TABLE I Patient and Surgical Characteristics and Outcomes According to Hospital Volume

		Hospital Volume			
	Overall	Low (≤12/yr)	Medium (13-31/yr)	High (≥32/yr)	P Value
Total no. of patients	4803 (100.0%)	1585	1612	1606	
Sex					0.119
Male	2531 (52.7%)	827 (52.2%)	822 (51.0%)	882 (54.9%)	
Female	2272 (47.3%)	758	790	724	
Age in yr					
≤49	1178 (24.5%)	16.3%	27.3%	29.9%	
50-69	1894 (39.4%)	40.6%	36.8%	40.9%	
≥70	1731 (36.0%)	43.2%	35.9%	29.2%	
Age*	59.7 ± 18.9 yr	64.3 ± 16.6 yr	58.6 ± 19.3 yr	56.3 ± 19.7 yr	<0.001†
Diagnosis					<0.001†
Primary malignant bone tumor	587 (12.2%)	5.6%	14.0%	17.0%	
Primary malignant soft-tissue tumor	3163 (65.9%)	56.4%	72.8%	68.2%	
Metastatic bone tumor	1053 (21.9%)	38.0%	13.3%	14.8%	
Type of surgery					<0.001†
Bone tumor resection w/o prosthesis	991 (20.6%)	23.4%	16.9%	21.7%	
Soft-tissue tumor resection w/o prosthesis	2975 (61.9%)	52.6%	68.9%	64.3%	
Resection + prosthesis	689 (14.3%)	20.9%	11.3%	10.9%	
Amputation	148 (3.1%)	3.1%	3.0%	3.2%	
Duration of anesthesia in min‡					<0.001†
<120	842 (17.6%)	23.7%	14.2%	15.0%	
120-240	2090 (43.6%)	45.7%	41.0%	44.1%	
>240	1862 (38.8%)	30.6%	44.8%	40.9%	
Preop. comorbidities					
Diabetes mellitus	404 (8.4%)	10.5%	8.1%	6.6%	<0.001†
Chronic lung disease	88 (1.8%)	2.0%	1.7%	1.9%	0.855
Cardiac disease	151 (3.1%)	4.5%	3.7%	1.2%	<0.001†
Cerebrovascular disease	21 (0.4%)	0.7%	0.4%	0.2%	0.095
Chronic renal failure	39 (0.8%)	1.0%	0.8%	0.6%	0.476
Liver disease	10 (0.2%)	0.3%	0.3%	0.1%	0.272
At least one comorbidity	650 (13.5%)	16.8%	13.7%	10.1%	<0.001†
Postop. complications					
Surgical site infection	132 (2.7%)	2.8%	2.5%	2.9%	0.826
Sepsis	31 (0.6%)	0.6%	0.6%	0.7%	0.796
Pulmonary embolism	16 (0.3%)	0.4%	0.2%	0.4%	0.429
Cardiac events	64 (1.3%)	1.4%	1.5%	1.1%	0.643
Respiratory complications	51 (1.1%)	1.8%	0.8%	0.6%	0.001†
Cerebrovascular events	7 (0.1%)	0.2%	0.2%	0.1%	0.561
Acute renal failure	11 (0.2%)	0.4%	0.1%	0.2%	0.293
At least one complication	348 (7.2%)	8.6%	6.6%	6.5%	0.043†
In-hospital mortality	116 (2.4%)	4.9%	1.7%	0.7%	<0.001†
Postop. duration of stay§	19 d (11-36 d)	19 d (10-38 d)	19 d (12-37 d)	18 d (10-37 d)	0.032†

*The values are given as the mean and the standard deviation. †Significant at the $p < 0.05$ level. ‡Data were missing for nine patients. §The values are given as the median, with the interquartile range in parentheses.

TABLE II Postoperative Complications in All Patients

	No. of Patients	No. (%) with Complications	Univariate Analysis		Multivariate Analysis	
			OR (95% CI)	P Value	OR (95% CI)	P Value
Total no. of patients	4803	348 (7.2)				
Sex						
Male	2531	204 (8.1)	Reference		Reference	
Female	2272	144 (6.3)	0.77 (0.62-0.96)	0.022*	0.81 (0.65-1.01)	0.063
Age in yr						
≤49	1178	74 (6.3)	Reference		Reference	
50-69	1894	130 (6.9)	1.10 (0.82-1.48)	0.529	1.10 (0.81-1.51)	0.558
≥70	1731	144 (9.3)	1.35 (1.01-1.81)	0.041*	1.35 (0.99-1.86)	0.061
Diagnosis						
Primary malignant bone tumor	587	53 (9.0)	Reference		Reference	
Primary malignant soft-tissue tumor	3163	201 (6.4)	0.68 (0.50-0.94)	0.018*	0.97 (0.61-1.55)	0.898
Metastatic bone tumor	1053	94 (8.9)	0.99 (0.69-1.40)	0.945	0.89 (0.60-1.32)	0.555
Type of surgery						
Bone tumor resection w/o prosthesis	991	85 (8.6)	1.47 (1.12-1.92)	0.005*	1.26 (0.83-1.92)	0.278
Soft-tissue tumor resection w/o prosthesis	2975	179 (6.0)	Reference		Reference	
Resection + prosthesis	689	69 (10.0)	1.74 (1.30-2.33)	<0.001*	1.47 (0.91-2.37)	0.117
Amputation	148	15 (10.1)	1.76 (1.01-3.07)	0.045*	1.61 (0.89-2.91)	0.113
Duration of anesthesia in min†						
<120	842	38 (4.5)	Reference		Reference	
120-240	2090	116 (5.6)	1.24 (0.85-1.81)	0.256	1.23 (0.84-1.79)	0.294
>240	1862	194 (10.4)	2.46 (1.72-3.52)	<0.001*	2.44 (1.68-3.53)	<0.001*
At least one preop. comorbidity	650	65 (10.0)	1.52 (1.25-2.02)	0.004*	1.33 (0.99-1.79)	0.057
Hospital volume						
Low	1585	136 (8.6)	Reference		Reference	
Medium	1612	107 (6.6)	0.76 (0.58-0.99)	0.039*	0.71 (0.54-0.94)	0.018*
High	1606	105 (6.5)	0.75 (0.57-0.97)	0.029*	0.73 (0.55-0.96)	0.027*

*Significant at the $p < 0.05$ level. †Data were missing for nine patients.

Results

We identified 4803 eligible patients among the 11.6 million inpatients included in the DPC database during 2007 to 2010. These patients were treated at 539 hospitals, of which 470 were in the low-volume group, forty-nine were in the medium-volume group, and twenty were in the high-volume group.

The mean age (and standard deviation) of the patients was 59.7 ± 18.9 years (Table I). The mean age was highest in the low-volume group ($p < 0.001$). Patients in the high-volume group were the most likely to have a primary malignant bone tumor, and patients in the low-volume group were the most likely to have a metastatic bone tumor ($p < 0.001$). A duration of anesthesia exceeding 240 minutes was more frequent in the medium and high-volume groups than in the low-volume group ($p < 0.001$). Patients in the low-volume group were more likely to have diabetes mellitus and cardiac disease ($p < 0.001$).

Postoperative complications included surgical site infections in 132 patients (2.7%), cardiac events in sixty-four (1.3%), respiratory complications in fifty-one (1.1%), sepsis in thirty-one (0.6%), pulmonary emboli in sixteen (0.3%), acute renal failure in eleven (0.2%), and cerebrovascular events in seven (0.1%). The rate of postoperative complications was 7.2% (348 of 4803) overall and was 8.6% in the low-volume group, 6.6% in the medium-volume group, and 6.5% in the high-volume group. The mortality rate was 2.4% (116 of 4803) overall and was 4.9% in the low-volume group, 1.7% in the medium-volume group, and 0.7% in the high-volume group. The postoperative duration of hospital stay was slightly shorter

TABLE III In-Hospital Mortality in All Patients

	No. of Patients	No. (%) of Deaths	Univariate Analysis		Multivariate Analysis	
			OR (95% CI)	P Value	OR (95% CI)	P Value
Total no. of patients	4803	116 (2.4)				
Sex						
Male	2531	68 (2.7)	Reference		Reference	
Female	2272	48 (2.1)	0.78 (0.54-1.14)	0.197	0.79 (0.53-1.16)	0.227
Age in yr						
≤49	1178	10 (0.8)	Reference		Reference	
50-69	1894	51 (2.7)	3.23 (1.64-6.39)	0.001*	1.70 (0.82-3.49)	0.155
≥70	1731	55 (3.2)	3.83 (1.95-7.55)	<0.001*	1.67 (0.81-3.47)	0.168
Diagnosis						
Primary malignant bone tumor	587	8 (1.4)	Reference		Reference	
Primary malignant soft-tissue tumor	3163	23 (0.7)	0.53 (0.24-1.19)	0.124	0.62 (0.22-1.77)	0.375
Metastatic bone tumor	1053	85 (8.1)	6.36 (3.06-13.22)	<0.001*	3.67 (1.66-8.09)	0.001*
Type of surgery						
Bone tumor resection w/o prosthesis	991	45 (4.5)	6.69 (3.97-11.29)	<0.001*	1.73 (0.73-4.10)	0.210
Soft-tissue tumor resection w/o prosthesis	2975	21 (0.7)	Reference		Reference	
Resection + prosthesis	689	41 (6.0)	8.90 (5.22-15.16)	<0.001*	1.63 (0.66-4.02)	0.285
Amputation	148	9 (6.1)	9.11 (4.10-20.25)	<0.001*	3.81 (1.42-10.20)	0.008*
Duration of anesthesia in min						
<120	842	18 (2.1)	Reference			
120-240	2090	42 (2.0)	0.94 (0.54-1.64)	0.824		
>240	1862	56 (3.0)	1.42 (0.83-2.43)	0.201		
At least one preop. comorbidity	650	27 (4.2)	1.98 (1.28-3.07)	0.002*	1.40 (0.88-2.21)	0.154
Hospital volume						
Low	1585	77 (4.9)	Reference		Reference	
Medium	1612	27 (1.7)	0.33 (0.21-0.52)	<0.001*	0.65 (0.41-1.05)	0.076
High	1606	12 (0.7)	0.15 (0.08-0.27)	<0.001*	0.26 (0.14-0.50)	<0.001*

*Significant at the p < 0.05 level.

in the high-volume group, and the duration differed significantly between patients with postoperative complications (thirty-six days) and those without complications (eighteen days, p < 0.001) as well as between patients who died in the hospital (forty-six days) and those who were discharged alive (eighteen days, p < 0.001).

Univariate and multivariate analyses of the postoperative complication rate are shown in Table II. In the univariate analyses, the rate was higher in male compared with female patients (p = 0.022), patients at least seventy years of age compared with patients less than fifty years of age (p = 0.041), patients with a primary malignant bone tumor compared with a primary malignant soft-tissue tumor (p = 0.018), patients who underwent bone or soft-tissue tumor resection with prosthetic reconstruction compared with soft-tissue tumor resection without prosthetic reconstruction (p < 0.001), patients with at least one comorbidity compared with no comorbidities (p = 0.004), and patients in the low-volume group compared with the high-volume group (p = 0.029) and the medium-volume group (p = 0.039). Among the preoperative comorbidities, diabetes mellitus (p = 0.052), cardiac disease (p = 0.056), and chronic renal failure (p = 0.013) were significant predictors of postoperative complications.

Multivariate logistic regression analyses revealed a significant association between a higher postoperative complication rate and a duration of anesthesia exceeding 240 minutes compared with less than 120 minutes (odds ratio [OR], 2.44; 95%

confidence interval [CI], 1.68 to 3.53; p < 0.001). Compared with patients in the low-volume group, patients in the medium-volume group (OR, 0.71; 95% CI, 0.54 to 0.94; p = 0.018) or the high-volume group (OR, 0.73; 95% CI, 0.55 to 0.96; p = 0.027) had lower complication rates.

Univariate and multivariate analyses of the in-hospital mortality rate are shown in Table III. In the univariate analyses, the in-hospital mortality rate was significantly higher in patients who were fifty to sixty-nine years of age (p = 0.001) or at least seventy years of age (p < 0.001) compared with patients who were less than fifty years of age, in patients with a metastatic bone tumor compared with a primary malignant bone tumor (p < 0.001), in patients who underwent surgery other than soft-tissue tumor resection without prosthetic reconstruction (p < 0.001), in patients with at least one comorbidity compared with no comorbidities (p = 0.002), and in patients in the low-volume group compared with the medium and high-volume groups (p < 0.001). Among preoperative comorbidities, cardiac disease (p = 0.023) and chronic renal failure (p = 0.004) were significant predictors of in-hospital mortality.

Multivariate logistic regression analyses revealed significantly higher in-hospital mortality rates in patients with a metastatic bone tumor compared with a primary malignant bone tumor (OR, 3.67; 95% CI, 1.66 to 8.09; p = 0.001) and in patients who underwent amputation compared with soft-tissue tumor resection without prosthetic reconstruction (OR, 3.81; 95% CI, 1.42 to 10.20; p = 0.008). Patients in the high-volume group had a lower mortality rate than those in the low-volume group (OR, 0.26; 95% CI, 0.14 to 0.50; p < 0.001).

We also performed similar logistic regression analyses focusing on subgroups of patients with primary bone tumors (n = 587), primary soft-tissue tumors (n = 3163), and metastatic bone tumors (n = 1053) (see Appendix). These subgroup analyses revealed volume-outcome relationships that were generally similar to the analyses involving all patients (n = 4803) with regard to the OR values, but the 95% CIs were broader and the p values were relatively high because of the smaller sample sizes and reduced statistical power. For example, in the subgroup analyses of patients with metastatic bone tumors, the in-hospital mortality rate was again significantly lower in the high-volume group than in the low-volume group (9.6% compared with 3.8%; OR, 0.39; 95% CI, 0.19 to 0.81; p = 0.012), but the postoperative complication rate no longer differed significantly between the high and low-volume groups (10.1% compared with 5.9%; OR, 0.54; 95% CI, 0.29 to 1.00; p = 0.051).

Discussion

Musculoskeletal tumor surgery is challenging and is potentially associated with a high complication rate. Decreasing the complication rate would improve patient outcomes. The purpose of the present study was to clarify the relationships between hospital volume and the rates of postoperative complications and in-hospital mortality. The results supported our hypothesis that high-volume hospitals were associated with lower rates of postoperative complications and in-hospital mortality.

The relationship between hospital volume and outcomes is of current interest, and regionalization of surgery to high-volume hospitals has been proposed in order to improve outcomes. Several studies have demonstrated associations between higher hospital volume and better surgical outcomes in orthopaedic surgery and cancer surgery[1-8]. To our knowledge, the present study is the first to specifically examine the relationship between hospital volume and the rates of both in-hospital mortality and postoperative complications after musculoskeletal tumor surgery.

The univariate analysis revealed a significant difference in the in-hospital mortality rate among patients treated in low-volume hospitals (4.9%), medium-volume hospitals (1.7%), and high-volume hospitals (0.7%). The multivariate regression analysis also revealed a significantly lower in-hospital mortality rate in patients treated in high-volume compared with low-volume hospitals (p < 0.001). We are aware of no previous study examining the relationship between musculoskeletal tumor surgery volume and the in-hospital mortality rate, but our observations are consistent with several studies suggesting associations between higher hospital volume and lower mortality rates in various other fields of surgery[18,19]. Dudley et al. concluded that a number of patient deaths could potentially be avoided if more patients were treated at high-volume hospitals[19].

There was also a difference in the postoperative complication rate among patients treated in low-volume hospitals (8.6%), medium-volume hospitals (6.6%), and high-volume hospitals (6.5%). The multivariate regression analysis also revealed that the complication rate was significantly lower in both the medium-volume and high-volume groups compared with the low-volume group. The difference in the complication rate was >2%, which cannot be disregarded. Our observations are consistent with a review of 135 studies, involving twenty-seven diagnoses and procedures, in which examination of the relationships between hospital volume and clinical outcomes revealed a significant association between higher hospital volume and better outcomes in approximately 70% of the studies[18]. Several recently conducted studies comparing surgical volume and outcomes in orthopaedic surgery, including total knee arthroplasty, total hip arthroplasty, and spine surgery, also indicated similar results[5-9].

It is worthy of special mention that we identified an independent association between hospital volume and outcomes after adjusting for patient demographic characteristics with use of multivariate logistic regression analysis. Subgroup analyses focusing on patients with primary bone tumors, soft-tissue tumors, and metastatic bone tumors revealed ORs for outcomes according to hospital volume that were generally similar to those of the analyses involving all patients. Although the medical conditions in these three subgroups are quite different, higher hospital volume was predictive of better outcomes in each of the subgroups, and particularly in the soft-tissue and metastatic tumor subgroups. A possible explanation for this relationship between hospital volume and outcomes is that higher hospital volume results in improved surgical techniques, especially in a condition such as musculoskeletal tumor surgery, which is extremely rare compared with most other orthopaedic surgery or most other cancer surgery. Surgeons in high-volume hospitals could be more familiar with intraoperative and postoperative care, resulting in shorter operative times, less blood loss, and fewer postoperative complications. In addition, hospitals with better outcomes may attract patient referrals from other hospitals, resulting in higher volumes in these hospitals and a further improvement in outcomes.

Although higher hospital volume is associated with better outcomes, there is ongoing controversy regarding the practical implications of predicting outcomes according to hospital volume. In the United States, growing interest in volume-outcome relationships has influenced policy changes, including regionalization of procedures to high-volume hospitals[20]. The mean number of patients undergoing musculoskeletal tumor surgery per hospital in Japan is extremely low. The data from the DPC database indicated that 4803 patients were treated in 539 hospitals. Considering the rarity of these diseases and the specialized surgical procedures required to treat them, it is obvious that the current situation in Japan is not desirable. Our findings suggest that musculoskeletal tumor surgery should be regionalized and performed in high-volume hospitals in Japan.

Our study has several limitations. First, the use of an administrative claims database could have led to an underestimation or overestimation of comorbidities or postoperative complications as a result of incomplete reporting. Second, the participation rate of small hospitals in the DPC database was relatively low, which may have resulted in a sample selection bias. Third, we were unable to determine complications and deaths that occurred after discharge or transfer to another hospital, which may have resulted in an underestimation of these outcomes. Fourth, we were not able to identify several important clinical parameters that may have affected the rates of postoperative complications and mortality; these parameters included the histological diagnosis, clinical stage of the tumor, severity of preoperative comorbidities, adjuvant chemotherapy and radiation therapy, and details of the surgery. For example, treatment for a metastatic bone tumor may involve internal fixation of a pathological fracture or prophylactic internal fixation of an impending pathological fracture, but such procedures did not fit into our treatment categories. Finally, it is possible that individual patients may have been counted more than once in the DPC database if they initially received inappropriate surgical management at a local hospital that did not participate in the DPC survey and then underwent surgery in a specialized hospital. However, such cases are rare in Japan because there are a limited number of hospitals specializing in musculoskeletal oncology and patients are usually referred to such a specialized hospital if musculoskeletal sarcoma is suspected.

Appendix

eA Tables showing the results of the multivariate logistic regression analyses for postoperative complications and in-hospital mortality are available with the online version of this article as a data supplement at jbjs.org. ■

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ORIGINAL ARTICLE

Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) of the whole spine and its association with lumbar spondylosis and knee osteoarthritis: the ROAD study

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Abstract We aimed to assess the prevalence of diffuse idiopathic skeletal hyperostosis (DISH) and its association with lumbar spondylosis (LS) and knee osteoarthritis (KOA) using a population-based cohort study entitled Research on Osteoarthritis/osteoporosis Against Disability (ROAD). In the baseline ROAD study, which was performed between 2005 and 2007, 1,690 participants in mountainous and coastal areas underwent anthropometric measurements and radiographic examinations of the whole spine (cervical, thoracic, and lumbar) and both knees. They also completed an interviewer-administered questionnaire. Presence of DISH was diagnosed according to Resnick criteria, and LS and KOA were defined as Kellgren-Lawrence (KL) grade ≥3. Among the 1,690 participants, whole-spine radiographs of 1,647 individuals (97.5 %; 573 men, 1,074 women; mean age, 65.3 years) were evaluated. Prevalence of DISH was 10.8 % (men 22.0 %, women 4.8 %), and was significantly higher in older participants (presence of DISH 72.3 years, absence of DISH 64.4 years) and mainly distributed at the thoracic spine (88.7 %). Logistic regression analysis revealed that presence of DISH was significantly associated with older age [+1 year, odds ratio (OR): 1.06, 95 % confidence interval (CI): 1.03–1.14], male sex (OR: 5.55, 95 % CI: 3.57–8.63), higher body mass index (+1 kg/m^2, OR: 1.08, 95 % CI: 1.02–1.14), presence of LS (KL2 vs KL0: 1, OR: 5.50, 95 % CI: 2.81–10.8) (KL ≥3 vs KL0: 1, OR: 4.09, 95 % CI: 2.08–8.03), and presence of KOA (KL ≥3 vs KL0: 1, OR: 1.89, 95 % CI: 1.14–3.10) after adjusting for smoking, alcohol consumption, and residential area (mountainous vs coastal). This cross-sectional population-based study clarified the prevalence of DISH in general inhabitants and its significant association with LS and severe KOA.

Keywords Prevalence · Diffuse idiopathic skeletal hyperostosis · Knee osteoarthritis · Lumbar spondylosis · ROAD study

Introduction

Diffuse idiopathic skeletal hyperostosis (DISH) is characterised by calcification and ossification of soft tissue such as entheses and joint capsules [1]. Resnick and Niwayama specifically defined DISH as the radiographic finding of calcification or ossification along the anterolateral aspects of at least 4 contiguous vertebral levels (across 3 disc spaces), with relative preservation of disc height in the involved vertebral segments and without degenerative disc disease [2]. In 1998, Mata and co-workers [3] developed a

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scoring system such that the presence of DISH could be assessed reproducibly. This system scores individuals who fulfill the Resnick criteria by numerically classifying each vertebral level based on the amount of ossification and whether partial or complete bridging of the disc space is present [3].

Although some reports have indicated a significant association between DISH and ossification of the posterior longitudinal ligament (OPLL) [4–7], DISH is thought to be an asymptomatic condition in many affected individuals; however, several clinical symptoms have been described including pain, limited range of spinal motion, and increased susceptibility to unstable spinal fractures after trivial trauma [8]. In addition, dysphagia and airway obstruction at the cervical levels [8, 9], as well as radiculopathy and spinal injury after spinal fracture [10–12], have been reported as clinical manifestations of DISH.

Although the condition is recognised in many parts of the world [13–20], there are relatively few population-based studies concerning its prevalence. Such data are important in order to characterise the burden of the disease. In addition, regarding its characteristics, several epidemiologic studies have reported that DISH is observed mainly in the elderly, and that prevalence increases with age [18, 19]. Men are affected by DISH much more frequently than women [20]. Although metabolic disturbance is hypothesised to be a factor [21, 22], the aetiology of the condition remains unknown.

Based on the definition of DISH as the radiographic finding of calcification or ossification, it appears that the condition might be associated with osteoarthritis (OA) of the spine. The severity of OA, as observed on radiography, was determined according to Kellgren-Lawrence (KL) grading as follows [23]: KL0, normal; KL1, slight osteophytes; KL2, definite osteophytes; KL3, joint or intervertebral space narrowing with large osteophytes; and KL4, bone sclerosis, joint or intervertebral space narrowing, and large osteophytes. KL2 is commonly used as the diagnostic criterion for lumbar spondylosis (LS) or OA at other sites. Thus, LS—defined as KL2 (defined as the definite presence of osteophytes)—could easily be associated with DISH. However, there are few reports to confirm the association between DISH and severe LS with the criterion of KL3 (defined as the presence of intervertebral space narrowing) or KL4 (defined as the presence of bone sclerosis). In addition, there are few reports to clarify the association between DISH and OA at other sites, such as the knees.

We conducted a survey, known as the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study, using a population-based cohortto determine the prevalence of DISH using lateral whole-spine radiography in recently examined subjects, which included men and women in Japan. Another aim of our study was to clarify the association of DISH with LS and knee osteoarthritis (KOA) based on KL grade.

Materials and methods

Outline of the ROAD study

We conducted the present study using the cohorts established in 2005 for the ROAD study—a nationwide, prospective study of OA comprising population-based cohorts in several communities in Japan. Details of the cohort profile have been reported elsewhere [24, 25]. Briefly, from 2005 to 2007, we developed a baseline database that included clinical and genetic information of 3,040 residents of Japan (1,061 men, 1,979 women) with a mean age of 70.3 (SD, 11) years [men: 71 (SD, 10.7) years, women: 69.9 (SD, 11.2) years]. Subjects were recruited from resident registration listings in three communities with different characteristics: 1,350 subjects (465 men, 885 women) from an urban region in Itabashi, Tokyo; 864 (319 men, 545 women) from a mountainous region in Hidakagawa, Wakayama; and 826 (277 men, 549 women) from a coastal region in Taiji, Wakayama.

Participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information, such as occupation, smoking habits, alcohol consumption, family history, medical history, physical activity, reproductive variables, and health-related quality of life. The questionnaire was prepared by modifying the questionnaire used in the Osteoporotic Fractures in Men Study (MrOS) [26]; some new items also were added to the modified questionnaire. Participants were asked whether they took prescription medication daily or nearly every day (no = 0, yes = 1). If the participants did not know the reason for the prescribed medication, they were asked to bring their medication to the medical doctor (NY).

Anthropometric measurements, including height (cm), body weight (kg), arm span (cm), bilateral grip strength (kg), and body mass index (BMI, kg/m^2) were recorded for each patient. Medical information was recorded by experienced orthopaedic surgeons on systematic, local, and mental status, including information on back, knee, and hip pain; swelling and range of motion of the joints; and patellar and Achilles tendon reflexes.

Eligible subjects of the present study

In the ROAD study, radiographic examination of the thoracic spine was performed only in subjects in mountainous and coastal regions. These subjects also underwent blood and urinary examinations. In the present study, among 1,690 subjects (596 men, 1,094 women) in mountainous and coastal regions in the ROAD study, we excluded 43 whose radiograph quality was so poor that it was difficult to observe the sites of thoracic–lumbar junction and lumbosacral junction; thus, we analysed 1,647 participants (573 men, 1,074 women) ranging in age from 23 to 94 years (mean: 65.3 years, men: 66.3 years, women: 64.7 years).

Study participants provided written informed consent, and the study was approved by the ethics committees of the University of Wakayama Medical University (No. 373) and the University of Tokyo (No. 1264 and No. 1326).

Radiographic assessment

Plain radiographs of the cervical, thoracic, and lumbar spine in the anteroposterior and lateral views, and bilateral knees in the anteroposterior view with weight-bearing and foot-map positioning were obtained. DISH was diagnosed according to the following criteria, defined by Resnick and Niwayama [2]: (1) flowing ossification along the lateral aspect of at least 4 contiguous vertebral bodies, (2) relative preservation of intervertebral disc height in the involved segments, and (3) absence of epiphyseal joint bony enclosing and sacroiliac joint erosion. In the assessment of lateral radiographs, since it was difficult to read the C7/Th1 to T3/4 vertebral levels, 'whole spine' in the present study implies radiographs assessed from the C0/1 to C6/7, Th4/5 to Th12/L1, and L1/L2 to L5/S1 levels.

The radiographic severity of OA was determined according to the above-mentioned KL grade [20]. Radiographs of each site (i.e., vertebrae and knees) were examined by a single experienced orthopaedic surgeon (SM) who was blinded to the participants' clinical status. In the present study, the maximum grade, diagnosed in at least 1 intervertebral level of the lumbar spine or at least 1 knee joint, was regarded as the subject's KL grade.

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 presence of DISH and LS and/or KOA, we used logistic regression analysis. In the analysis, we used presence of DISH as the objective variable (absence = 0, presence = 1), and severity of prevalent LS (KL0, 1 = 0 vs. KL2 = 1; KL0, 1 = 0 vs. KL3 or 4 = 2) and KOA (KL0, 1 = 0 vs. KL2 = 1; KL0, 1 = 0 vs. KL3 or 4 = 2) as explanatory variables, in addition to basic characteristics such as age (+1 year), sex (men = 1, women = 0), BMI (+1 kg/m^2), and regional differences (mountainous area = 0, coastal area = 1). Other potential associated factors were selected with significant or marginal ($p < 0. 1$) association with DISH status in a simple linear analysis. The selected explanatory variables for logistic regression analysis are described in the Results section.

Results

Prevalence of DISH was 10.8 % (men: 22.0 %, women: 4.8 %), and was significantly higher in men than in women. Figure 1 shows the prevalence of DISH according to age and sex. Prevalence increased with age in both men and women. Prevalence in subjects classified by age-strata—<50, 50–59, 60–69, 70–79, and ≥80 years—was 1.8, 11.7, 15.4, 32.6, and 39.6 % in men, and 0.7, 1.5, 3.5, 7.6, and 11.8 % in women, respectively.

Table 1 shows the baseline characteristics of the 1,647 participants with and without DISH. In total, subjects with DISH tended to be older, taller, heavier, and have higher BMI than those without DISH ($p < 0.0001$). In the comparison classified by sex, age was significantly higher in those with DISH in both men and women ($p < 0.0001$). In women, mean weight and BMI were significantly higher in those with DISH than in those without DISH (weight: $p < 0.05$, BMI: $p < 0.0001$).

Prevalence of DISH was lower in individuals residing in a coastal area. Individuals with DISH had a higher frequency of smoking and alcohol consumption ($p < 0.05$). The difference in the residing area was significantly observed in men. However, in the comparison classified by sex, differences in smoking and drinking were diluted (Table 1).

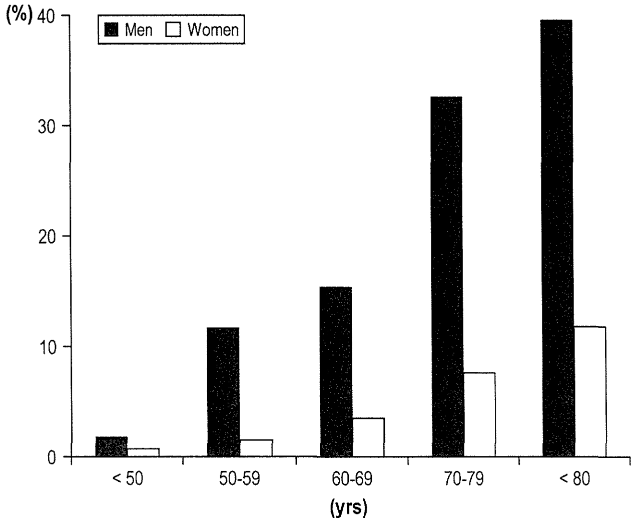

Fig. 1 Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) according to sex and age

Table 1 Mean values (standard deviations) of the anthropometric measurements and the prevalence of lifestyle factors for the participants classified by presence or absence of DISH

	Total ($n = 1647$)			Men ($n = 573$)			Women ($n = 1074$)		
	DISH (−) $n = 1470$	DISH (+) $n = 177$	p	DISH (−) $n = 447$	DISH (+) $n = 126$	p	DISH (−) $n = 1023$	DISH (+) $n = 51$	p
Age (years)	64.4 (12.1)	72.3 (8.4)	<0.0001***	64.6 (12.1)	72.4 (8.2)	<0.0001***	64.3 (12.2)	71.9 (8.8)	<0.0001***
Height (cm)	154.7 (9.2)	158.6 (8.8)	<0.0001***	163.7 (7.3)	162.5 (6.7)	0.0918	150.8 (7.0)	148.9 (5.5)	0.0589
Weight (kg)	55.9 (10.6)	60.1 (10.5)	<0.0001***	62.3 (11.0)	62.1 (10.0)	0.8806	51.9 (8.8)	55.0 (10.3)	0.0126*
BMI (kg/m^2)	22.9 (3.4)	23.8 (3.3)	0.0005***	23.2 (3.2)	23.5 (2.9)	0.3378	22.8 (3.4)	24.7 (3.9)	0.0001***
Residing in the coastal area (%)	50.48	40.11	0.009**	50.3	35.7	0.004**	50.5	51.0	0.951
Current smoking habit (regularly, ≥1 month) (%)	11.9	21.3	<0.001***	29.9	29.0	0.858	3.8	2.0	0.506
Current alcohol consumption (regularly, ≥1 month) (%)	38.7	48.0	0.017*	68.5	61.1	0.122	25.7	15.7	0.108
Presence of LS (KL grade ≥2) (%)	59.1	93.8	<0.001***	72.0	94.4	<0.001***	53.4	92.2	<0.001***
Presence of LS (KL grade ≥3) (%)	35.6	48.0	0.001**	35.4	45.2	0.043*	35.7	54.9	0.005**
Presence of KOA (KL grade ≥2) (%)	48.2	65.5	<0.001***	35.5	58.7	<0.001***	53.8	83.3	<0.001***
Presence of KOA (KL grade ≥3) (%)	18.4	34.5	<0.001***	11.0	27.0	<0.001***	21.7	54.2	<0.001***

DISH diffuse idiopathic skeletal hyperostosis, *BMI* body mass index, *LS* lumbar spondylosis, *KOA* knee osteoarthritis, *KL grade* Kellgren-Lawrence grade

DISH (−) absence of DISH, *DISH (+)* presence of DISH

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 1 also shows the prevalence of LS and KOA defined by KL grade ≥2 and grade ≥3, according to DISH status. In total, the prevalence of LS was higher in those with DISH than in those without DISH ($p = 0.001$). A similar tendency was observed in the prevalence of KOA ($p < 0.001$). This tendency also was noted in the comparison classified by sex.

We classified subjects with DISH into 4 types: (1) cervical, ossification along the lateral aspect of at least 4 contiguous vertebral bodies only in the cervical region (C0/1–C6/7); (2) thoracic, ossification along the lateral aspect of at least 4 contiguous vertebral bodies only in the thoracic region (Th4/5–Th12/L1); (3) lumbar, ossification along the lateral aspect of at least 4 contiguous vertebral bodies only in the lumbar region (L1/2–L5/S1); and (4) diffuse, ossification along the lateral aspect of at least 4 contiguous vertebral bodies in more than 2 regions or through more than 2 regions. Table 2 shows the prevalence of DISH classified by location in the spine. A total of 89 % was shown to be thoracic, whereas the remaining was diffuse; there were no subjects with cervical-type or lumbar-type DISH.

Figure 2 shows the distribution of DISH classified by vertebral level (Th4/5–LS/S1). Among diffuse-type DISH, although 2 subjects had ossification in the cervical region, the cervical site is excluded from the figure. Figure 2 shows that ossification was observed mainly in the middle-lower thoracic sites (Th7/8–Th9/10).

Logistic regression analysis was performed with DISH as the objective variable, LS and KOA as explanatory variables, and patient characteristics including age, sex, BMI, regional differences, smoking, and alcohol consumption as potential risk factors. Presence of DISH was significantly associated with presence of LS (KL2 vs KL0: 1, KL ≥3 vs KL0: 1) and KOA (KL ≥3 vs KL0: 1). Among other potential associated factors, older age, male sex, and higher BMI remained as significantly associated with the presence of DISH (Table 3).

Table 2 Number (proportion, %) of DISH (+) patients classified by spinal ossification site

Type of DISH	Total	Men	Women
Cervical type	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Thoracic type	157 (88.7 %)	111 (88.1 %)	46 (90.2 %)
Lumbar type	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)
Diffuse type	20 (11.3 %)	15 (11.9 %)	5 (9.8 %)
Total	177 (100.0 %)	126 (100.0 %)	51 (100.0 %)

Cervical type: Ossification along the lateral aspect of at least four contiguous vertebral bodies existing only in the cervical region (C0/1–C6/7)

Thoracic type: Ossification along the lateral aspect of at least four contiguous vertebral bodies existing only in the thoracic region (Th4/5–Th12/L1)

Lumbar type: Ossification along the lateral aspect of at least four contiguous vertebral bodies existing only in the lumbar region (L1/2–L5/S1)

Diffuse type: Ossification along the lateral aspect of at least four contiguous vertebral bodies existing in more than 2 regions or through more than 2 regions

Finally, to clarify the association of DISH with LS and KOA, we performed logistic regression analysis using DISH as an objective variable, LS and KOA as explanatory variables, and patient characteristics including age, sex, BMI, regional differences, smoking, and alcohol consumption as potential risk factors. Presence of DISH was significantly associated with presence of LS (KL2 vs KL0: 1, KL ≥3 vs KL0: 1) and KOA (KL ≥3 vs KL0: 1) independently (Table 4).

Discussion

In the present study, using lateral whole-spine radiographs of recently examined population-based samples, we estimated that the prevalence of DISH was one-tenth of the population, which consisted of participants from the ROAD study. The subjects with DISH tended to be older and had bigger body build than those without DISH. In addition, DISH was observed more frequently in men than

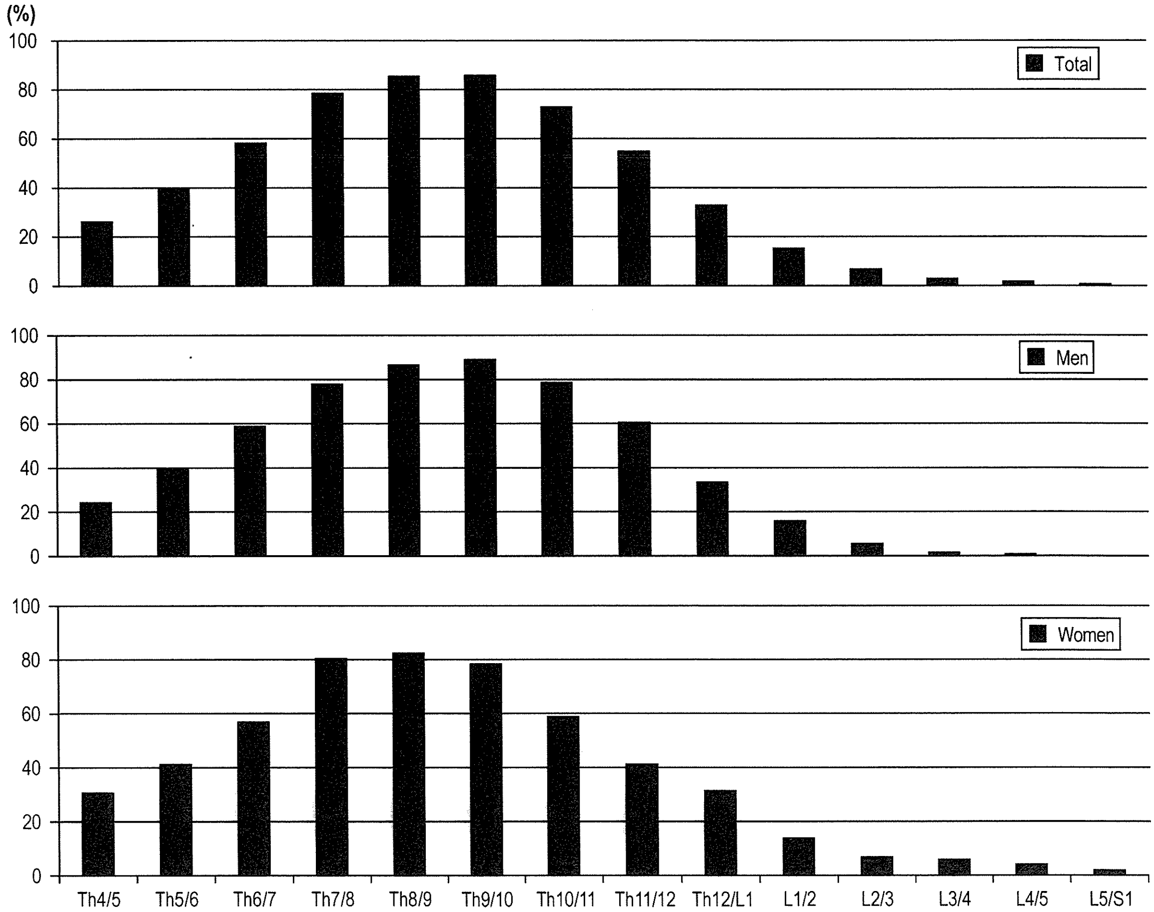

Fig. 2 Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) in each vertebral level, classified by sex

Table 3 Odds ratios of lumbar spondylosis or knee osteoarthritis, and potentially associated factors for the presence of DISH vs. absence of DISH

Explanatory variables	Category	OR	95 % CI	*p*
Lumbar spondylosis				
Presence of LS	0: KL grade = 0, 1, 1: KL grade = 2	5.80	2.97–11.3	<0.001***
	0: KL grade = 0, 1, 2: KL grade $\geq$3	4.54	2.34–8.84	<0.001***
Age (years)	+1 year	1.07	1.05–1.09	<0.001***
Gender	1: men, 0: women	4.61	3.05–6.99	<0.001***
Region	0: mountainous area, 1: coastal area	0.88	0.61–1.26	0.475
BMI (kg/m^2)	+1 kg/m^2	1.11	1.05–1.17	<0.001***
Smoking	0: ex or never smoker, 1: current smoker	1.65	1.04–2.63	0.034*
Alcohol consumption	0: ex or never drinker, 1: current drinker	0.82	0.56–1.22	0.329
Knee osteoarthritis				
Presence of KOA	0: KL grade = 0, 1, 1: KL grade = 2	1.34	0.85–2.10	0.211
	0: KL grade = 0, 1, 2: KL grade $\geq$3	2.15	1.32–3.52	0.002**
Age (years)	+1 year	1.07	1.04–1.09	<0.001***
Gender	1: men, 0: women	6.90	4.48–10.6	<0.001***
Region	0: mountainous area, 1: coastal area	0.95	0.65–1.37	0.771
BMI (kg/m^2)	+1 kg/m^2	1.09	1.03–1.15	0.002**
Smoking	0: ex or never smoker, 1: current smoker	1.52	0.95–2.42	0.079
Alcohol consumption	0: ex or never drinker, 1: current drinker	0.85	0.58–1.26	0.431

DISH diffuse idiopathic skeletal hyperostosis, *BMI* body mass index, *LS* lumbar spondylosis, *KOA* knee osteoarthritis, *KL grade* Kellgren-Lawrence grade

OR odds ratios, *95 % CI* 95 % confidence interval

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 4 Odds ratios of lumbar spondylosis and knee osteoarthritis, and potentially associated factors for the presence of DISH vs. absence of DISH

Explanatory variables	Category	OR	95 % CI	*p*
Presence of LS (KL grade = 2)	vs. KL grade = 0, 1	5.50	2.81–10.8	<0.001***
Presence of LS (KL grade $\geq$3)	vs. KL grade = 0, 1	4.09	2.08–8.03	<0.001***
Presence of KOA (KL grade = 2)	vs. KL grade = 0, 1	1.22	0.77–1.92	0.404
Presence of KOA (KL grade$\geq$ 3)	vs. KL grade = 0, 1	1.89	1.14–3.10	0.013**
Age (years)	+1 year	1.06	1.03–1.14	<0.001***
Gender	1: men, 0: women	5.55	3.57–8.63	<0.001***
Region	0: mountainous area, 1: coastal area	0.88	0.60–1.29	0.522
BMI (kg/m^2)	+1 kg/m^2	1.08	1.02–1.14	0.008**
Smoking	0: ex or never smoker, 1: current smoker	1.59	1.00–2.55	0.052
Alcohol consumption	0: ex or never drinker, 1: current drinker	0.81	0.54–1.21	0.298

DISH diffuse idiopathic skeletal hyperostosis, *BMI* body mass index, *LS* lumbar spondylosis, *KOA* knee osteoarthritis, *KL grade* Kellgren-Lawrence grade

OR odds ratios, *95 % CI* 95 % confidence interval

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

in women, and the most common site was the thoracic vertebrae. Presence of DISH was significantly associated with the presence of KOA and LS, after adjusting for potential associated factors.

There have been several epidemiologic studies on DISH in many parts of the world [12–19]. The results indicate that DISH is observed mainly in men and the elderly; prevalence increases with age, and it is distributed mostly in the thoracic spine. These results are supported by the results of the present study. However, there are considerable differences in the prevalence. Weinfeld et al. [20] reported that genetic or hereditary differences are important predisposing factors for DISH. Their previous study involved patients from ethnic populations, including 667 white, 144 black, 72 Native American, 11 Hispanic, and 30 Asian patients. They showed that the Asian, black, and Native American populations had a remarkably lower prevalence of DISH; however, their study population was small. In a recent study, Kim et al. [18] reported that race influences the prevalence of DISH. Their prevalence of DISH was 5.4 % in men and 0.8 % in women aged over 80 years in a Korean population, which is remarkably lower than the prevalence in our study, despite the similar race. Our prevalence was similarly high as the white population in Weinfield's report. Therefore, it is believed that genetic factors influence the prevalence of DISH more than race.

The present study clarified that most cases of DISH were observed in the thoracic vertebrae. There were no cases of DISH located in only the cervical or lumbar region. All cases of DISH in the cervical region were categorised as diffuse-type. Even if subjects were categorised into diffuse-type DISH, thoracic vertebrae were found to be the most affected. In addition, among the thoracic vertebrae, we found the predilection site to be the middle thoracic vertebrae (Th7–Th9). Holton et al. [27] reported that the distribution of the lowest level of DISH in 298 male subjects aged ≥65 years was 38 % in the thoracic region, 49 % in the thoracolumbar region, and 13 % in the lumbar region. It is interesting that DISH has predilection sites, which might be due to anatomic alignment of the vertebrae. For example, the middle thoracic vertebrae are likely to be affected by compressive mechanical stress because the Th8 is located nearly at the top in physiologic kyphosis. DISH originates mainly from the thoracic spine and extends to the cervical and/or lumbar spine by mechanical stress. In the present cross-sectional study, we could not evaluate whether DISH tends to occur in the thoracic vertebrae and then forms in the lumbar spine secondarily; however, we were able to follow-up on the ROAD study and clarify the disease course of thoracic DISH.

Regarding the definition of DISH, it might be easy to imagine that LS, defined by KL2 (defined as radiographically definite osteophytes), is associated with DISH. However, there are few reports to confirm the association between DISH and severe LS with the criterion of KL3 or 4. In the present study, we confirmed the significant association between DISH and LS, not only with the criterion of KL2, but also with KL ≥3. In addition, there are few reports to clarify the association between DISH and OA of other sites. In the present study, we also confirmed the significant association between DISH and KOA. In fact, the OR of the presence of DISH for KOA significantly increased according to the severity of KOA. The effects of LS and KOA coexisted independently. This result suggests that DISH and OA might be in a similar vein of disease, for example, the so-called 'bone proliferative group'. There have been several reports regarding the association between DISH and OPLL [4–7]. Resnick et al. [4] described 4 patients with coexisting DISH and cervical OPLL, and found OPLL in 50 % of 74 additional patients with DISH after reviewing their cervical spine radiographs. However, there has been no report on the association of DISH and OA; thus the etiology of ossification might not be similar to that of OA. Therefore, with only the results of the present study, we cannot definitely claim that DISH and OA are in a similar disease group, even though DISH tends to have similar associated factors, such as age, overweight (bigger BMI), and mechanical stress, as OA.

Another hypothesis is that there might be hidden associated factors that might affect both DISH and OA. We considered risk factors for metabolic syndrome as potential confounders. Several constitutional and metabolic abnormalities have been reported to be associated with DISH including obesity, large waist circumference, hypertension, diabetes mellitus, hyperinsulinemia, dyslipidemia, and hyperuricemia [21, 28–30]. In addition, both LS and KOA are well known to be associated with obesity [31]. We have already reported on the presence of hypertension and impaired glucose tolerance, and shown that the accumulation of metabolic risk factors is associated with the presence and occurrence of KOA [32, 33]. In addition, we found that current smoking, a known risk factor for cardiovascular disease as well as metabolic risk factors, was significantly associated with DISH. These findings may indicate that DISH is a candidate surrogate index for metabolic risk factors as a predictor of OA, or vice versa. We could not evaluate this hypothesis at present, but we would clarify the association including the causal relationships between DISH, OA, and metabolic risk factors in a further study.

Alternatively, we considered associated factors for inflammation or cartilage metabolic turnover as potential confounders between DISH and OA. These factors might coexist as risk factors for DISH and OA. Thus, there might be a direct or indirect pathway between DISH and OA via hidden associated factors, which should be investigated in a further study.

This study has several limitations. First, although the ROAD study includes a large number of participants, these subjects may not truly represent the general population. To address this, we compared the anthropometric measurements and frequencies of smoking and alcohol consumption between study participants and the general Japanese population; no significant differences were found, with the exception that male ROAD study participants aged 70–74 years were significantly smaller in terms of body structure than the overall Japanese population ($p < 0.05$)

[25]. This difference should be considered when evaluating potential risk factors in men aged 70–74 years; factors such as body build, particularly greater weight, are known to be associated with LS and KOA. Therefore, our results may be an underestimation of the prevalence of these conditions. Second, in the present study, we used only the data of the baseline study. Thus, we were not able to confirm a causal relationship between DISH status and other associated factors, as mentioned above. Nevertheless, we have performed a follow-up study, so we will be able to clarify the causal relationship between DISH status and OA in the near future. Third, this study could not evaluate the cervicothoracic junction (C7–Th4) because we assessed only radiographs. Although most cases of DISH existed in the inferior thoracic spine, as Fig. 2 shows, the lack of findings in the C7/C1–Th3/Th4 levels might have underestimated the prevalence of DISH. To evaluate the cervicothoracic junction, it would be necessary to use computed tomography or magnetic resonance imaging of the whole spine, which appeared impossible to perform on more than 1,600 subjects. Fourth, LS defined by KL2 may have been included in cases of DISH, but there is no method to confirm the overlap of the presence of DISH and LS of KL2 using the radiographic diagnostic criteria. DISH is observed mainly in the thoracic region, and only the diffuse type expands partly into the lumbar region. Therefore, there is a small possibility that LS of KL2 might be contaminated into DISH. Finally, in the present study, we could not evaluate other sites of OA besides the knee and lumbar spine, such as the hands or hip. To evaluate DISH and other sites of OA, we should evaluate the presence or occurrence of OA at other sites in a further study.

In conclusion, in the present population-based study, we found that the prevalence of DISH was 10.8 % in the overall population. Prevalence was significantly higher in older subjects, and mainly distributed at the thoracic spine. Logistic regression analysis revealed that the presence of DISH was significantly associated with older age, male sex, higher BMI, and presence of severe KOA.

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Conflict of interest All authors declare that (1) no author has received corporate support for the submitted work; (2) the authors have no relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) the authors' spouses, partners, or children do not have financial relationships that may be relevant to the submitted work; and (4) the authors have no nonfinancial interests that may be relevant to the submitted work.

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ORIGINAL ARTICLE

Incidence of disability and its associated factors in Japanese men and women: the Longitudinal Cohorts of Motor System Organ (LOCOMO) study

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Abstract We investigated the incidence of disability and its risk factors in older Japanese adults to establish an evidence-based disability prevention strategy for this population. For this purpose, we used data from the Longitudinal Cohorts of Motor System Organ (LOCOMO) study, initiated in 2008 to integrate information from cohorts in nine communities across Japan: Tokyo (two regions), Wakayama (two regions), Hiroshima, Niigata, Mie, Akita, and Gunma prefectures. We examined the annual occurrence of disability from 8,454 individuals (2,705 men and 5,749 women) aged $\geq$65 years. The estimated incidence of disability was 3.58/100 person-years (p-y) (men: 3.17/100 p-y; women: 3.78/100 p-y). To determine factors associated with disability, Cox's proportional hazard model was used, with the occurrence of disability as an objective variable and age (+1 year), gender (vs. women), body build (0: normal/overweight range, BMI 18.5–27.5 kg/m^2; 1: emaciation, BMI <18.5 kg/m^2; 2: obesity, BMI >27.5 kg/m^2), and regional differences (0: rural areas including Wakayama, Niigata, Mie, Akita, and Gunma vs. 1: urban areas including Tokyo and Hiroshima) as explanatory variables. Age, body build, and regional difference significantly influenced the occurrence of disability (age, +1 year: hazard ratio 1.13, 95 % confidence interval 1.12–1.15, $p < 0.001$; body build, vs. emaciation: 1.24, 1.01–1.53, $p = 0.041$; body build, vs. obesity: 1.36, 1.08–1.71, $p = 0.009$; residence, vs. living in rural areas: 1.59, 1.37–1.85, $p < 0.001$). We concluded that higher age,

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both emaciation and obesity, and living in rural areas would be risk factors for the occurrence of disability.

Keywords Nation-wide population-based cohort study · Epidemiology · Incidence · Disability · Body build

Introduction

In Japan, the proportion of the population aged 65 years or older has increased rapidly over the years. In 1950, 1985, 2005, and 2010, this proportion was 4.9, 10.3, 19.9, and 23.0 %, respectively [1]. Further, this proportion is estimated to reach 30.1 % in 2024 and 39.0 % in 2051 [2]. The rapid aging of Japanese society, unprecedented in world history, has led to an increase in the number of disabled elderly individuals requiring support or long-term care. The Japanese government initiated the national long-term care insurance system in April 2000 in adherence with the Long-Term Care Insurance Act [3]. The aim of the national long-term care insurance system was to certify the level of care needed by elderly adults and to provide suitable care services to them according to the levels of their long-term care needs. According to the recent National Livelihood Survey by the Ministry of Health, Labour and Welfare in Japan, the number of elderly individuals certified as needing care services increases annually, having reached 5 million in 2011 [4].

However, few prospective, longitudinal, and cross-national studies have been carried out to inform the development of a prevention strategy against disability. To establish evidence-based prevention strategies, it is critically important to accumulate epidemiologic evidence, including the incidence of disability, and identify its risk factors. However, few studies have attempted to estimate the incidence of the disability and its risk factors by using population-based cohorts. In addition, to identify the incidence of disability, a study should have a large number of subjects. Further, to determine regional differences in epidemiological indices, a survey of cohorts across Japan is required.

The Longitudinal Cohorts of Motor System Organ (LOCOMO) study was initiated in 2008, through a grant from Japan's Ministry of Health, Labour and Welfare, for the prevention of knee pain, back pain, bone fractures, and subsequent disability. It aimed to integrate data gathered from cohorts from 2000 onwards and follow-up surveys from 2006 onwards, using a unified questionnaire, with an ultimate goal being the prevention of musculoskeletal diseases. The present study specifically aims at using LOCOMO data, which is based on the long-term care insurance system, to investigate the occurrence of disability in order to clarify its incidence and risk factors, especially in terms of body build and regional differences.

Materials and methods

Participants were residents of nine communities located in Tokyo (two regions: Tokyo-1, principal 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 (coastal 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 [5]. Figure 1 shows the location of each cohort in Japan.

Disability in the present study was defined as 'cases requiring long-term care', as determined by the long-term care insurance system. The procedure for identifying these cases is as follows: (1) each municipality establishes a long-term care approval board consisting of clinical experts, physicians, and specialists at the Division of Health and Welfare in each municipal office; (2) The long-term care approval board investigates the insured person by using an interviewer-administered questionnaire consisting of 82 items regarding mental and physical conditions, and makes a screening judgement based on the opinion of a regular doctor; (3) 'Cases requiring long-term care' are determined according to standards for long-term care certification that are uniformly and objectively applied nationwide [6].

In order to identify the incidence of disability, data were collected from participants aged 65 years and older within the above-mentioned cohorts. In Japan, most individuals certified as 'cases requiring long-term care' are 65 years and older. Table 1 shows the number of subjects per region, as well as the data obtained within the first year of the observation. The smallest cohort consisted of 239 subjects, residing in Mie, while the largest consisted of 1,758, who resided in Gunma.

The earliest baseline data were collected in 2000 in Hiroshima, while the latest were obtained in 2008 in Tokyo-2. The cohorts were subsequently followed until 2012. Data regarding participants' deaths, changes of residence, and occurrence or non-occurrence of certified disability were gathered annually from public health centres of the participating municipalities. As an index of body build, baseline data on participants' height and weight were collected, and used to calculate body mass index (BMI, kg/m^2). Participants were classified as follows: normal or overweight (BMI = 18.5–27.5), obese (BMI >27.5), or emaciated (BMI <18.5). These cut-off points were determined according to a WHO report [7]. From 2008 onwards, follow-up data was obtained using the unified questionnaire.

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

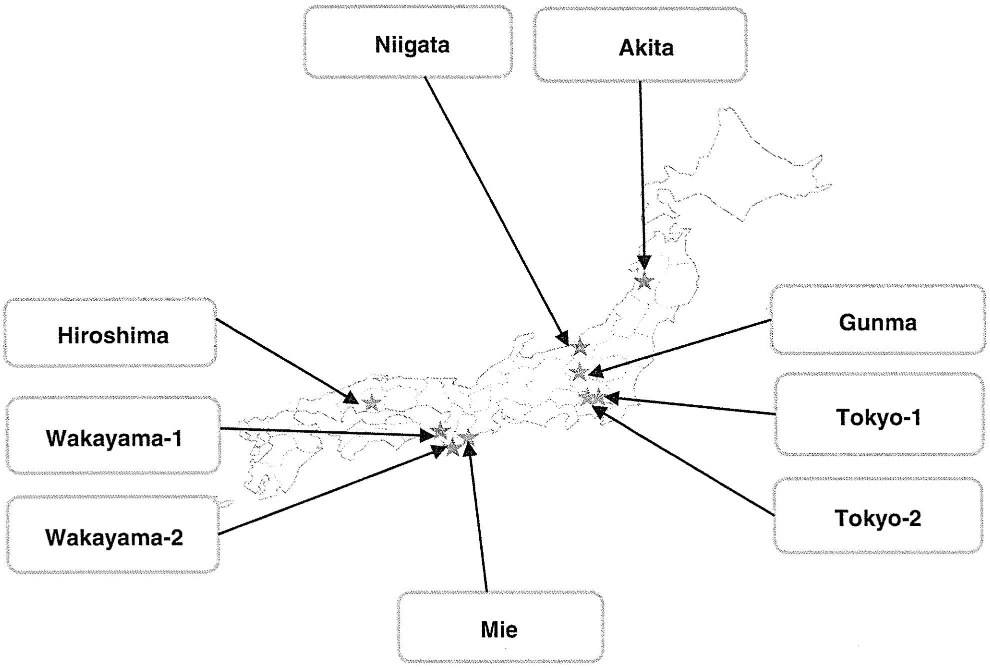

Fig. 1 Location of nine regions from which the study cohorts were selected

Table 1 Number of subjects classified by regions of each cohort

Region	Start year	Total	Men	Women
Tokyo-1	2005	1,332	461	871
Tokyo-2	2008	1,453	59	1,394
Wakayama-1 (Mountainous)	2005	610	239	371
Wakayama-2 (Coastal)	2006	357	129	228
Hiroshima	2000	1,341	351	990
Niigata	2007	805	343	462
Mie	2001	239	95	144
Akita	2006	559	223	336
Gunma	2005	1,758	805	953
Total		8,454	2,705	5,749

(no. 5), Wakayama (no. 373), the Radiation Effects Research Foundation (RP 03-89), Niigata University (no. 446), Mie University (nos. 837 and 139), Keio University (no. 16–20), and the National Center for Geriatrics and Gerontology (no. 249). Careful consideration was given to ensure the safety of the participants during all of the study procedures.

Statistical analysis

All statistical analyses were performed using STATA (STATA Corp., College Station, Texas, USA). Differences in proportions were compared using the chi-squared test. Differences in continuous variables were tested using an analysis of variance (ANOVA) with Scheffe's least significant difference test for post-hoc pairwise comparisons. To test the association between the occurrence of disability and other variables, Cox's proportional hazard regression analysis was used. Hazard ratios (HRs) were estimated using the occurrence of disability as an objective variable (0: non-occurrence, 1: occurrence) and the following explanatory variables: age (±1 year), gender (vs. female), body build (0: normal and overweight vs. 1: emaciation vs. 2: obesity), and 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). All *p* values and 95 % confidence intervals (CI) of two-sided analyses are presented.

Results

Table 2 shows the number of participants classified by age and gender. The majority of participants were 75–79 years old; two-thirds of the participants were women.

Selected characteristics of the study population, including age, height, weight, and BMI, are shown in Table 3. The mean values of age, height, and weight were significantly greater in women than in men ($p < 0.001$), but BMI did not significantly differ between men and women ($p = 0.479$).

The estimated incidence of disability is shown in Fig. 2. In total, the incidence of disability among individuals aged 65 years and older was 3.58/100 person-years (p-y) (p-y; men: 3.17/100 p-y; women: 3.78/100 p-y). The incidence of disability was 0.83/100 p-y, 1.70/100 p-y, 3.00/100 p-y,

Table 2 Number of subjects classified by age and gender

Age strata (years)	Total (%)	Men (%)	Women (%)
65–69	1,390 (16.4)	555 (20.5)	835 (14.5)
70–74	1,704 (20.2)	668 (24.7)	1,036 (18.0)
75–79	2,923 (34.6)	812 (30.0)	2,111 (36.7)
80–84	1,810 (21.4)	463 (17.1)	1,347 (23.4)
≥85	627 (7.4)	207 (7.7)	420 (7.3)
Total	8,454 (100.0)	2,705 (100.0)	5,749 (100.0)

Table 3 Baseline characteristics of subjects classified by age and gender

Variables	Men	Women	*p* (men vs. women)
Age (years)	75.3 (6.4)	76.5 (6.0)	<0.001
Height (cm)	160.5 (6.5)	147.7 (6.1)	<0.001
Weight (kg)	58.7 (9.1)	49.8 (8.4)	<0.001
BMI (kg/m^2)	22.7 (2.9)	22.8 (3.5)	0.479
Living in rural area (%)	84.8	58.5	<0.001

Values are represented as mean (standard deviation)

BMI body mass index

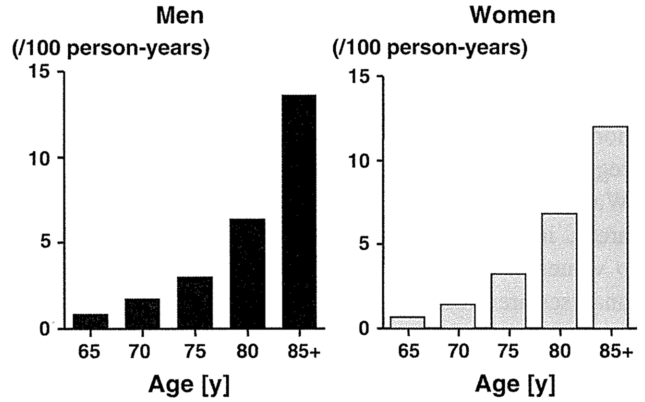

Fig. 2 Incidence of disability according to age and gender

6.36/100 p-y, and 13.54/100 p-y in 65–69-, 70–74-, 75–79-, 80–84-, and ≥85-year-old men, respectively. In women, the incidence of disability was 0.71/100 p-y, 1.40/100 p-y, 3.25/100 p-y, 6.85/100 p-y, and 12.01/100 p-y in the age ranges of 65–69, 70–74, 75–79, 80–84, and 85 or more years, respectively (Table 4).

Cox's proportional hazard regression analysis showed that occurrence of disability was significantly influenced by age, body build, and regional differences, but not gender (age, +1 years: hazard ratio 1.13, 95 % confidence interval 1.12–1.15, $p < 0.001$; sex, vs. female: 1.13, 0.97–1.31, $p = 0.125$; body build: emaciation: 1.24, 1.01–1.53, $p = 0.041$; body build; obesity: 1.36, 1.08–1.71, $p = 0.009$; residence, vs. living in rural areas: 1.59, 1.37–1.85, $p < 0.001$).

Discussion

Using the data of the LOCOMO study, we determined the incidence of disability and identified age, emaciation, obesity, and residence in rural areas as risk factors for the occurrence of disability. More specifically, we integrated data collected from subjects aged 65 and older in individual cohorts established in nine regions across Japan to determine the incidence of disability in the specified regions. We found an association between various risk factors and disability; these include age, emaciation, and obesity, as well as residence in rural areas.

The LOCOMO study was the first nation-wide prospective study to track a large number of the subjects from several population-based cohorts. The LOCOMO study aimed to integrate information from these cohorts, to prevent musculoskeletal diseases and subsequent disability. The data shed light on the prevalence and characteristics of targeted clinical symptoms such as knee pain or lumbar pain, or defined diseases such as knee osteoarthritis (KOA), lumbar spondylosis (LS), and osteoporosis (OP), as well as their prognosis in reference to either mortality or chances of developing a disability. In the present study, we also

Table 4 Hazard ratios (HRs) of potential risk factors for the occurrence and non-occurrence of disability

Disability (occurrence vs. non-occurrence)

Explanatory variable	Reference	HR	95 % confidence interval	*p*
Age (years)	+1 year	1.13	1.12–1.15	<0.001***
Gender	0: men, 1: women	1.13	0.97–1.31	0.125
Body build	0: 18.5 ≤ BMI ≤ 27.5, 1: BMI < 18.5	1.24	1.01–1.53	0.041*
	0: 18.5 ≤ BMI ≤ 27.5, 2: BMI >27.5	1.36	1.08–1.71	0.009**
Type of residential area	0: urban area, 1: rural area	1.59	1.37–1.85	<0.001***

BMI body mass index

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

compared the above-mentioned symptoms, diseases, and prognoses between regions.

The overall incidence of disability among individuals aged 65 years and older was 3.58/100 person-years. When results from the present study are applied to the total age-sex distribution derived from the Japanese census in 2010 [1], it could be assumed that 1,110,000 people (410,000 men and 700,000 women) aged 65 years and older are newly affected by disability and require support. It has been reported that the total number of subjects who were certified as needing care increases annually [4]; however, few of these reports estimate the number of newly certified cases through a population-based cohort. Clarifying the incidence of disability and its risk factors was viewed as the first step toward preventing its occurrence.

Emaciation and obesity were both identified as risk factors for disability; thus, there appears to be a U-shaped association between BMI and disability as well as between BMI and mortality [8, 9]. According to the recent National Livelihood Survey, the leading cause of disabilities that require support and long-term care is cardiovascular disease (CVD), followed by dementia, senility, osteoarthrosis, and fractures [4]. Obesity is an established risk factor for chronic diseases, including hypertension, dyslipidemia, and diabetes mellitus, which increase the risk for CVD [10]; in turn, CVD causes ADL-related disabilities in older adults. In addition, numerous reports have shown an association between overweight or obesity and KOA [11–17]. In previous reports, we found a significant association between BMI and not only the presence of KOA, but also the occurrence and progression of KOA [18, 19]. In addition, emaciation is an established risk factor for OP and OP-related fractures [20]. OP might be related to low nutrition due to chronic wasting diseases.

The current study also found an association between living in a rural area and the occurrence of disability. There have been reports of regional differences in the certification rate of disability in Japan. For instance, Kobayashi reported a prefectural difference in the certification rate of disability, which was particularly prominent among individuals aged 75 years and older at lower nursing care levels in the long-term care insurance system [21]. In addition, Shimizutani et al. [22] pointed out that the financial condition of the insurer influenced the certification rate of disability. Further, Nakamura found that the certification of lower care levels was influenced by social and/or individual factors, such as the type of service provider, the application rate, and number of medical treatment recipients. However, certification of advanced nursing care levels was influenced by CVD and lifestyle-related diseases [23].

Other than differences in the social backgrounds of individuals in each prefecture, we posited that regional differences (rural or urban) in the occurrence of disability might be due to differences in the frequency of diseases and ailments that cause disability in each area. The prevalence of musculoskeletal diseases, such as KOA and LS, differs among mountainous, coastal, and urban areas [24]. Evidence also exists for regional differences in the incidence of hip fractures [25–27]. It was also found that mortality and incidence of ischemic stroke, which is related to CVD, was higher in the northeastern than in the southwestern part of Japan [28]. However, there is currently no information on regional differences in dementia prevalence and incidence in Japan. In general, differences in the frequency of diseases causing disability might influence regional differences in disability rates. In relation to this, in a future study on follow-up data from the LOCOMO study, it might be necessary to collect information on the prevalence and frequency of diseases that cause disability, such as musculoskeletal diseases, CVD, and dementia. This future study should also attempt to clarify mutual associations among risk factors for disability, so as to inform the development of measures for its primary prevention.

Despite its contribution to existing knowledge, the present study has several limitations. First, its sample does not truly represent the entire Japanese population, because our cohorts were not drawn from the northernmost and southernmost parts of Japan (e.g., Okinawa prefecture or Hokkaido prefecture). This limitation must be taken into consideration, especially when determining the generalisability of the results. However, the LOCOMO study is the first large-scale, population-based prospective study with approximately 9,000 participants aged 65 years and older. Second, data collected from the cohorts were not uniform, as certain information was obtained from some participants, but not others. For example, the X-ray examinations of subjects' knees were performed in Tokyo-1, Wakayama-1, Wakayama-2, Niigata, and Mie; lumbar spine X-ray examinations were performed in Tokyo-1, Wakayama-1, Wakayama-2, Hiroshima, and Mie. Therefore, we could not evaluate the presence or absence of KOA, LS, or OP as a possible cause of disability by using the data of the entire LOCOMO study. Further investigation following the integration of information on musculoskeletal disorders would enable us to evaluate all the factors that are associated with disability.

Nevertheless, our study has several strengths. As mentioned above, the large sample size is the study's biggest strength. The second strength is that we collected data from nine cohorts across Japan, which enabled us to compare regional differences in the incidence of disability. In addition, the variety of measures and assessments used in this study enabled us to collect a substantial amount of detailed information. However, given the fact that not all of the measures were administered in all cohorts, regional selection bias in the analysis should be considered when interpreting the results.