most often seen in association with DD [12,36] and tumor necrosis factor–immunoreactive nerves have also been reported in DD [37]. Both the present results and a previous study indicate that the association between ESC and LBP appears to be stronger than that between DD and LBP [29]. Regarding the association between the level of ESC and LBP, Kuisma et al. [32] reported that both Modic type I and II lesions at L5–S1, but not at upper levels, are associated with LBP. However, the present study showed that the OR of LBP with Modic type I and II lesions at L3–L4 was higher than that at L5–S1. We speculate that the association of LBP symptoms with the L3–L4 level might be because of mechanical factors and alignment of the whole spine, but the pathophysiology of this phenomenon needs further investigation.

In the present study, SN alone was not significantly associated with LBP. In addition, most SNs were combined with DD. In fact, SN was not itself a risk factor for back pain but was an indicator of DD in the previous reports [13,14,28]. Furthermore, SN occurs when the cartilaginous end plate of the vertebral body has been disrupted [38]. Such a disruption can be produced by an intrinsic abnormality of the end plate itself or by alterations in the subchondral bone of the vertebral body [39]. Therefore, LBP might be a multifactorial condition arising from a combination of DD, ESC, and SN in the lumbar region.

Study limitations

The present study has several limitations. First, it is a cross-sectional study, so the transition from DD, ESC, and SN cannot be clarified. Second, more than 1,000 participants included in the present study may not represent the general population, as they were recruited from only 2 areas. To confirm whether the participants of the Wakayama Spine Study are representatives of the Japanese population, we compared anthropometric measurements and frequencies of smoking and alcohol drinking between the study participants and the general Japanese population. No significant differences in BMI were observed (men: 23.7 and 24.0, p=.33 and women: 23.1 and 23.5, p=.07). Furthermore, the proportions of current smokers and drinkers (those who regularly smoked or drank more than one drink per month) among men and that of current drinkers among women were significantly higher in the general Japanese population than in the study population, and no significant difference in current smokers was observed among women (men smokers, 32.6% in the Japanese population and 25.2% among study participants, p=.015; women smokers, 4.9% in the Japanese population and 4.1% among study participants, p=.50; men drinkers, 73.9% in the Japanese population and 56.8% among study participants, p<.0001; and women drinkers, 28.1% in the Japanese population and 18.8% among study participants, p<.0001). These results suggest the likelihood that participants in this study had healthier lifestyles than the general Japanese population [40]. This "healthy" selection bias should be taken into consideration when generalizing the results obtained from the Wakayama Spine Study. Third, distinction of the type of Modic changes was not possible because owing to cost and time limitations, only T2-weighted images were obtained. However, Ohtori et al. [35] reported that both Modic type I and II changes were significantly associated with inflammation induced by tumor necrosis factor. Furthermore, the prevalence of Modic Type I was lower than that of Type II in a systematic review [41]. Therefore, we propose that high-intensity ESC on T2-weighted images is informative in the assessment of LBP. Fourth, the definition of LBP is different among many studies [24,32], and the result of association between LBP and radiographic change might be changed depending on the definition. We decided that the definition of LBP was "LBP on most days during the past month, in addition to now" from the previous reports [20–24].

Finally, the radiographic changes of DD, ESC, and SN in the lumbar region might not be strongly correlated with LBP. Low back pain can be caused by multiple factors including osteoporosis, back muscle strain, and psychosocial problems; thus, we can explain only a portion of the associated factors of LBP from MRI findings. Future investigations should include continued follow-up surveys of psychosocial and other factors.

Conclusions

We first investigated combinations of the radiographic changes DD, ESC, and SN in the lumbar region and at each intervertebral level and their association with LBP in a large population of individuals ranging in age from 21 to 97 years old. Our data suggest that DD alone is not an associated factor for LBP. By contrast, the combination of DD, ESC, and SN at L1–L2, L4–L5, and L5–S1 was significantly associated with LBP. Furthermore, the combination of DD and ESC at L3–L4, L4–L5, and L5–S1 was also significantly associated with LBP. Low back pain is caused by multiple factors beyond the scope of MRI findings. However, this study clarified that DD alone was not associated with LBP, whereas, by contrast, the combination of DD, ESC, and/or SN was associated with LBP. Although they may not be immediately applicable to clinical practice, these findings contribute to the progress of LBP research. Further investigations along with continued follow-up surveys will continue to elucidate the causes of LBP.

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Clinical Study

The prevalence of cervical myelopathy among subjects with narrow cervical spinal canal in a population-based magnetic resonance imaging study: the Wakayama Spine Study

Keiji Nagata, MD, PhD[a], Noriko Yoshimura, MD, PhD[b], Hiroshi Hashizume, MD, PhD[a,*], Shigeyuki Muraki, MD, PhD[c], Yuyu Ishimoto, MD, PhD[a], Hiroshi Yamada, MD, PhD[a], Noboru Takiguchi, MD, PhD[a], Yukihiro Nakagawa, MD, PhD[a], Akihito Minamide, MD, PhD[a], Hiroyuki Oka, MD[b], Hiroshi Kawaguchi, MD, PhD[d], Kozo Nakamura, MD, PhD[e], Toru Akune, MD, PhD[c], Munehito Yoshida, MD, PhD[a]

[a]*Department of Orthopaedic Surgery, Wakayama Medical University, 811-1, Kimiidera, Wakayama City, 641-8510, Japan*

[b]*Department of Joint Disease Research, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8654, Japan*

[c]*Department of Clinical Motor System Medicine, 22nd Century Medical & Research Center, Faculty of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8654, Japan*

[d]*Japan Community Health Care Organization Tokyo Shinjuku Medical Center, 6-1-1 Shinjuku, Shinjuku-ku, Tokyo 160-8402, Japan*

[e]*Rehabilitation Services Bureau, National Rehabilitation Center for Persons with Disabilities, 1, Namiki 4-chome, Tokorozawa City, Saitama Prefecture 359-8555, Japan*

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Abstract

BACKGROUND CONTEXT: A narrow cervical spinal canal (CSC) is a well-known risk factor for cervical myelopathy (CM). However, no epidemiologic data of the CSC based on a population-based cohort are available.

PURPOSE: The purpose of the study was to investigate the age-related differences in CSC diameters on plain radiographs and to examine the associated magnetic resonance imaging (MRI) abnormalities including cervical cord compression and increased signal intensity (ISI) as well as the clinical CM with the narrow CSC.

STUDY DESIGN/SETTING: This was a cross-sectional study.

PARTICIPANT SAMPLE: Data were obtained from the baseline survey of the Wakayama Spine Study that was performed from 2008 to 2010 in a western part of Japan. Finally, a total of 959 subjects (319 men and 640 women; mean age, 66.4 years) were included.

OUTCOME MEASURES: The outcome measures included in the study were the CSC diameter at C5 level on plain radiographs, cervical cord compression and ISI on sagittal T2-weighted MRI, and physical signs related to CM (eg, the Hoffmann reflex, hyperreflexia of the patellar tendon, the Babinski reflex, sensory and motor function, and bowel/bladder symptoms).

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* Corresponding author. Department of Orthopaedic Surgery, Wakayama Medical University, 811-1 Kimidera, Wakayama City, Wakayama 641-8510, Japan. Tel.: +81-73-441-0645; fax.: +81-73-448-3008.

E-mail address: hashizum@wakayama-med.ac.jp (H. Hashizume)

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METHODS: The age-related differences of CSC diameters in men and women were investigated by descriptive statistics. The prevalence of MRI abnormalities and clinical CM was compared among the groups divided by the CSC diameter (less than 13, 13–15, and 15 mm or more). In addition, a logistic regression analysis was performed to determine the association of the CSC diameter with cervical cord compression/clinical CM after overall adjustment for age, sex, and body mass index.
RESULTS: The CSC diameter was narrower with increasing age in both men and women. The prevalence of cervical cord compression, ISI, and the clinical CM was significantly higher in the narrower CSC group. The prevalence of cervical cord compression, ISI, and CM among subjects with CSC diameter less than 13 mm was 38.0%, 5.4%, and 10.1%, respectively. In the logistic model, the CSC diameter was a significant predictive factor for the clinical CM ($p<.0001$).
CONCLUSIONS: This study firstly confirmed the age-related differences in CSC diameters and the significant association of the narrow CSC diameter with CM in a population-based cohort.

Keywords: Cervical spine; Spinal canal stenosis; Cervical myelopathy; Magnetic resonance imaging; Population-based cohort; Epidemiology

Introduction

In cervical spinal disorders such as cervical myelopathy (CM) and spinal cord injury, developmental cervical spinal canal (CSC) stenosis has been considered as an effective predictor of clinical outcome [1,2]. The spinal cord area should be evaluated after comparing with data obtained from asymptomatic subjects of each age group. Age-dependent data are required because the spinal cord may change with age, just as the cerebrum decreases in size with age in elderly subjects. The spinal canal should also be considered in asymptomatic subjects when treating cervical spinal disorders because patients with a tight spinal canal are more susceptible to spinal cord damage. However, the prevalence of spinal cord disorders and CM among patients with CSC of narrow diameter is not known. To date, few studies have focused on age-related differences in the cervical spinal cord and CSC [3,4]. Recent advances in magnetic resonance imaging (MRI) have made it possible to noninvasively obtain clear images of the cervical spinal cord, thereby making evaluation of traumatic spinal cord injury and cervical cord compression more applicable in routine practice. This study was undertaken to clarify age-related differences in the cervical spinal cord and CSC using magnetic resonance imaging (MRI) to establish the basis for morphometric evaluation of patients with cervical spinal cord disorders. More specifically, the purposes of this study were to investigate age-related changes of the CSC in a population-based cohort in Japan and to examine the associated MRI abnormalities including cervical cord compression and increased signal intensity (ISI) as well as the clinical CM with the narrow CSC diameters.

Participants and methods

Participants

The present study is a part of "The Wakayama Spine Study: a population-based cohort," which was a large-scale population-based MRI study. Because a detailed profile of the Wakayama Spine Study has already been described elsewhere, only a brief summary is provided here [5,6]. The Wakayama Spine Study was conducted between 2008 and 2010 in a mountainous region in Hidakagawa, Wakayama, and a coastal region in Taiji, Wakayama. From inhabitants of the Hidakagawa and Taiji regions, 1,063 potential study subjects were recruited for MRI examinations. Among those 1,063 candidates, 52 declined the examination; therefore, 1,011 inhabitants were registered in the present study. Among those 1,011 participants, individuals with MRI-sensitive implanted devices (such as a pacemaker) and other disqualifiers were excluded. Ultimately, the cervical spine was scanned with MRI in 985 participants. Four participants who had undergone a previous cervical operation were excluded from the analysis, and another four participants whose MRI interpretation was difficult because of poor image quality were also excluded. After these exclusions, the present study had 977 participants. Radiographic evaluation of the cervical spine was also performed in 959 of the subjects. In total, both MRI and radiographic results were available for 959 participants (319 men and 640 women) with an age range of 21 to 97 years (mean, 67.3 years for men and 65.9 years for women). The participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information; and anthropometric and physical performance measurements were taken. All study participants provided informed consent, and the study design was approved by the appropriate ethics review boards.

Anthropometric measurements included height (meter), weight (kilogram), and body mass index (BMI; weight [kilogram]/height^2 [m^2]). Medical information concerning neck pain, sensory disturbances, the Hoffmann reflex, the Babinski reflex, and the deep tendon reflex of the patellar tendon was gathered by an experienced orthopedic surgeon. The Hoffmann reflex was elicited with the hand in a neutral position by flicking the distal phalanx of the middle finger and observing flexion of the distal phalanx of the thumb [7,8].

The Babinski reflex was elicited by firmly sweeping from the lateral part of the sole to the base of the toes with a pointed end of a reflex hammer and observing the hallux extensor response [9,10]. Hyperreflexia of the patellar tendon, a positive Hoffmann reflex, and a positive Babinski reflex were defined as aggravation on both sides. A myelopathic sign was defined as the presence of hyperreflexia of the patellar tendon, Hoffmann reflex, or Babinski reflex.

Measurements of CSC diameter and canal-to-body ratio on radiographs

All subjects also underwent lateral radiography with their neck in the neutral position. They were told by an X-ray technician to look straight ahead in a relaxed position. The radiographic data were scanned and calibrated using the ruler, which was put on the film. The sagittal spinal canal diameter at the C5 level was measured as the shortest distance from the midpoint between the vertebral body's superior and inferior end plates to the spinolaminar line. The canal-to-body ratio (CBR) was obtained by dividing the diameter of the spinal canal by that of the vertebral body to assess the tightness of the spinal canal and also to eliminate the magnification effect of radiographs.

Magnetic resonance imaging

An MRI scan of the cervical spine was obtained for each participant using a 1.5-T Excelart imaging system (Toshiba, Tokyo, Japan). All scans were taken in the supine position, except for participants with a rounded back, who used a triangular pillow under their heads and knees. The imaging protocol included a sagittal T2-weighted fast spin-echo pulse sequence (repetition time: 4,000 ms; echo time: 120 ms; and field of view: 300 × 320 mm) and an axial T2-weighted fast spin-echo pulse sequence (repetition time: 4,000 ms; echo time: 120 ms; and field of view: 180 × 180 mm).

MRI measures

Midsagittal T2-weighted images were assessed by an experienced orthopedic surgeon (Keiji Nagata), who was blinded to participants' clinical status.

Evaluation of cervical cord compression

Cervical cord compression was defined as compression with an anterior and/or a posterior component of the spinal cord [6]. Cervical cord compression was evaluated at each intervertebral level from C2–C3 to C7–T1.

Evaluation of signal intensity of the spinal cord

Increased signal intensity was defined as a high-intensity area in contrast with the adjacent isointensity portion of the spinal cord [11]. The ISI was evaluated in the area from C2 to T1.

Measurement of spinal cord diameter

The spinal cord diameter was measured manually at the midpoint of the C5 vertebral body level using the imaging software OsiriX (http://www.osirix-viewer.com/).

Definition of clinical CM

Myelopathy is defined clinically by the presence of myelopathic signs (eg, the Hoffmann reflex, hyperreflexia of the patellar tendon, and the Babinski reflex), usually accompanied by bilateral sensory deficits or sensory level and bowel/bladder symptoms. Among participants with myelopathic signs, cervical cord compression was the essential condition for diagnosing CM.

Statistical analyses

A comparison of baseline characteristics between sexes was performed using the Student *t* test. Differences in the CSC diameter, vertebral body, spinal cord, and CBR among men and women were determined using the Student *t* test. One-way analysis of variance was used to evaluate the differences in CSC diameter, vertebral body, spinal cord, and CBR among different age groups. The chi-square test was used to assess the presence of ISI among different age groups.

For categorical data, the chi-square test was used to assess the presence of significant differences among different diameters of the CSC. For continuous outcomes, the analysis of variance test was used to assess differences among different diameters of the CSC. In addition, to determine the association of ISI, CSC diameter, and CBR with cervical cord compression and CM, logistic regression analysis was used after overall adjustment for age, sex, and BMI. All statistical tests were performed at a significance level of .05 (two-sided). Data analyses were performed using JMP, version 8 (SAS Institute, Inc, Cary, NC, USA).

Results

Characteristics of the participants

The baseline characteristics of the 977 participants, including data for anthropometric measurements and physical performance, are listed in Table 1. There was no

Table 1
Characteristics of men and women participating in the present study

Characteristic	Men	Women
N	319	640
Age, y	67.3±13.8	65.9±13.3
Height, cm	164.6±7.2**	151.6±7.2
Weight, kg	64.4±11.6**	53.0±9.4
Body mass index, kg/m^2	23.7±3.4*	23.1±3.7
Grip strength, kg	37.9±9.1**	23.9±5.9

Note: Significantly different from women by the Student *t* test (*p<.01; **p<.001).
Values are the mean±standard deviation.

Table 2
Radiographic and MRI measures stratified by gender and age strata

	Radiographic measures		MRI measures	
Age strata	Diameter of cervical spinal canal (mm)	Canal-to-body ratio	Increased signal intensity, N (%)	Diameter of spinal cord (mm)
Men				
Overall	14.8±1.3	0.82±0.12	15 (4.6)	6.9±0.9
<50 y	15.2±1.3	0.86±0.09	2 (5.2)	7.3±0.8
50–59 y	14.8±1.7	0.85±0.13	4 (6.9)	7.1±0.9
60–69 y	14.9±1.2	0.82±0.11	3 (4.5)	6.9±0.7
70–79 y	14.8±1.2	0.82±0.11	2 (2.3)	6.9±0.8
≥80 y	14.4±1.1	0.79±0.12	4 (5.5)	6.6±0.9
Women				
Overall	14.1±1.2	0.92±0.13	11 (1.7)	6.8±0.9
<50 y	14.5±1.3	0.99±0.14	1 (1.1)	6.9±0.9
50–59 y	14.4±1.3	0.96±0.12	1 (0.0)	7.0±0.7
60–69 y	14.1±1.1	0.91±0.12	0 (0)	6.8±0.8
70–79 y	13.9±1.1	0.89±0.12	6 (3.5)	6.8±0.9
≥80 y	13.8±1.0	0.86±0.12	3 (2.5)	6.7±0.9

Note: Otherwise indicated, values are mean±standard deviation for each age strata in men and women.

significant difference in age between sexes. Height, weight, and BMI were significantly higher in men than in women.

Age and sex differences of CSC diameter, CBR, ISI, and spinal cord diameter

Table 2 lists the age-related differences in diameters of the CSC, the CBR on radiograph, ISI, and spinal cord diameter on MRI in men and women among different age groups. The CSC diameter was significantly narrower with age in women ($p<.0001$). In men, the CSC diameter had a tendency to be narrower with age, but it was not significantly different in women. The mean diameter of the CSC was not significantly different between men and women. The diameter of the vertebral body was significantly higher in men and women with increasing age ($p<.0001$). The mean CBR in men and women was 0.82 and 0.92, respectively, and it was significantly higher in women than in men at the C5 vertebral level. The CBR was significantly lower with increasing age in both sexes (men, $p=.0004$; women: $p<.0001$).

The prevalence of ISI in all participants was 2.7% (4.6% in men and 1.7% in women) and was significantly higher in men than in women ($p=.007$). The prevalence of ISI was not significantly different with age between sexes. The diameter of the spinal cord was significantly lower with increasing age in both sexes (men, $p=.0012$; women, $p=.0068$). The mean diameter of the spinal cord was not significantly different between men and women.

Prevalence of MRI measures and CM among different diameters of the CSC

Anthropometric measures such as CSC diameter were found to be significantly different according to age (Table 3). Regarding MRI measures, significant differences between different CSC diameters were found with respect to cervical cord compression ($p<.0001$), ISI ($p<.0001$), and spinal cord diameter ($p<.0001$), except for ISI in women. The prevalence of cervical cord compression, ISI, and CM in subjects with a CSC diameter less than 13 mm was 61.9%, 23.8%, and 4.8% in men, respectively. Meanwhile, the prevalence of cervical cord compression, ISI, and CM among female subjects with a CSC diameter less than 13 mm was 33.3%, 1.9%, and 11.1%, respectively. Multiple logistic regression analysis was performed to estimate the predictive factors for CM in MRI and radiographic measurements after adjustment for age, sex, and BMI (Table 4). As an overall result, ISI, CSC diameter, and CBR were significant predictive factors for CM ($p<.01$). There was a positive association between cervical cord compression and spinal cord diameter, whereas spinal cord diameter itself was not a significant predictive factor for CM.

Discussion

The present study is the first population-based study to clarify the normal value of the diameter of the CSC and its association with cervical cord compression, ISI, and CM in Japanese men and women. We clarified that the CSC diameter was narrower with age in both men and women in the population-based cohort. The prevalence of the clinical CM was significantly higher in the narrower CSC group. Furthermore, in the logistic model, the CSC diameter was a significant predictive factor for clinical CM.

In this study, the CSC and vertebral body diameters were measured using plain radiographs because the posterior longitudinal ligament could not be distinguished from the vertebral body on MRI. There have been several reports on the diameter of the CSC. Porter et al. [12] reported that canal size did not appear to change significantly with biomechanical stress and aging. Meanwhile, Goto et al. [3] and Kato et al. [4] reported that the younger generation (younger than 40 years of age) had a statistically wider CSC. Our result was consistent with the latter reports. Why do younger persons have a wider CSC than elderly persons? There are two possible reasons for the differences in CSC diameter between generations. First, the CSC diameter becomes narrower with aging. A CSC with a small diameter is primarily a developmental and not a degenerative phenomenon. However, Hukuda and Kojima [13] reported that the diameter of the vertebral body was wider in older people compared with younger people. Those morphologic changes of the vertebral component may affect the diameter of the CSC. Second, the changes in Japanese eating habits and physique in the past few decades may have contributed to the changes in the diameter of the CSC. The variation of CSC diameter with different generation may be a limited phenomenon in Japan. However, we believe the results prompt future investigations into the various factors affecting the CSC dimensions, apart from aging.

Table 3
Prevalence of MRI measures and cervical myelopathy among different diameter of cervical spinal canal

	Diameter of cervical spinal canal (mm)			
Factors	<13	13–15	≥15	p value
Men				
N	21	162	136	
Age, y	69.5±12.0	69.1±12.8	64.9±14.9	.027
Height, cm	163.7±5.6	163.6±6.8	165.8±7.7	.025
Weight, kg	67.6±10.5	61.7±10.6	67.0±12.3	.0002
Body mass index, kg/m^2	25.2±3.3	23.0±3.2	24.2±3.4	.0006
MRI measures				
Cervical cord compression, N (%)	13 (61.9)	58 (35.8)	22 (16.2)	<.0001
Increased signal intensity, N (%)	5 (23.8)	9 (5.6)	1 (0.7)	<.0001
Diameter of spinal cord (mm)	6.2±0.5	6.8±0.8	7.2±0.8	<.0001
Cervical myelopathy, N (%)	1 (4.8)	2 (1.2)	0 (0)	.09
Women				
N	108	383	149	
Age, y	68.7±13.3	67.2±12.8	60.4±13.4	<.0001
Height, cm	149.1±7.2	151.4±7.1	153.9±6.7	<.0001
Weight, kg	49.8±8.1	53.2±9.6	54.8±9.4	.0001
Body mass index, kg/m^2	22.4±3.2	23.2±3.7	23.2±3.8	.12
MRI measures				
Cervical cord compression, N (%)	36 (33.3)	92 (24.0)	11 (7.4)	<.0001
Increased signal intensity, N (%)	2 (1.9)	8 (2.1)	0 (0)	.21
Diameter of spinal cord (mm)	6.5±0.9	6.9±0.8	7.0±0.8	<.0001
Cervical myelopathy, N (%)	12 (11.1)	12 (3.1)	0 (0)	<.0001

MRI, magnetic resonance imaging.

Note: For categorical data, the chi-square test was used to assess the presence of significant differences among different diameters of the cervical spinal canal.

For continuous outcomes, comparison was made by the analysis of variance test differences among different diameters of the cervical spinal canal.

Regarding MRI measurements, the prevalence of cervical cord compression and ISI among persons with a CSC diameter less than 13 mm, which was considered to be developmental canal stenosis [14], was 61.9% and 23.8% in men and 33.3% and 1.9% in women, respectively. Above all, a CSC diameter less than 13 mm was observed in more than 10% of the participants. Of those with a CSC diameter less than 13 mm, cervical cord compression (ie, the preliminary step in the development of CM) was also observed in 61.9% of men and 33.3% of women. From these results, the number of people who have a risk for CM was considered quite high in the general population. Countee and Vijayanathan [15] reported that congenital stenosis in men with a cervical canal diameter of 14 mm or less was associated with quadriplegia after trauma. In the present study, we noted that the narrower the diameter of the CSC, the higher the prevalence of ISI. Of note, the distribution of prevalence between men and women was different. Increased signal intensity was seen in approximately 10% of men younger than 60 years, whereas it was seen in only 1% of women younger than 60 years, and was relatively higher in older people. In the present study, the prevalence of the clinical CM was significantly higher in the narrower CSC group. The result may show that patients with a narrowed spinal canal are more likely to develop CM. Further longitudinal studies are needed to clarify the causal

Table 4
The odds ratio and 95% confidence interval of increased signal intensity, diameter of spinal cord, diameter of cervical spinal canal, and canal-to-body ratio for cervical myelopathy

	Cervical cord compression		Cervical myelopathy	
Variables	OR* (95% CI)	p value	OR (95% CI)	p value
Age, y (+10 y)	23.6 (9.62–60.0)	<.0001	11.0 (1.15–133.9)	.047
Women (vs. men)	1.41 (1.03–1.92)	.032	4.33 (1.50–18.4)	.018
Body mass index, kg/m^2 (+1 SD)	2.12 (0.87–5.16)	.095	1.04 (0.94–1.15)	.41
Increased signal intensity positive	18.8 (6.87–66.4)	<.0001	6.32 (1.36–21.8)	.007
Diameter of spinal cord, mm (−1 mm)	1.40 (1.17–1.68)	.0002	1.46 (0.93–2.31)	.11
Diameter of cervical spinal canal, mm (−1 mm)	1.67 (1.45–1.93)	<.0001	2.73 (1.83–4.23)	<.001
Canal-to-body ratio (−10%)	1.85 (1.60–2.16)	<.0001	2.12 (1.47–3.16)	.0001

OR, odds ratio; CI, confidence interval; SD, standard deviation.

* OR was calculated by multiple logistic regression analysis after adjustment for age, gender, and body mass index.

relationship between narrowed spinal canal and CM. In addition, we clarified the positive association between cervical cord compression and spinal cord diameter, whereas the diameter of the spinal cord itself was not a significant predictive factor for CM. This may indicate that the spinal cord can become atrophied in individuals with cervical cord compression or in those who have a congenitally narrow spinal cord.

The present study also clarified the difference in age- and sex-related changes in the CSC diameter and CBR. The CSC has been the focus as a risk factor for CM [14,16]. However, in recent years, the CBR rather than CSC diameter has been reported to be a useful predictor for CM because of a magnification error resulting from the focus-to-film distance and the object-film distance on MRI [17]. However, Blackley et al. [18] showed that there is currently a poor correlation between the CBR and the true sagittal diameter of the spinal canal on computed tomography scans because of the wide normal variations in the diameter of the vertebral body. Therefore, the characteristics of the variations between the CSC diameter and the CBR should be considered. Of note, the present study found the CSC diameter to be higher in men than in women. However, the CBR was higher in women than in men, which is the reason for the increased diameter of the vertebral body in men. Therefore, the differences between the sexes should be taken into account when considering the CBR as a risk factor for CM.

Study limitations

The present study had several limitations. First, although more than 1,000 participants were included in the present study, these participants may not represent the general population because they were recruited from only two areas of Japan. However, anthropometric measurements were compared between the participants of the present study and the general Japanese population [19], and no significant differences in BMI were found between the participants in the present study and the Japanese population at large in both sexes (BMI [standard deviation] in men: 23.71 kg/m^2 [3.41 kg/m^2] and 23.95 kg/m^2 [2.64 kg/m^2], p=.33, respectively; BMI [standard deviation] in women: 23.06 kg/m^2 [3.42 kg/m^2] and 23.50 kg/m^2 [3.69 kg/m^2], p=.07, respectively). Second, the distribution of the CSC diameter applies to only a small portion of the Japanese population and cannot be extrapolated to other populations.

Conclusions

This study confirmed the significant association of the narrow CSC diameter with CM in a population-based cohort. The results prompt future studies to look into the various factors affecting the dimensions of the CSC, apart from aging.

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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

Noriko Yoshimura · Toru Akune · Saeko Fujiwara · Yoko Shimizu · Hideyo Yoshida · Go Omori · Akihiro Sudo · Yuji Nishiwaki · Munehito Yoshida · Hiroshi Shimokata · Takao Suzuki · Shigeyuki Muraki · Hiroyuki Oka · Kozo Nakamura

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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

N. Yoshimura (✉) · H. Oka
Department of Joint Disease Research, 22nd Century Medical and Research Center, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: yoshimuran-ort@h.u-tokyo.ac.jp

T. Akune · S. Muraki
Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

S. Fujiwara
Hiroshima Atomic Bomb Casualty Council, Hiroshima, Japan

Y. Shimizu · H. Yoshida
Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan

G. Omori
Center for Transdisciplinary Research, Institute for Research Promotion, Niigata University, Niigata, Japan

A. Sudo
Department of Orthopaedic Surgery, Mie University Graduate School of Medicine, Mie, Japan

Y. Nishiwaki
Department of Environmental and Occupational Health, School of Medicine, Toho University, Tokyo, Japan

M. Yoshida
Department of Orthopedic Surgery, School of Medicine, Wakayama Medical University, Wakayama, Japan

H. Shimokata
Graduate School of Nutritional Sciences, Nagoya University of Arts and Sciences, Aichi, Japan

T. Suzuki
National Center for Geriatrics and Gerontology, Aichi, Japan

K. Nakamura
National Rehabilitation Center for Persons with Disabilities, Saitama, Japan

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,

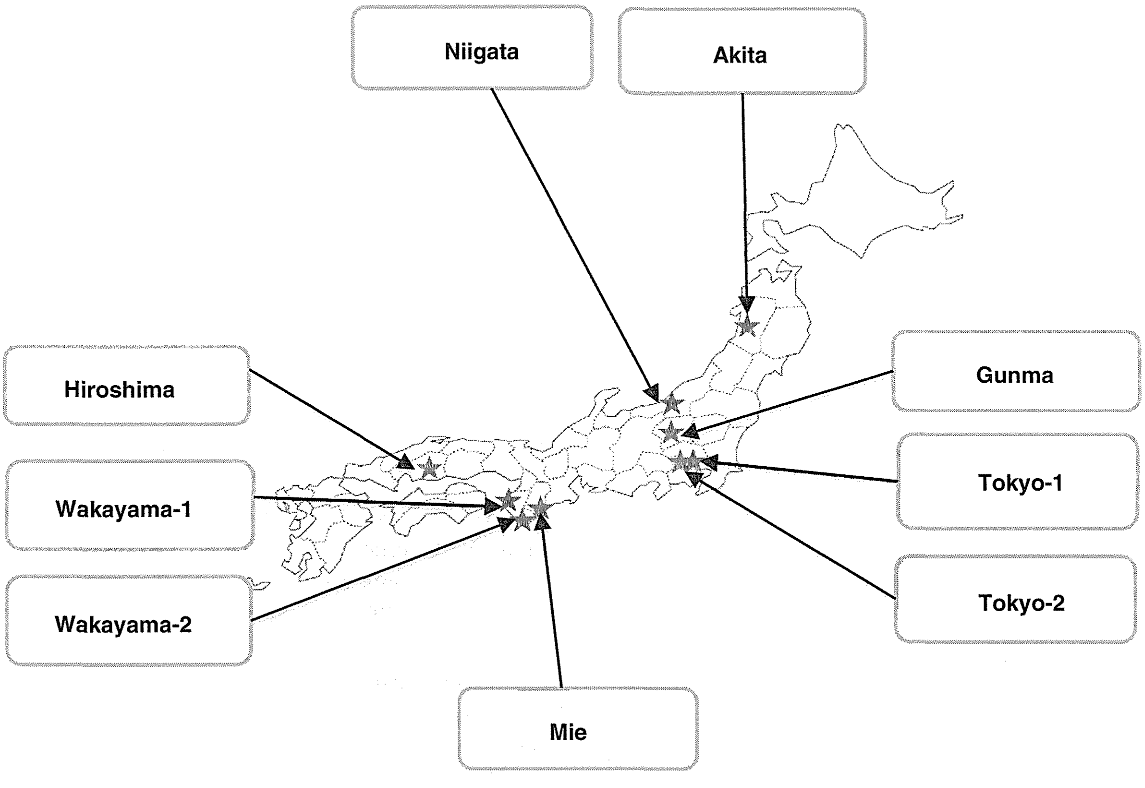

Fig. 1 Locations of the nine different regions from which the study cohorts were derived

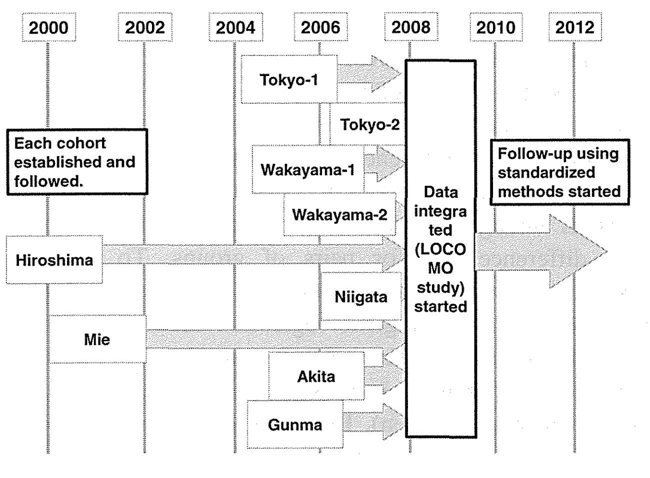

Fig. 2 Timeline of the LOCOMO study

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 $\geq$60 years, and

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

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

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

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

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

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

Values are represented as mean (standard deviation)

BMI body mass index

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

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

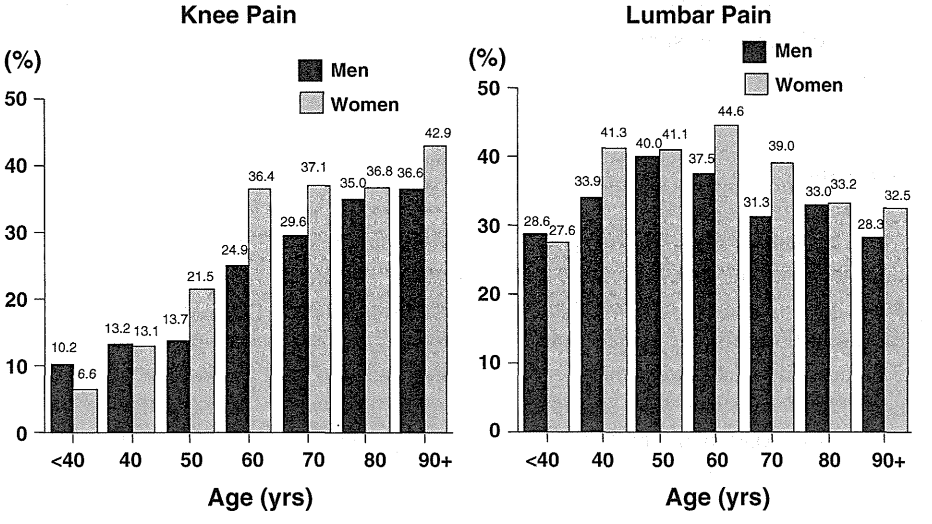

Fig. 3 Prevalence of knee pain and lumbar pain according to age and gender

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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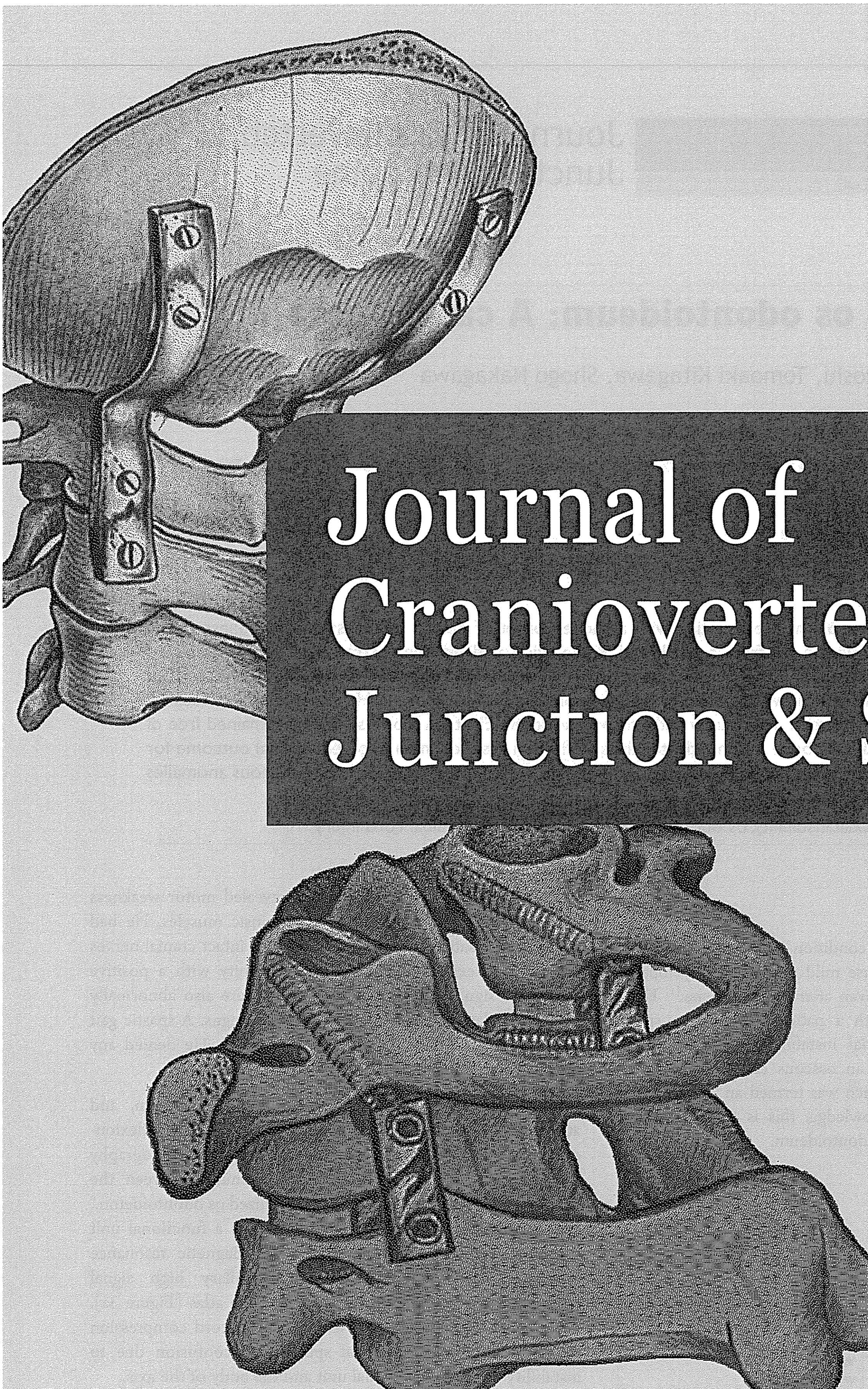

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