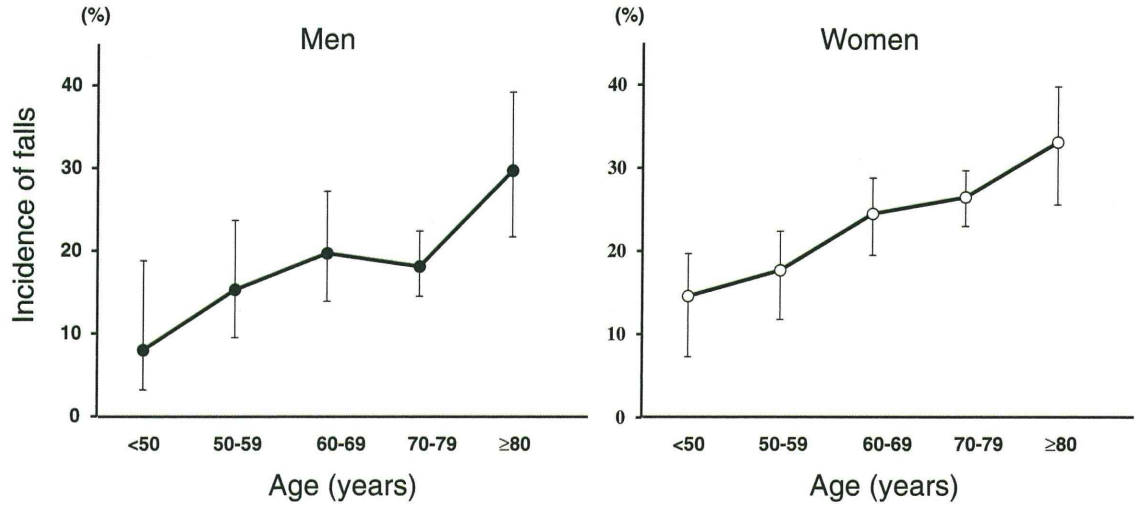

Fig. 1 Incidence rate of falls (95 % CI) by gender and age

muscles and increased postural sway associated with knee OA [8, 40], both of which are known to be independent risk factors for falls [7, 41]. In men, muscle strength is higher than that in women in all decades [42], which may obscure the association between radiographic knee OA and falls. LS was not a risk factor for falls in this study. Thus, falls may be more strongly associated with problems of the lower limbs rather than the trunk.

After adjustment for age, BMI, walking speed, and radiographic knee OA, knee pain was independently associated with the incidence of falls in women. Given that the significant association of radiographic knee OA with falls disappeared after adjustment, falls may occur due to symptoms such as pain caused by radiographic knee OA rather than radiographic changes in the knee itself. Our study and other previous cross-sectional studies also suggested that knee pain was significantly associated with falls [6, 24]. In addition, a prospective study also showed that knee pain increases in falls risk in Tasmanian men and women [10]. Jones et al. showed that, for the hand, the presence of pain is what weakens grip strength [43]. In a similar way, knee pain may weaken leg strength, leading to falls. In other words, falls may be preventable when pain is relieved by medical care, even if subjects have radiographic knee OA.

In the present study, after adjustment for knee OA and knee pain, slower walking speed was an independent risk factor for falls in men and women. Verghese et al. also showed that risk for falls increased to approximately 7 % as walking speed decreased per 0.1 m/s [44], although bone and joint diseases were not included and men and women were not separately analyzed in the study. In the present study, multiple logistic regression analysis after adjustment for knee OA and knee pain showed that, as walking speed decreased per 0.1 m/s, the risk for falls were 15 and 5 % higher in men and women, respectively, indicating that slower walking speed may more strongly affect the risk of falls in men than women. Although dependent on the availability of equipment, quantitative gait measures can be easily and quickly collected in clinical and research settings without requiring attachment of monitoring devices or extensive training. The present study may indicate that walking speed is a simple and quick option for measuring fall risk, particularly in men.

The present study has several limitations. First, our subjects lived in the community, and thus, our findings may not

Table 2 Comparison of characteristics among nonfallers and fallers in men and women

	Men			Women		
	Nonfallers	Fallers	*p* value	Nonfallers	Fallers	*p* value
Number of subjects	604	141		1,108	362	
Age (years)	68.9±11.2	71.8±10.2	0.003	67.3±11.4	70.3±10.8	<0.001
Height (cm)	163.3±6.9	162.6±5.4	0.18	150.8±6.2	149.0±6.5	<0.001
Weight (kg)	62.2±10.0	62.1±9.8	0.92	52.1±8.6	51.7±8.2	0.34
BMI (kg/m^2)	23.3±3.0	23.5±3.3	0.51	22.9±3.4	23.3±3.4	0.06
Grip strength (kg)	34.8±8.9	33.0±8.2	0.02	22.4±6.2	21.1±6.1	<0.001
Walking speed (m/s)	1.30±0.36	1.11±0.28	<0.001	1.25±0.33	1.15±0.33	<0.001

Values are presented as the mean ± SD, except where indicated. Nonpaired Student's *t* test was used to determine the differences in age, height, weight, BMI, grip strength, and walking speed between nonfallers and fallers

BMI body mass index

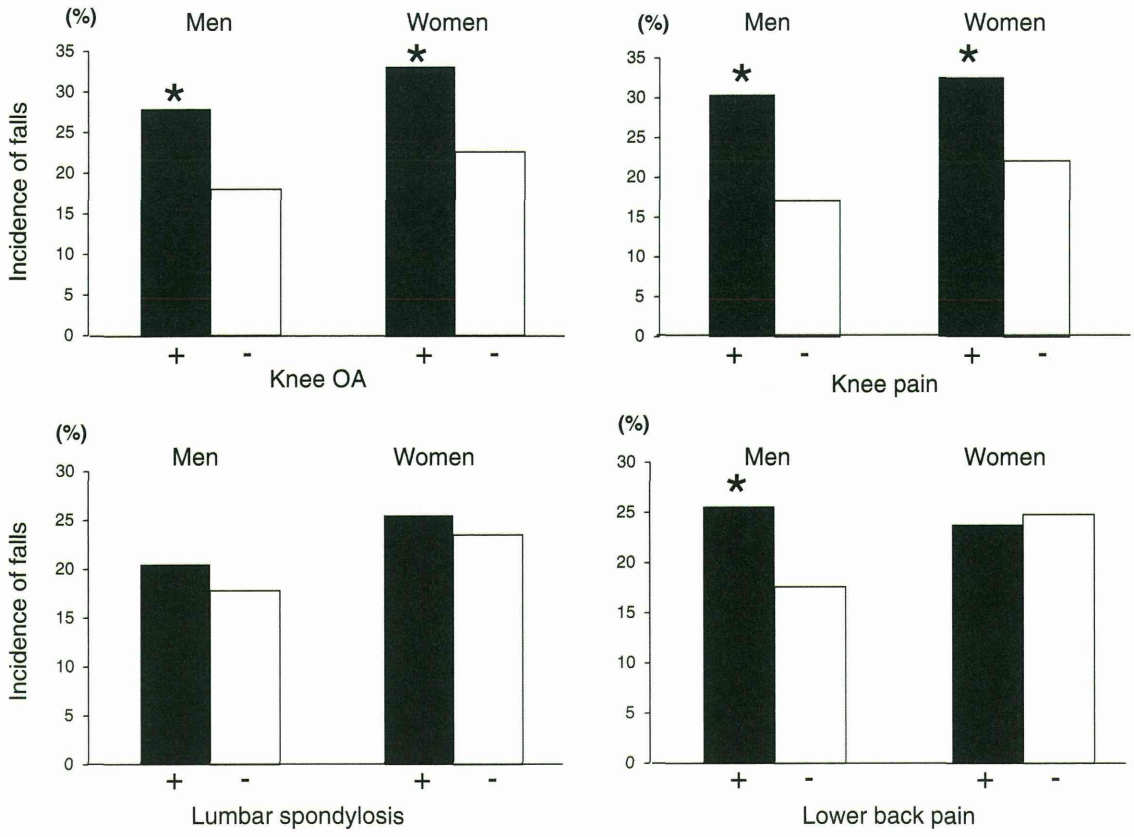

Fig. 2 Incidence of falls by knee OA, knee pain, LS, and lower back pain. *$p<0.05$ vs. subjects without knee OA, LS, knee pain, and lower back pain, respectively, by chi-square test

apply to elderly persons residing in institutions. Second, we did not include other weight-bearing OAs such as hip OA in the analysis, although this disorder also affect falls [45]. However, the prevalence of KL=3 or 4 hip OA is 1.4 and 3.5 % in Japanese men and women [46], respectively, which is smaller than that of KL=3 or 4 knee OA in the present study. Thus, it is possible that hip OA would not strongly affect the results of the present study.

In conclusion, the present longitudinal analysis using a large-scale population from the ROAD study revealed the incidence and risk factors for falls in men and women. Slower walking speed was a risk factor for falls in men

Table 3 Association of physical performance and bone and joint diseases with the incidence of falls in men and women

	Men			Women		
	Crude OR (95 % CI)	Adjusted OR_1 (95 % CI)	Adjusted OR_2 (95 % CI)	Crude OR (95 % CI)	Adjusted OR_1 (95 % CI)	Adjusted OR_2 (95 % CI)
Grip strength (5-kg decrease)	1.14 (1.02–1.27)	1.05 (0.92–1.20)	–	1.20 (1.09–1.33)	1.10 (0.98–1.25)	–
Walking speed (0.1-m/s decrease)	1.19 (1.11–1.25)	1.16 (1.10–1.25)	1.15 (1.09–1.23)	1.10 (1.05–1.14)	1.06 (1.02–1.11)	1.05 (1.01–1.10)
Radiographic knee OA	1.76 (0.98–3.06)	1.52 (0.83–2.67)	1.12 (0.59–2.08)	1.69 (1.27–2.24)	1.43 (1.05–1.93)	1.21 (0.87–1.66)
Knee pain	2.12 (1.31–3.36)	1.99 (1.22–3.18)	1.63 (0.96–2.70)	1.71 (1.31–2.22)	1.54 (1.17–2.02)	1.38 (1.03–1.84)
LS	1.19 (0.83–1.73)	1.04 (0.71–1.52)	–	0.90 (0.71–1.14)	0.74 (0.57–0.94)	–
Low back pain	1.61 (1.02–2.51)	1.59 (0.99–2.49)	–	0.95 (0.79–1.27)	0.91 (0.67–1.23)	–

Multiple logistic regression analysis was used to calculate the odds ratio (OR) and 95 % confidence interval (CI) compared with nonfallers. Adjusted OR_1 was calculated using multiple logistic regression analysis after adjustment for age and BMI. Adjusted OR_2 was calculated using multiple logistic regression analysis with age, BMI, walking speed, radiographic knee OA, and knee pain as independent variables. Radiographic knee OA and LS were defined as KL grade 3 or 4

OA osteoarthritis

and women. Knee pain was a risk factor for falls in women. Further studies, along with continued longitudinal surveys in the ROAD study, will help elucidate the background of knee OA and LS and their relationship with falls.

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Conflicts of interest None.

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Associations between radiographic lumbar spinal stenosis and clinical symptoms in the general population: the Wakayama Spine Study

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SUMMARY

Objective: Many asymptomatic individuals have radiographic lumbar spinal stenosis (LSS), but the prevalence of symptoms among individuals with radiographic LSS has not yet been established. The purpose of this study was to clarify the association between radiographic LSS and clinical symptoms in the general population.

Methods: In this cross-sectional study, data from 938 participants (308 men, 630 women; mean age, 66.3 years; range, 40–93 years) were analyzed. The severity of radiographic LSS, including central stenosis, lateral stenosis, and foraminal stenosis, was assessed by mobile magnetic resonance imaging and rated qualitatively. Assessment of clinical symptoms was based on the definition of symptomatic LSS in the North American Spine Society guideline.

Results: We found that 77.9% of participants had more than moderate central stenosis and 30.4% had severe central stenosis. Logistic regression analysis after adjustment for age, sex, body mass index, and severity of radiographic LSS showed that severe central stenosis was related to clinical symptoms. However, only 17.5% of the participants with severe central stenosis were symptomatic.

Conclusion: Although radiographic LSS was common in our cohort, which resembled the general Japanese population, symptomatic persons were relatively uncommon.

Introduction

Radiographic lumbar spinal stenosis (LSS) is defined as a narrowing of the lumbar canal with encroachment of neural structures by surrounding bone and soft tissue[1]. Symptomatic LSS, which requires both the presence of clinical symptoms and radiographic LSS[2], is usually associated with impaired walking and other disabilities in the elderly[1,3] and is the most frequent indication for spinal surgery in patients older than 65 years[4]. Because of the high number of elderly persons in Japan, there is an urgent need for evidence-based data regarding radiographic LSS occurring as a result of degenerative changes. However, little information is available regarding the epidemiology of radiographic LSS. This is because previous studies on radiographic LSS have not included subjects who were part of the general population[5–7]. Furthermore, for radiographic LSS to be diagnosed, the detection of minute changes of the intervertebral discs and ligaments using a tool like magnetic resonance imaging (MRI) is essential[8,9], but to the best of our knowledge, no studies of radiographic LSS among the general population have been performed using MRI.

LSS symptoms include a range of possible clinical presentations resulting from dilatation of the intrinsic vessels of the nerve roots[10]. However, inconsistent with this observation, severe radiographic LSS is often present in asymptomatic patients[7], and little is known of the prevalence of symptoms among individuals with radiographic LSS. Previous studies have reported on the relationship between radiographic LSS and quality of life, function, and pain due to symptoms in symptomatic patients[11–14]. To the best of our knowledge, there has been no study on the association between radiographic LSS and clinical symptoms among the general population, which includes both symptomatic and asymptomatic individuals.

In this study, we aimed to determine the prevalence of radiographic LSS assessed by MRI and its association with clinical symptoms using mobile MRI in a population-based cohort.

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Methods

Participants

The present study, entitled The Wakayama Spine Study, assessed a subcohort drawn from Research on Osteoarthritis/Osteoporosis Against Disability (ROAD), which is a large-scale, prospective study of bone and joint diseases among population-based cohorts established in several communities throughout Japan. As the detailed profile of the ROAD study is described elsewhere, only a brief summary is provided here[15–18]. A database including baseline clinical and genetic information relating to 3,040 inhabitants (1,061 men, 1,979 women) with a mean age of 70.6 years (range, 23–95 years) has been created. We recruited individuals listed in resident registrations in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama. All participants provided written, informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Participants completed an interviewer-administered questionnaire that included 400 items covering lifestyle information, and they underwent anthropometric measurements and assessments of physical performance. Blood and urine samples were collected for biochemical and genetic examinations.

The ROAD study team made a second visit to the mountainous region of Hidakagawa and the coastal region of Taiji between 2008 and 2010. Of the inhabitants who participated in this second visit, 1,063 volunteers were recruited for MRI. Fifty-two of these declined to attend the examination, and the remaining 1,011 were registered in the Wakayama Spine Study. All participants provided their written, informed consent for the MRI examination. Participants who had sensitive implanted devices (such as a pacemaker) or other disqualifiers were excluded. In total, 977 participants underwent lumbar spine MRI. Ten participants who had undergone a previous lumbar operation for LSS were excluded, and 29 participants who were younger than 40 years were excluded because LSS is a degenerative disease. Thus, MRI results were available for 938 participants (308 men and 630 women) with an age range of 40–93 years (mean, 68.3 years for men and 66.9 years for women).

Similar to the baseline study, the second ROAD study included an interviewer-administered questionnaire that included 400 items that covered lifestyle information such as smoking habits, alcohol consumption, family history, past history, physical activity, reproductive variables, and health-related quality of life. Anthropometric measurements included height, weight, bilateral grip strength, and body mass index (BMI) (kg/m^2). Co-morbidities were defined according to blood data (diabetes: HbA1c $> 6.5\%$[19], hyperuricemia: uric acid > 7.0 mg/dL[20], hyperlipidemia: high-density lipoprotein cholesterol < 40 mg/dL[21]). The ankle-brachial index (ABI) of all participants was measured using PWV/ABI (OMRON Co., Kyoto, Japan).

MRI

All participants underwent total spinal MRI with a mobile MRI unit (Excelart 1.5 T; Toshiba, Tokyo, Japan) on the same day as the examination. MRI exclusion criteria included the presence of a cardiac pacemaker, claustrophobia, or other reasons. The participants were supine during the MRI, and those with rounded backs used triangular pillows under their head and knees. The imaging protocol included sagittal T2-weighted fast spin echo (FSE) (repetition time [TR]: 4,000 ms/echo, echo time [TE]: 120 ms, field of view [FOV]: 300 mm $\times$ 320 mm) and axial T2-weighted FSE (TR: 4,000 ms/echo, TE: 120 ms, FOV: 180 mm $\times$ 180 mm). Sagittal images were taken of the entire spine, but axial images were taken at each lumbar intervertebral level (L1/2–L5/S1) parallel to the vertebral endplates.

Qualitative ratings

The severity of radiographic LSS was qualitatively assessed after all examinations were completed. An experienced orthopedic surgeon (YI) without knowledge of the participants' symptom status examined the images, which were provided on films. The features assessed included the severity of central, lateral recess, and foraminal stenosis, rated on a four-grade scale. We used Fardon and Millette's[22] definition of lateral recess: a recess extending from the medial edge of the facet to the edge of the neuroforamen. We also applied the classification included in a general guideline[2] in which mild stenosis was defined as narrowing of one-third of the normal area or less, moderate stenosis as narrowing of between one- and two-thirds, and severe stenosis as narrowing of more than two-thirds of the area. Central stenosis and lateral recess stenosis were rated on the axial images and foraminal stenosis on the sagittal images. For lateral and foraminal stenosis, the rating for the side with the worst score was used. To evaluate the intraobserver variability of the severity rating, 50 randomly selected lumbar MRI films were scored by the same observer more than 1 month after the first reading. Fifty other lumbar MRI films were also scored by two experienced orthopedic surgeons (YI & KN) to determine the interobserver variability. The intraobserver variabilities in severity rating were confirmed by kappa analysis to be sufficient for the assessment of central, lateral, and foraminal stenosis (0.82, 0.71, and 0.66, respectively); interobserver variability was also sufficient (0.77, 0.66, and 0.66, respectively).

Assessment of clinical symptoms

An experienced orthopedic surgeon (YI) took the medical history and performed the physical examination of all the participants. The history included information about the presence of lower back pain, buttock pain, and leg pain; areas of pain or other discomfort; the presence of intermittent claudication (IC) and its distance; and items on a modified Zurich Claudication Questionnaire[23] (except six items about satisfaction and a history of lumbar surgery for symptomatic LSS). Physical examination included assessments to determine whether any symptoms could be induced by lumbar extension or were improved or induced by lumbar flexion, floor finger distance (cm), and peripheral circulation (good or poor); a straight-leg raising test; manual muscle testing of both the upper and lower extremities; tendon reflex testing for both the upper and lower extremities; and Babinski reflex testing. In addition, an MRI study of the entire spine was performed for all participants on the same day as the physical examination.

Assessment of clinical symptoms in the present study was based on the LSS definition in the North American Spine Society (NASS) guideline[24] and required one or more of the following symptoms: pain, numbness and neurological deficits in the lower extremities and buttocks, and bladder/bowel dysfunction. In addition, the above symptoms were required to be induced or exacerbated by walking or prolonged standing and relieved by lumbar flexion, sitting, and recumbency.

Statistical analysis

All statistical analyses were performed using JMP, version 8 (SAS Institute Japan; Tokyo, Japan). Differences between men and women in age, height, weight, and BMI were examined using non-paired Student's t test., co-morbidities, and clinical symptoms were compared between men and women with the chi-square test. The chi-square test was also used to determine the association between radiographic LSS and age stratum. Logistic regression analysis was performed stratified for sex to determine the effect of age and BMI

on severe stenosis of all locations or the severest stenosis in each area, with the latter as an objective variable and age and BMI as explanatory factors. A further logistic regression analysis was performed stratified for sex to determine the effect of age, BMI, and each level of severity of central stenosis with clinical symptoms, using radiographic LSS as an objective variable and age, BMI, and each severity level as explanatory factors. We constructed a set of two dummy variables defining the three different central stenosis groups (none/mild, moderate, and severe).

Results

Table I summarizes characteristics of the 938 participants (308 men and 630 women; mean age 67.3 years, range 40–93 years), including age and anthropometric measurements. Two-thirds of them were women. Mean age was not significantly different between men and women. BMI was significantly lower in women than in men.

For all locations except central L1/2 and L2/3, several MRIs were found to be inadequate for interpretation; in particular, the sample for qualitative analysis of foraminal L1/2 was reduced to 907 (Table II). Regarding both central and lateral canal stenosis, the prevalence of severe stenosis was highest at L4/5, followed by L3/4. One-third of the participants had severe canal stenosis of at least one level. On the other hand, the distribution of the prevalence of severe foraminal stenosis was entirely different from that of central and lateral severe stenosis. The level with the highest prevalence of severe foraminal stenosis was L5/S1, followed by L4/5. There were few participants with more than moderate stenosis at the upper levels of the foramen. Concerning severe stenosis in all locations, multiple logistic regression analysis after adjustment for age and BMI revealed that more men had severe stenosis at lateral L2/3, L3/4, and L4/5 than women (odds ratios [ORs] and 95% confidence intervals [CIs] for lateral stenosis were 2.05, 1.13–3.73 at L2/3; 1.95, 1.34–2.86 at L3/4; and 1.52, 1.11–2.08 at L4/5). To identify factors related to the severest stenosis at each location, we performed a further multiple logistic regression analysis with age, BMI, and sex as explanatory variables. Age was significantly associated with severe stenosis at all locations for both sexes (ORs and 95% CIs were 1.06, 1.04–1.07 for central stenosis; 1.09, 1.07–1.10 for lateral stenosis; and 1.11, 1.08–1.15 for foraminal stenosis). BMI was also significantly associated with severe central stenosis in the overall cohort and in men, but not in women (overall: 1.06, 1.02–1.10; men: 1.08, 1.00–1.17; women: 1.05, 0.99–1.10). There was no significant difference in the prevalence of central stenosis of more than moderate severity between agricultural/forestry/fishery workers or not ($P = 0.60$). There was also no significant difference in radiographic LSS between persons with diabetes, hyperuricemia, and hyperlipidemia or not, each (Diabetes: $P = 0.21$, hyperuricemia: $P = 0.65$, hyperlipidemia: $P = 0.71$).

Table I
Characteristics of participants

	Total	Men	Women
No. of participants	**938**	**308**	**630**
Age group (years)			
<49	96	26	70
50–59	175	59	116
60–69	222	65	157
70–79	258	87	171
≧80	187	71	116
Demographic characteristics			
Age, years	67.3 ± 12.4	68.3 ± 12.5	66.9 ± 12.3
Height, cm	155.7 ± 9.3	164.4 ± 6.9**	151.4 ± 7.1
Weight, kg	56.7 ± 11.4	64.3 ± 11.3**	53.0 ± 9.4
BMI, kg/m^2	23.3 ± 3.6	23.7 ± 3.3*	23.1 ± 3.6
Job titles, no.			
Clerical workers/technical experts	197	79	118
Agricultural/forestry/fishery workers	105	62	43
Factory/construction workers	48	23	25
Others	588	144	444
Co-morbidities, no.			
Diabetes	48	23*	25
Hyperuricaemia	71	54**	17
Hyperlipidemia	41	30**	11

A non-paired t-test was used to determine differences in demographic characteristics and measurements of physical performance between men and women. Values are the means ± standard deviation. *$P < 0.05$, **$P < 0.01$.

Fig. 1 shows the prevalence of moderate and severe radiographic LSS for the severest stenosis identified in each area and classified by age and sex. Both central and lateral stenosis of more than moderate severity were quite common among the elderly, but foraminal stenosis of more than moderate severity was less common. The prevalence of severe stenosis at each location was significantly higher with increasing age stratum in both sexes (central, men: $P = 0.008$; central, women: $P < 0.0001$; lateral, both: $P < 0.0001$; foraminal, both: $P < 0.0001$ [all by chi-square test]).

There were 105 individuals with clinical symptoms (men: 35, women: 70). There was no significant difference between sexes in the prevalence of clinical symptoms ($P = 0.91$). Fifty-four of the 105 participants identified as having clinical symptoms had IC. Five of these 54 participants presented with an ABI <0.9. However, these five participants also had symptomatic LSS, and their leg symptoms were dependent on position. These five cases were unspecified IC, caused by both neurogenic and vascular claudication. We used cases of central stenosis to clarify the association between radiographic LSS and clinical symptoms. The prevalence of clinical symptoms significantly increased with increasing severity of central stenosis, for both sexes, according to chi-square test (men: $P = 0.009$; women: $P = 0.004$). Furthermore, to clarify the relationship between individuals with clinical symptoms and each grade of severity, we performed a logistic regression analysis to estimate the OR and 95% CI after adjustment for age, BMI, sex, and severity of radiographic LSS, and we constructed a set of two dummy variables defining the three central stenosis groups (none/mild, moderate, and severe). Severe central stenosis was confirmed to be related to symptomatic individuals, but moderate stenosis was not (men, severe vs none/mild: 4.42, 1.44–17.0; men, moderate vs none/mild: 1.53, 0.49–5.86; women, severe vs none/mild: 2.50, 1.44–17.0; women, moderate vs none/mild: 1.83, 0.82–4.66). Among symptomatic persons ($n = 105$), there were 16 taking painkillers, seven taking trigger injections, and 13 in rehabilitation. We added these treatment statuses to the multivariate model and logistic regression analysis for the association between radiographic LSS and clinical symptoms, but the result was unchanged (Table III).

Discussion

In this study, we evaluated the prevalence of radiographic LSS assessed by MRI and its association with clinical symptoms in the general population. The intervertebral level with the highest prevalence of both severe central stenosis and severe lateral stenosis was L4/5; the prevalence of severe foraminal stenosis was greatest at L5/S. The prevalence of moderate or severe central stenosis was 64.0% in patients in their 50s and 93.1% in those in their 80s. There was a significant association between the severity of central stenosis and the presence of clinical symptoms. Of those with severe central stenosis, 17.5% had clinical symptoms. In addition, logistic regression after adjustment for age, BMI, sex, and severity of radiographic LSS revealed that severe central stenosis was related to clinical symptoms.

The most frequent intervertebral level of severe stenosis was consistent with the intervertebral location of severe stenosis that is most frequently seen in clinical settings. However, to the best of our

Table II
Prevalence of central, lateral, and foraminal stenosis

	L1/2	L2/3	L3/4	L4/5	L5/S1	Severest
Central stenosis						
No. of total†	938	938	937	937	936	938
None	112 (11.9)	57 (6.1)	36 (3.8)	31 (3.3)	163 (17.4)	13 (1.4)
Mild	606 (64.6)	435 (46.4)	305 (32.6)	276 (29.5)	580 (62.0)	194 (20.7)
Moderate	205 (21.9)	389 (41.5)	445 (47.5)	406 (43.3)	161 (17.2)	446 (47.5)
Severe	15 (1.6)	57 (6.1)	151 (16.1)	224 (23.9)	32 (3.4)	285 (30.4)
Lateral stenosis*						
No. of total†	933	933	929	931	925	938
None	439 (47.1)	199 (21.3)	80 (8.6)	29 (3.1)	333 (36.0)	11 (1.2)
Mild	393 (42.1)	454 (48.7)	347 (37.4)	251 (27.0)	414 (44.8)	205 (21.9)
Moderate	90 (9.6)	231 (24.8)	359 (38.6)	368 (39.5)	126 (13.6)	380 (40.5)
Severe	11 (1.2)	49 (5.0)	143 (15.4)	283 (30.4)	52 (5.6)	342 (36.5)
Foraminal stenosis*						
No. of total†	907	915	930	930	926	937
None	676 (74.5)	535 (58.5)	316 (34.0)	154 (16.6)	265 (28.6)	84 (9.0)
Mild	210 (23.2)	335 (36.6)	513 (55.2)	524 (56.3)	421 (45.5)	474 (50.6)
Moderate	18 (2.0)	42 (4.6)	90 (9.7)	220 (23.7)	202 (21.8)	313 (33.4)
Severe	3 (0.3)	3 (0.3)	11 (1.2)	32 (3.4)	38 (4.1)	66 (7.0)

Number (%). Percentage shows the prevalence at the same location.
* The rating of the most severely affected side was used.
† Participants were omitted if interpretation of their MRI was difficult because of poor image quality at each level.

knowledge, there has been no study on the prevalence of radiographic LSS assessed by MRI among the general population. We found a differential distribution in the prevalence of canal stenosis (including central and lateral stenosis) and foraminal stenosis, which may be partly explained by the difference in anatomy between these two locations. Canal stenosis consists of a bulging disk, thickening of the ligamentum flavum, and hypertrophy of the facet joints, whereas loss of disk height, disk protrusion, and facet joint osteoarthritis (OA) lead to foraminal stenosis[1]. The difference in anatomy between canal stenosis and foraminal stenosis (in terms of compression of the nerve root) may be related to the differential distribution of prevalence.

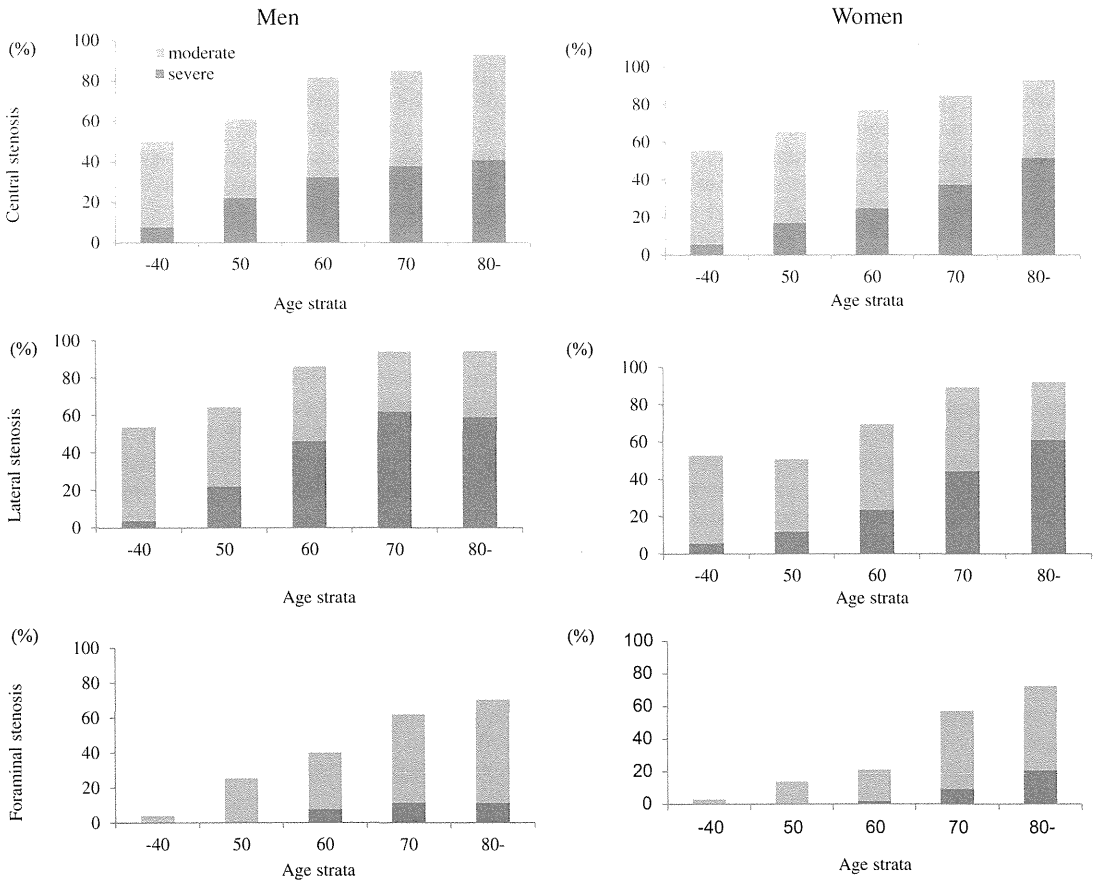

Fig. 1. Prevalence of severe central stenosis, severe lateral stenosis, and compressing foraminal stenosis classified by age and sex for 938 participants from a community cohort in Japan.

Table III
The association of radiographic LSS with clinical symptoms

	None/Mild	Moderate	Severe	Total
Men				
Radiographic LSS*	66	144	98	308
Clinical symptoms	4 (6.1)	12 (8.3)	19 (19.4)	35 (11.4)
Women				
Radiographic LSS*	141	302	187	630
Clinical symptoms	7 (5.0)	32 (10.6)	31 (16.6)	70 (11.1)
Total				
Radiographic LSS*	207	446	285	938
Clinical symptoms	11 (5.3)	44 (9.9)	50 (17.5)	105 (11.2)

Number (%).
* Radiographic LSS means central stenosis.

Many participants had radiographic LSS, although most were asymptomatic: 77.9% had more than moderate central stenosis and about 30.4% had severe central stenosis. Boden *et al.*[7] reported that 21% of 14 asymptomatic volunteers who were over 60 years of age had spinal stenosis, but their criteria for spinal stenosis (loss of epidural fat with compression of neural tissue within the canal) were different from ours. To our best knowledge, there is no report on the prevalence of radiographic LSS using MRI in a large population-based cohort. These findings indicate that radiographic LSS is quite common among the elderly.

We found that severe central stenosis was significantly associated with clinical symptoms, but only 17.5% of participants with severe central stenosis were symptomatic. Previous studies of the relationship between disabilities and radiographic LSS have yielded varied results[11–14]. One study with a 12-year follow-up[11] period showed a clear association between Oswestry Disability Index (ODI) and degree of stenosis. The subjects were assessed by myelography, but only 56.0% (75/134) were followed up and the ODI was determined by telephone interview. Ogikubo *et al.*[12] reported an association between the cross-sectional area of the lumbar spine and walking distance and pain among patients who subsequently underwent surgery. On the other hand, Amundsen *et al.*[13] found no relationship between the degree of stenosis measured by myelography and computed tomography (CT) and clinical symptoms in 100 symptomatic patients. Lohman *et al.*[14] also found no relationship between cross-sectional areas of the canal measured by CT and clinical symptoms in 117 patients who were referred from a primary health service because of chronic lower back pain and clinical suspicion of spinal stenosis. Jenson *et al.*[25] noted that abnormal MRI findings in individuals with lower back pain may frequently be coincidental. Thus, although one would expect that associations between radiographic LSS and symptoms or other disabilities due to LSS would be related to the degree of stenosis, previous studies have yielded varied results. In this study, severe central stenosis was related to clinical symptoms, but less than 20% of those with severe central stenosis were symptomatic. It thus seems to be impossible to clarify the cause of clinical symptoms by imaging alone; an expert clinician's opinion of both clinical assessment and imaging studies is essential for interventions such as surgery in symptomatic individuals.

There were several limitations to the present study. First, our participants may not represent the general population, as they were recruited from only two areas. However, anthropometric measurements were compared between the participants and the general Japanese population, and no significant differences in BMI were found (men: 23.71 [3.41] vs 23.95 [2.64], women: 23.06 [3.42] vs 23.50 [3.69])[26]. In addition, the proportions of current smokers and current drinkers (those who regularly smoked or drank more than one drink per month) in the general Japanese population were compared with those in the study population. The proportions of current smokers and drinkers (men) and current drinkers (women) were significantly higher in the general Japanese population than in the study population (smokers, men: 32.6% of the Japanese population vs 25.2% of the study participants; smokers, women: 4.9% of the Japanese population vs 4.1% of the study participants; drinkers, men: 73.9% of the Japanese population vs 56.8% of the study participants; drinkers, women: 28.1% of the Japanese population vs 18.8% of the study participants). This suggests the study participants (both men and women) likely had healthier lifestyles than the general Japanese population. Second, this was a cross-sectional study, so it does not provide conclusive evidence of any causal relationship between radiographic LSS and clinical symptoms. Third, this study only represented the Japanese population, and the prevalence in other countries may be quite different. Fourth, this study investigated elderly participants who lived independently rather than those who lived in institutional settings, so the calculated prevalence may be an underestimate. Fifth, we excluded 10 subjects who had already had surgery for LSS, and this could have influenced the results. However, LSS surgery is a major intervention that interferes with radiographic assessment of LSS, because it involves decompression and instrumentation that could produce artifacts. Finally, concerning facet OA and disc degeneration, which are important factors for radiographic LSS, we reported the prevalence of radiographic lumbar spondylosis assessed by Kellgren/Lawrence grading elsewhere[15,17]. We did not assess facet OA in this MRI study. We have been assessing disc degeneration in this cohort and will have results to report about this important investigation in the near future.

Nevertheless, this is the first trial to evaluate the prevalence of radiographic LSS and its association with clinical symptoms in the general population using MRI. In addition, the Wakayama Spine Study is a longitudinal survey, so future results will help to elucidate any causal relationships.

In conclusion, the present study evaluated the prevalence of radiographic LSS and clarified its association with clinical symptoms in a population-based cohort. Many participants had radiographic LSS, but few had clinical symptoms. The prevalence of clinical symptoms increased with increasing severity of radiographic LSS.

Contributors

All authors worked collectively to develop the protocols and methods described in this paper. YI, SM, KN, NO, HO, TA, and NY were the principal investigators responsible for the fieldwork in the Wakayama Spine Study. YI and SM performed the statistical analysis. YI, HY, SM, KN, HH, HO, TA, MY, and NY contributed to the analysis and interpretation of results. YI wrote the report. All authors read and approved the final report.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Role of the funding source

The study sponsors played no role in the study design, the collection, analysis, and interpretation of data, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data and had the final decision to submit for publication.

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ORIGINAL ARTICLE

Profiles of vitamin D insufficiency and deficiency in Japanese men and women: association with biological, environmental, and nutritional factors and coexisting disorders: the ROAD study

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Abstract
Summary Assessments of serum 25-hydroxyvitamin D levels in 1,683 Japanese from a population-based cohort revealed prevalences of vitamin D insufficiency and deficiency were 81.3 and 1.2 %, respectively. Vitamin D deficiency was significantly associated with female sex, examined month, current smoking, lack of regular walking, higher intact parathyroid hormone (iPTH), and poor daily vitamin D intake.
Introduction To clarify the characteristics of subjects with vitamin D insufficiency and deficiency among men and women in the general Japanese population.
Methods We initiated research on osteoarthritis/osteoporosis against disability (ROAD), a large-scale population-based cohort study, in 2005–2007. Blood examination was performed to measure serum 25-hydroxyvitamin D (25D) and iPTH levels and biochemical markers of bone turnover in 1,683 participants (595 men, 1,088 women). Participants completed an interviewer-administered questionnaire, measurements of bone mineral density, and x-ray examination. Vitamin D deficiency and insufficiency were defined by serum 25D levels <10 and ≥10 but <30 ng/mL, respectively.
Results The prevalence of vitamin D insufficiency and deficiency was 81.3 and 1.2 %, respectively. Multinominal logistic regression analyses using potentially confounding variables revealed vitamin D insufficiency was significantly associated with age (+1 year, relative risk ratio, 0.98; 95 % confidence interval, 0.96–0.99), gender (women vs. men, 2.28; 1.59–3.30), residing areas (coastal area vs. mountainous area, 0.58; 0.41–0.81), examined month (October, November, December vs. January, 0.51; 0.34–0.76), and serum levels of iPTH (+1 pg/mL, 1.02; 1.01–1.03). Vitamin D deficiency was significantly characterised by female sex (20.5; 3.1–136.7), examined month (0.28; 0.09–0.95), current smoking habit (6.39; 1.78–23.0), lack of regular outside walking (3.96; 1.34–11.7), higher iPTH (1.02; 1.01–1.03) and poor daily vitamin D intake (+10 μg/day, 0.48; 0.24–0.93).
Conclusions A high prevalence of vitamin D insufficiency and a low prevalence of vitamin D deficiency were found in

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Japanese men and women, and the characteristics of vitamin D status were clarified.

Keywords Epidemiology · Population-based study · Prevalence · Risk factor · Vitamin D deficiency · Vitamin D insufficiency

Introduction

Vitamin D influences bone quality and is important, in particular, for maintaining bone density [1, 2]. Vitamin D deficiency results in decreased bone mineralisation, secondary hyperparathyroidism, and increased cortical bone loss, and has been linked to the pathogenesis of osteoporosis (OP) and hip fractures [1, 3]. Furthermore, vitamin D supplementation may help decrease fractures and falls [4, 5].

However, vitamin D status in populations varies widely. Mithal et al. reviewed the population-based reports regarding vitamin D status in six different regions in the world (i.e., Asia, Europe, the Middle East and Africa, Latin America, North America, and Oceania) and observed that serum 25-hydroxyvitamin D (25D) levels below 75 nmol/L (<30 ng/mL) were prevalent in every region studied, and that levels below 25 nmol/L (<10 ng/mL) were most common in regions such as South Asia and the Middle East [6]. In addition, the International Osteoporosis Foundation (IOF) has reported vitamin D deficiency in postmenopausal women (defined as 25D levels <30 ng/mL), to be approximately, 50 % in Thailand and Malaysia, 75 % in the United States, and 90 % in eastern Asia [7].

The prevalence of vitamin D inadequacy in postmenopausal women in Japan is well known to be very high [8, 9]. Regarding reports of vitamin D concentrations of community-dwelling inhabitants in Japan, Nakamura et al. measured serum levels of 25D of 600 postmenopausal women, and found that higher serum 25D concentrations are associated with higher bone mineral density (BMD) of the femoral neck, and at least 20 ng/mL is needed to achieve normal PTH levels and prevent low BMD [10]. In terms of the Japanese elderly, Suzuki et al. screened 2,957 elderly men and women with an age range of 65–92 years and reported a low 25D level was significantly associated with a high prevalence of falls in Japanese elderly women because of their inferior physical performance [11]. However, little detailed information is still available on the profiles of vitamin D insufficiency and deficiency in the general population, especially in premenopausal women and men. In addition, there is yet little information regarding associated factors for vitamin D insufficiency and deficiency, such as biochemical markers of bone turnover, lifestyle factors (e.g., dietary habits), and other coexisting disorders.

In the present study, we performed a survey using the population-based cohort known as the research on osteoarthritis/osteoporosis against disability (ROAD), which consists of a large number of participants and various outcomes. The ROAD study uses a questionnaire survey consisting of lifestyle factors and nutrition, blood and urinary examinations, measurements of BMD, and x-ray examinations [12, 13]. The aim of our study was to clarify the prevalence of vitamin D insufficiency and deficiency in the general population, including among men and premenopausal and postmenopausal women, and to examine the association of biological, environmental, and nutritional factors and coexisting disorders with vitamin D insufficiency and deficiency.

Subjects and methods

Outlines of the ROAD study

We conducted the present study using the cohorts established in 2005 for the ROAD study. The ROAD study is a nationwide, prospective study of osteoarthritis (OA) comprised of population-based cohorts in several communities in Japan. Details of the cohort profile have been reported elsewhere [12, 13]. Briefly, in 2005–2007, we created a baseline database that included clinical and genetic information for 3,040 residents of Japan (1,061 men and 1,979 women); the mean age (standard deviation (SD)) of the participants was 70.3 (11.0) years (71.0 (10.7) years for men and 69.9 (11.2) years for women). The subjects were recruited from resident registration listings in three communities with different characteristics: 1,350 subjects (465 men, 885 women) in an urban region in Itabashi, Tokyo; 864 subjects (319 men, 545 women) in a mountainous region in Hidakagawa, Wakayama; and 826 subjects (277 men, 549 women) in 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 QOL. A questionnaire was prepared by modifying the questionnaire used in the Osteoporotic Fractures in Men Study [14], and some new items were added to the modified questionnaire. The participants were asked whether they took prescription medication daily or nearly every day (0: no, 1: yes). If participants did not know the reason for the prescribed medication, they were asked to bring their medications to the medical doctor (NY).

Anthropometric measurements included height, weight, and body mass index (BMI; weight/height^2, kg/m^2). Systolic and diastolic blood pressure (BP) was measured by an experienced public health nurse using a mercury sphygmomanometer. Medical information, including information on knee joints, was

collected by experienced orthopaedic surgeons (SM and HO). All participants underwent radiographic examination of both knees and the lumbar spine.

In addition, the brief diet history questionnaire (BDHQ) was used for the dietary assessment. Each participant was given the questionnaire and provided with a detailed explanation on how to fill it out at home; the unclear parts were addressed by well-trained interviewers. BDHQ is a 4-page structured questionnaire that inquires about the consumption frequency of 80 principal foods, with specified serving sizes described in terms of a natural portion or the standard weight and volume measurement of servings commonly consumed in general Japanese populations. It was modified from a comprehensive (16-page) version of a validated self-administered diet history questionnaire [15]. A total of 141 components, including energy and dietary nutrient intakes, were calculated using the ad hoc computer algorithm for BDHQ. Dietary intake levels of total energy and 27 nutrients (animal protein, vegetable protein, animal fat, vegetable fat, carbohydrate, sodium, potassium, calcium, magnesium, phosphorus, iron, zinc, copper, manganese, vitamins B1, 2, 6, and 12, niacin, folate, vitamins C, D, E, and K, cholesterol, dietary fibre, and salt) were analysed. We used the values obtained for these nutrients to estimate the total amount of calcium, phosphorus, and vitamin D intake during a day.

Eligible subjects of the present study

Among the above-mentioned regions, the measurements of BMD were performed on subjects in the mountainous and coastal regions. For all 1,690 participants (596 men, 1094 women) in the mountainous and coastal regions, BMD was measured for the lumbar spine and the proximal femur using dual energy x-ray absorptiometry (DXA) (Hologic Discovery; Hologic, Waltham, MA, USA) during the baseline examination.

Blood and urinary examinations had also been performed in subjects in mountainous and coastal regions. Among the participants, we were able to measure the serum levels of 25D in 1,683 individuals (99.6 %; 595 men, 1,088 women). Hence, the data from these 1,683 subjects were used for the analysis in the present study. The study participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo (No 1264).

Blood and urine examinations

Samples were collected from the end of October to the middle of January in both mountainous and coastal areas. All blood and urine samples were extracted between 0900 and 1500 hours. After centrifugation of the blood samples, the sera and urine samples were immediately placed on dry ice and transferred to a deep freezer within 24 h. These samples were stored at −80 °C until assayed.

The blood samples were used to measure haemoglobin A1c (HbA1c, Japan Diabetes Society), blood sugar, high-density lipoprotein cholesterol (HDL-cho), total cholesterol, triglyceride, and creatinine levels. The analyses were performed at the same laboratory within 24 h of extraction (Osaka Kessei Research Laboratories, Inc., Osaka, Japan).

Serum levels of 25D were measured by radioimmunoassay with a ^{125}I-labelled tracer (DiaSorin, Stillwater, MN, USA) [16], and intact parathyroid hormone (iPTH) was measured by an electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). As a marker of bone formation, serum N-terminal propeptide of type I procollagen (PINP) was measured using a radioimmunoassay (Orion Diagnostics, Espoo, Finland). The urinary levels of β-isomerized C-terminal cross-linking telopeptide of type I collagen (β-CTX), a bone resorption marker, were determined using an enzyme-linked immunosorbent assay (Fujirebio, Inc. Tokyo, Japan). Urinary β-CTX values were standardised to urinary creatinine concentrations.

Definitions of vitamin D insufficiency and deficiency

For revealing the severity of 25D status worldwide, the IOF reported vitamin D status on a global map using four categories defined according to the mean (or median) 25D levels as follows: 30, 20–30, 10–20, and <10 ng/mL [17]. In the present study, based on the IOF report, vitamin D deficiency was defined as 25D serum levels <10 ng/mL, whereas vitamin D insufficiency was defined as 25D serum levels ≥10 and <30 ng/mL.

Radiographic assessment

Plain radiographs of the lumbar spine in the anteroposterior and lateral views and bilateral knees in the anteroposterior view with weight-bearing and foot map positioning were obtained. The severity of radiographic OA was determined according to Kellgren–Lawrence (KL) grading as follows [18]: KL0, normal; KL1, slight osteophytes; KL2, definite osteophytes; KL3, joint or intervertebral space narrowing with large osteophytes; KL4, bone sclerosis, joint or intervertebral space narrowing and large osteophytes. In the ROAD study, participants were classified into KL3 if they had joint or intervertebral space narrowing without large osteophytes. Radiographs at each site, i.e., the knees, hips and vertebrae, were examined by a single, experienced orthopaedic surgeon (SM), who was masked regarding participants' clinical status. If at least one knee joint was graded as KL2 or higher, the participant was diagnosed with

radiographic knee osteoarthritis. Similarly, if at least one intervertebral level of the lumbar spine was graded as KL2 or higher, the participant was diagnosed with radiographic lumbar spondylosis.

Definition of coexisting disorders, such as hyperparathyroidism, OP, hypertension, dyslipidaemia, impaired glucose tolerance, and renal dysfunction

For clarifying the association between vitamin D status and comorbidities, the prevalence of the following disorders was investigated in relation to vitamin D status: hyperparathyroidism; OP at the lumbar spine (L2–4), the femoral neck, or both sites; hypertension; dyslipidaemia; impaired glucose tolerance; and renal dysfunction. Hyperparathyroidism was defined by serum iPTH >65 pg/mL. OP was defined based on World Health Organization criteria, in which OP was mainly diagnosed when the BMD T-scores were lower than peak bone mass by −2.5 SDs [19]; the mean (SD) for the L2–4 BMD in young adult men and women, as measured by the Hologic DXA in Japan, was 1.011 (0.119) g/cm^2 [20]. The present study therefore defined OP at the lumbar spine as an L2–4 BMD <0.714 g/cm^2. Furthermore, the mean (SD) for the femoral neck BMD in young adult men and women was 0.863 (0.127) g/cm^2 and 0.787 (0.109) g/cm^2, respectively [20]. Therefore, OP at the femoral neck in men and women was defined as a femoral neck BMD <0.546 g/cm^2 and <0.515 g/cm^2, respectively.

In the present study, hypertension was defined as a systolic BP ≥130 mm Hg and/or a diastolic BP ≥85 mm Hg [21]. Dyslipidaemia was defined by a serum HDL-cho level <40 mg/dL [21, 22]; and impaired glucose intolerance, by a serum HbA1c level ≥5.5 % [22]. Renal dysfunction was defined as chronic kidney disease at stage 3 or higher, which was determined by an estimated glomerular filtration rate <60 mL/min/1.73 m^2 [23].

Furthermore, subjects being treated with medication for OP, hypertension, dyslipidaemia, impaired glucose intolerance and/or diabetes mellitus, or renal disease were regarded as having these respective conditions.

Statistical analysis

All statistical analyses were performed using STATA statistical software (STATA Corp., College Station, Texas, 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 vitamin D insufficiency and deficiency and various biological, environmental, behavioural, and nutritional factors, we used multinominal logistic regression analysis. In the analysis, we used the presence of vitamin D insufficiency and vitamin D deficiency as the objective variable (0: group with normal vitamin D levels, 1: vitamin D insufficiency group, 2: vitamin D deficiency group) and selected explanatory variables in addition to the basic characteristics, such as age (+1 year), gender (0: men, 1: women), BMI (+1 kg/m^2), regional differences (0: mountainous area, 1: coastal area), month of examination (October, November, December vs. January). The following potential risk factors were included in the multinominal logistic regression analysis and showed a significant or marginal (p <0.1) association with vitamin D status in the simple linear analysis: smoking (0: never, ever, 1: current), alcohol consumption (0: never, ever, 1: current), lack of regular walking outside (0: ≥5 times/week, 1: <5 times/week), regular exercise outdoors (0: yes, 1: no), serum levels of iPTH (+1 pg/mL), serum levels of PINP (+1 SD), urinary levels of β-CTX (+1 SD), daily total energy from amount of intake (+100 Kcal/day), calcium (+100 mg/day), phosphorus (+100 mg/day), vitamin D (+10 μg/day) calculated based on the BDHQ questionnaire, and the values of the baseline BMD at the lumbar spine (+1 SD) or femoral neck (+1 SD). Selected explanatory variables for each analysis are described in the Results section. After the multinominal logistic regression analysis, the relative risk ratios (RRRs) were evaluated.

Results

Figure 1 shows the prevalence of vitamin D insufficiency and deficiency according to gender and age groups. The overall prevalence of vitamin D insufficiency and deficiency was 81.3 and 1.2 %, respectively, and was higher in women than in men (vitamin D insufficiency, men, 72.1 %; women, 86.3 %; vitamin D deficiency, men, 0.3 %; women, 1.7 %) (p <0.001). In terms of menstrual status, 926 women (85.1 %) had postmenopausal status. The prevalence of vitamin D insufficiency and deficiency classified by menstrual status was 89.4 and 2.5 % in premenopausal women and 85.8 and 1.5 % in postmenopausal women, respectively. No significant differences were observed in the prevalence of vitamin D insufficiency and deficiency between pre- and postmenopausal women (p=0.181). Figure 1 also shows the prevalence of vitamin D insufficiency and deficiency according to age groups. The prevalence of vitamin D insufficiency (%) for individuals in their 30s and younger and those in their 40s, 50s, 60s, 70s, and 80s or older was 86.4, 91.2, 81.0, 80.8, 78.4, and 82.4, respectively. Similarly, the prevalence of vitamin D deficiency (%) for individuals in these same age groups was 2.3, 1.4, 1.0, 0.8, 1.5, and 1.3, respectively. The prevalence of vitamin D insufficiency and deficiency in men and women according to these different age groups is shown in Figure 1.

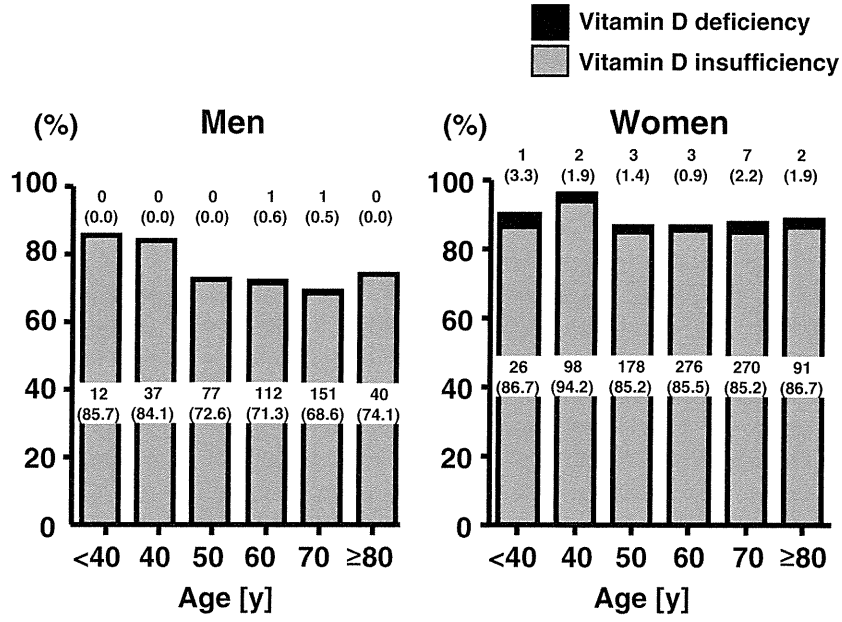

Fig. 1 The number of individuals (prevalence, %) with vitamin D insufficiency and deficiency as classified by gender. The numbers along the middle line indicate the number of individuals (prevalence, %) with vitamin D insufficiency for each bar, while those along the upper line indicate the number of individuals (prevalence, %) with vitamin D deficiency

The mean level (standard deviation, SD) of serum 25D in the total participants was 23.3 (6.6) ng/mL. The blood examinations were performed from October to January; consequently, we compared vitamin D levels classified by the month of examination. Mean values of serum 25D were the highest for the subjects in October (26.2 (6.3) ng/mL), followed by November (23.9 (7.1) ng/mL), December (23.1 (6.3) ng/mL), and January (22.0 (5.7) ng/mL). These results suggested the analysis to clarify the factors associated with 25D status should be adjusted for the month of the examinations.

Table 1 shows the results for the serum 25D levels, the anthropometric measurements, and the prevalence of lifestyle factors of individuals with vitamin D insufficiency and deficiency as compared to those with normal vitamin D levels. The mean levels (SD) of serum 25D were 33.2 (3.0) in the normal group; the individuals in this group tended to reside in the coastal area. Meanwhile, drinking alcohol, the habit of walking outside, and regular exercise were most common in individuals with normal vitamin D levels, less common in individuals with vitamin D insufficiency, and least common in those with vitamin D deficiency. Smokers were most common in the vitamin D-deficiency group, followed respectively by the normal vitamin D and vitamin D-insufficiency groups.

The mean levels of serum iPTH, PINP, and urinary β-CTX were compared across groups with normal vitamin D, vitamin D insufficiency, and vitamin D deficiency (Table 2). The serum iPTH and urinary β-CTX levels significantly increased across groups from the normal vitamin D group to the vitamin D-deficiency group (p=0.0076 and p=0.0003, respectively). No significant trends were observed in the serum levels of PINP and the vitamin D status. By contrast, the BMD values at both the lumbar spine (L2–4) and the femoral neck significantly decreased across groups from the normal vitamin D group to the vitamin D-deficiency group (L2–4, p=0.0094; femoral neck, p=0.0179). These various trends were observed across groups within both men and women; however, with the exception of iPTH values in women, none of these trends were significant.

Table 3 shows the mean values of the total nutrient intake per day in relation to vitamin D status. The daily amount of total energy and calcium, phosphorus, and vitamin D intake all significantly decreased across groups from the normal vitamin D group to the vitamin D insufficiency group. These trends were mainly due to the observations in women, since no significant association was observed between nutrient intake and vitamin D status in men.

Table 4 shows the relative risk ratios obtained from the multinominal logistic regression analysis using the presence of vitamin D insufficiency and vitamin D deficiency as the objective variable (0: normal vitamin D levels, 1: vitamin D insufficiency, 2: vitamin D deficiency), and the factors listed in the 'Subjects and methods' section, such as age (+1 year), gender (0: men, 1: women), regional differences (0: mountainous area, 1: coastal area), BMI (+1 kg/m^2), month of examination (0: October, November, December, 1: January), smoking (0: never, ever, 1: current), alcohol consumption (0: never, ever, 1: current), lack of regular walking outside (0: ≥5 times/week, 1: <5 times/week), regular exercise outdoors (0: yes, 1: no), serum levels of iPTH (+1 pg/mL), urinary levels of β-CTX (+1 SD), daily total energy from amount of intake (+100 Kcal/day), vitamin D (+10 μg/day) calculated based on the BDHQ questionnaire, and the values of the baseline BMD at the lumbar spine (+1 SD) or femoral neck (+1 SD). Daily intake of calcium (+100 mg/day) and

Table 1 Mean values (standard deviations) of the anthropometric measurements and the prevalence (%) of lifestyle factors for the participants classified at baseline by vitamin D status

	Total (N=1,683)				Men (N=595)				Women (N=1,088)			
	Normal (N=295)	Vitamin D insufficiency (N=1,368)	Vitamin D deficiency (N=20)	p for trend	Normal (N=164)	Vitamin D insufficiency (N=429)	Vitamin D deficiency (N=2)	p for trend	Normal (N=131)	Vitamin D insufficiency (N=939)	Vitamin D deficiency (N=18)	p for trend
Serum levels of 25 (OH) D (ng/mL)	33.2 (3.0)	21.4 (4.8)[a]	8.2 (1.2)[a,b]	<0.0001***	33.6 (3.3)	22.8 (4.6)[a]	9.0 (0.0)[a, b]	<0.0001***	32.8 (2.5)	20.7 (4.7)[a]	8.1 (1.2)[a,b]	<0.0001***
Age (years)	67.1 (11.1)	64.9 (12.1)[a]	66.0 (14.4)	0.0143*	67.6 (11.2)	65.8 (11.9)	72.5 (7.8)	0.1851	66.5 (11.0)	64.5 (12.2)	65.2 (14.9)	0.1865
Height (cm)	157.2 (9.7)	154.8 (9.2)[a]	154.8 (5.7)	0.0003***	162.8 (7.4)	163.6 (7.1)	161.6 (2.2)	0.4378	150.1 (7.4)	150.7 (6.9)	154.0 (5.5)	0.0755
Weight (kg)	56.8 (10.8)	55.4 (10.8)	53.5 (9.0)	0.0811	61.2 (10.5)	62.7 (11.0)	53.2 (8.2)	0.1557	51.4 (8.6)	52.1 (8.9)	53.5 (9.3)	0.5434
BMI (kg/m^2)	22.9 (3.3)	23.0 (3.4)	22.4 (4.0)	0.5983	23.0 (3.1)	23.3 (3.2)	20.3 (2.6)	0.2295	22.8 (3.5)	22.9 (3.5)	22.6 (4.1)	0.8983
Residing in the coastal area	59.0	46.7	45.0	0.001**	53.1	44.1	50.0	0.145	66.4	47.9	44.4	<0.001***
Blood examination performed in January	17.0	31.2	40.0	<0.001***	15.9	31.7	50.0	<0.001***	18.3	31.0	38.9	0.003**
Current smoking habit (regularly, ≥1/month)	16.2	12.3	25.0	0.056	27.6	30.6	50.0	0.643	1.6	3.7	22.2	<0.001***
Current alcohol consumption (regularly, ≥1/month)	50.2	37.7	25.0	<0.001***	71.8	64.6	100.0	0.152	23.1	25.4	16.7	0.602
Regularly walking outside (≥5 times/week, including job)	61.7	56.6	25.0	0.004**	68.0	60.7	50.0	0.261	53.7	54.7	22.2	0.023*
Regularly exercising outdoors (football, tennis, baseball, golf, etc.) after graduation from the last school	19.7	13.2	10.0	0.013*	33.5	32.4	0.0	0.594	2.3	4.4	11.1	0.186

25D 25-hydroxyvitamin D, *BMI* body mass index

*p <0.05; **p <0.01; ***p <0.001

[a] significantly different (p <0.05) from values of the normal group

[b] significantly different (p <0.05) from values of the VD-insufficient group

Table 2 Mean values (standard deviations) of serum iPTH, serum and urinary biochemical markers of bone turnover, and bone mineral densities for the participants classified at baseline by vitamin D status

	Total (N=1,683)				Men (N=595)				Women (N=1,088)			
	Normal (N=295)	Vitamin D insufficiency (N=1,368)	Vitamin D deficiency (N=20)	p for trend	Normal (N=164)	Vitamin D insufficiency (N=429)	Vitamin D deficiency (N=2)	p for trend	Normal (N=131)	Vitamin D insufficiency (N=939)	Vitamin D deficiency (N=18)	p for trend
Serum levels of iPTH (pg/mL)	36.7 (16.3)	42.2 (36.7)[a]	55.4 (24.9)	0.0076**	37.8 (17.0)	44.6 (60.2)	55.0 (28.3)	0.3415	35.4 (15.4)	41.1 (17.3)[a]	55.4 (25.5)[a,b]	<0.0001***
Serum levels of PINP (μg/L)	56.0 (26.9)	57.6 (26.9)	65.0 (28.8)	0.3078	46.4 (18.9)	47.5 (22.8)	48.1 (15.8)	0.8705	68.0 (30.4)	62.2 (27.3)	67.0 (29.7)	0.0716
Urinary levels of β-CTX (μg/mmol Cr)	166.6 (105.8)	188.3 (125.8)[a]	266.6 (171.1)[a,b]	0.0003***	121.8 (64.0)	132.6 (85.2)	157.0 (131.5)	0.3157	221.7 (120.3)	213.8 (133.0)	278.8 (173.5)	0.1032
BMD (L2-4) (g/cm^2)	0.965 (0.227)	0.926 (0.203)[a]	0.894 (0.183)	0.0094**	1.061 (0.214)	1.040 (0.200)	1.055 (0.234)	0.5360	0.844 (0.181)	0.873 (0.181)	0.876 (0.176)	0.2253
BMD (femoral neck) (g/cm^2)	0.692 (0.146)	0.669 (0.136)[a]	0.637 (0.133)	0.0179*	0.744 (0.146)	0.746 (0.126)	0.769 (0.113)	0.9595	0.625 (0.116)	0.633 (0.126)	0.622 (0.130)	0.7415

iPTH intact parathyroid hormone, *PINP* N-terminal propeptide of type I procollagen, β-*CTX* β-isomerized C-terminal cross-linking telopeptide of type I collagen, *BMD* bone mineral density, *L2–4* lumbar spine L2–L4

*p <0.05; **p <0.01; ***p <0.001

[a] significantly different (p <0.05) from values of the normal group

[b] significantly different (p <0.05) from values of the VD-insufficient group

Table 3 Mean values (standard deviations) of total amount of energy/(day) and nutrient intake of the participants classified at the baseline by vitamin D status

	Total (N=1,683)				Men (N=595)				Women (N=1,088)			
	Normal (N=295)	Vitamin D insufficiency (N=1,368)	Vitamin D deficiency (N=20)	p for trend	Normal (N=164)	Vitamin D insufficiency (N=429)	Vitamin D deficiency (N=2)	p for trend	Normal (N=131)	Vitamin D insufficiency (N=939)	Vitamin D deficiency (N=18)	p for trend
Total energy (Kcal)	2,079.6 (589.1)	1,911.3 (585.6)a	1,623.3 (435.0)[a]	<0.0001***	2,299.2 (595.2)	2,306.8 (679.5)	1,966.1 (283.2)	0.7615	1,806.3 (452.8)	1,730.7 (430.0)	1585.2 (437.5)	0.0562
Calcium (mg)	605.2 (237.9)	537.3 (229.1)[a]	503.4 (212.1)	<0.0001***	606.6 (245.3)	565.7 (263.8)	691.3 (275.2)	0.1896	603.5 (229.2)	524.3 (210.3)[a]	482.5 (203.0)	0.0002***
Phosphorus (mg)	1,208.2 (379.5)	1,084.9 (373.2)[a]	918.2 (320.7)[a]	<0.0001***	1,259.8 (394.6)	1,220.3 (428.7)	1,257.3 (141.3)	0.5903	1,144.1 (350.6)	1,023.1 (327.0)[a]	880.5 (314.2)[a]	0.0001***
Vitamin D (μg)	23.7 (12.9)	19.7 (12.4)[a]	13.3 (9.5)[a]	<0.0001***	24.3 (13.9)	22.2 (14.5)	28.8 (11.4)	0.2183	22.9 (11.6)	18.6 (11.1)[a]	11.6 (7.9)[a, b]	<0.0001***

*p <0.05; **p <0.01; ***p <0.001

[a] significantly different (p <0.05) from values of the normal group

[b] significantly different (p <0.05) from values of the VD insufficient group

phosphorus (+100 mg/day) were excluded from the model because of the high correlation coefficient (r) between daily intake of vitamin D (intake of calcium vs. vitamin D, r=0.73, p <0.001; intake of phosphorus and vitamin D, r=0.83, p <0.001).

Compared to normal vitamin D subjects, individuals with vitamin D insufficiency were significantly younger and significantly more likely to be female, to reside in a mountainous area, and undergone measurements in January. The serum iPTH levels of individuals with vitamin D insufficiency were higher than those of the normal vitamin D group. Meanwhile, individuals with vitamin D deficiency, when compared to those with normal vitamin D levels, were more likely to be female, to have undergone measurements in January, to have a smoking habit, and to perform less outside walking. In addition, serum levels of iPTH were significantly higher and mean intake of vitamin D significantly lower than those of the normal vitamin D group. This tendency remained after changing the variable of the baseline BMD at the lumbar spine to the baseline BMD at the femoral neck.

The prevalence of the coexisting disorders listed in the 'Subjects and methods' classified by vitamin D status are shown in Table 5. The prevalence of hyperparathyroidism diagnosed by the serum levels of iPTH was the highest in the group with vitamin D deficiency, followed respectively by the vitamin D insufficiency and normal groups (p <0.001). This trend was observed separately in both men and women (men, p=0.057, women, p <0.001). The prevalence of OP at L2–4 or femoral neck at the baseline tended to be the highest in the vitamin D-deficiency group, followed by the vitamin D insufficiency and normal groups, but was not significantly different across groups. The prevalence of lumbar spondylosis tended to be the highest in the normal group, followed by the vitamin D insufficiency and deficiency groups, but was not significantly different across groups, either. No significant differences in the prevalences of knee osteoarthritis, hypertension, dyslipidaemia, impaired glucose tolerance, and chronic kidney disease were observed.

Finally, to clarify the association of hyperparathyroidism and vitamin D status, we performed a multinominal logistic regression analysis using the presence of vitamin D insufficiency and vitamin D deficiency as the objective variable (0: normal vitamin D levels, 1: vitamin D insufficiency, 2: vitamin D deficiency), and presence of hyperparathyroidism (0: no, 1: yes) as an explanatory variable, after adjustment for age, gender, regional differences, BMI, and month of examination (0: October, November, December, 1: January). The results revealed that vitamin D deficiency was still significantly associated with hyperparathyroidism (RRR, 95 % confidence intervals, vitamin D insufficiency vs. normal group: 1.25, 0.75–2.09, p=0.385, vitamin D deficiency vs. normal group: 12.7, 4.52–35.7, p <0.001).

Discussion

In the present study, using the baseline samples from 1,683 individuals in the population-based cohort ROAD, we found a very high prevalence of vitamin D insufficiency and a low prevalence of vitamin D deficiency in Japanese men and women. These prevalences were not significantly different between pre- and postmenopausal women. It was clarified individuals with vitamin D insufficiency were characterised by a younger age, the female sex, residing in a mountainous area, measurements performed in January, and higher serum iPTH values. Meanwhile, vitamin D deficiency was characterised by the female sex, measurements performed in January, smoking habit, less outside walking, higher serum iPTH, and a low intake of vitamin D.

Several reports stated that vitamin D insufficiency in postmenopausal women in eastern Asia is very high [9, 10]. The high prevalence detected in the present study was consistent with the previous reports. By contrast, few studies have reported gender and age differences in terms of vitamin D insufficiency and deficiency using the data of a general population. In the present study, we found the prevalence of vitamin D insufficiency and deficiency were more common in women than in men and that the frequency of vitamin D inadequacy in women was not associated with menstrual status. In terms of gender difference in the prevalence of vitamin D inadequacy in the Japanese population, Suzuki et al. found the mean serum levels of 25D in elderly men were higher than those in women [11]. Greene-Finestone et al. [24] investigated the vitamin D status in a Canadian population, including men and premenopausal women, and reported that the proportion of individuals with serum vitamin D levels <30 ng/mL was higher in women (60.7 %) than that in men (57.5 %). These results show that vitamin D inadequacy is more prevalent in women than men in both western and eastern populations.

Regarding age differences in vitamin D inadequacy, we observed that in the vitamin D insufficiency group, an age of 1 year older decreased the risk of vitamin D insufficiency; however, this tendency was not found in the vitamin D deficiency group. Moreover, as shown in Table 1, the mean age of the normal vitamin D group, the vitamin D insufficiency group, and the vitamin D deficiency group was 67.1, 64.9, and 66.0 years, respectively, with the vitamin D insufficiency group showing the lowest mean age. We were unable to provide an adequate hypothesis for the U-shaped phenomenon in the vitamin D status in regards to age, in particular the association between age and the risk of vitamin D insufficiency. Nonetheless, one possible explanation is that this phenomenon might be due to the birth-cohort effect. However, because the design of the present study was cross-sectional, we were unable to confirm the cohort effect. Hence, we should follow our cohort longer and confirm whether the vitamin D insufficiency in the younger age group will develop into vitamin D deficiency.

Residents of the seaside town showed a significantly lower prevalence of vitamin D insufficiency and deficiency compared to those in the mountainous area. The total amount of sun exposure might be one of the factors affecting the vitamin D status of the residents. The Japan Meteorological Agency reported that the mean sunlight time in Ryujin town (the area neighbouring Hidakagawa, the mountainous area in the present study) was 1541.7 hours/year and in Shionomisaki (the neighbouring area of Taiji town, the seaside area in the present study) was 2201.2 hours/year [25], which suggests the total sun exposure in the seaside area is much higher than that in the mountainous area. Nutritional differences could also account for these geographical discrepancies. The mean intake of vitamin D estimated in the group residing in the seaside area was 21.1 μg/day and was significantly higher than that in the group residing in the mountainous region (19.6 μg/day, p <0.05). This difference in vitamin D intake might be due to the frequency of fatty fish intake. Indeed, we found that a low intake of vitamin D was one of the emphasised characteristics for vitamin D deficiency in the present study (Table 4). Moreover, in the multinominal logistic regression analysis to assess potentially associated factors, including regional differences and vitamin D intake evaluated in the same model, regional difference was no longer significantly associated with vitamin D deficiency, but vitamin D intake remained a significant explanatory variable.

In terms of iPTH levels and the vitamin D status, a number of reports have shown an inverse association between serum 25D and iPTH levels [1, 26, 27]. Moreover, a low-serum 25D concentration leads to a decrease in calcium absorption. The lower serum calcium concentration causes an increase in iPTH secretion and a relatively higher serum iPTH concentration. Regarding the Japanese population, hypovitaminosis D was reported to adversely affect serum iPTH levels, especially in the very elderly [28]. In the present study, this tendency was observed not only in the very elderly, but also in the middle-aged and aged Japanese population, while the mean values of serum iPTH in vitamin D deficiency remained within the upper limits of the normal range. However, since the current study was cross-sectional in nature, we unable to detect a causal relationship between serum iPTH and 25D status. Thus, we were unable to clarify whether lower 25D caused hyperparathyroidism or whether hyperparathyroidism lowered 25D. In a future follow-up study, we would like to clarify the causal relationship between 25D and iPTH.

By contrast, current smoking habit and less outside walking were emphasised characteristics for vitamin D deficiency in the present study. In terms of the smoking habit and vitamin D status, Lange et al. reported that vitamin D

Table 4 Relative risk ratios (RRR) of potentially associated factors for the presence of VD insufficiency and deficiency vs. normal VD

		Vitamin D insufficiency			Vitamin D deficiency		
Explanatory variables	Reference	RRR	95 % CI	*p*	RRR	95 % CI	*p*
Age (years)	+1 year	0.98	0.96–0.99	0.001**	1.01	0.96–1.06	0.726
Gender	0: men, 1: women	2.28	1.58–3.30	<0.001***	20.5	3.08–136.7	0.002**
Region	0: mountainous area, 1: coastal area	0.58	0.41–0.81	0.002**	0.65	0.19–2.25	0.492
BMI (kg/m^2)	+1 kg/m2	1.00	0.96–1.05	0.970	0.92	0.79–1.08	0.318
Month of examination (October, November, December)	vs. January	0.51	0.34–0.76	0.001**	0.28	0.09–0.95	0.040*
Smoking	0: ex or never smoker, 1: current smoker	1.05	0.69–1.59	0.822	6.39	1.78–23.0	0.005**
Alcohol consumption	0: ex or never drinker, 1: current drinker	0.78	0.56–1.07	0.120	0.57	0.18–1.80	0.339
Regularly walking outside	0: yes, 1: no	1.27	0.94–1.70	0.121	3.96	1.34–11.7	0.013*
Regularly exercising outdoors	0: yes, 1: no	1.09	0.73–1.63	0.657	0.95	0.17–5.18	0.950
Serum levels of iPTH (pg/mL)	+1 pg/mL	1.02	1.01–1.03	0.001**	1.02	1.01–1.03	<0.001***
Urinary levels of β-CTX (μg/mmol Cr)	+1 SD	0.95	0.81–1.10	0.471	1.41	0.94–2.12	0.099
BMD (L2–4) (g/cm^2)	+1 SD	0.98	0.84–1.15	0.828	1.42	0.82–2.46	0.208
Total energy (Kcal/day)	+100 Kcal	1.00	0.97–1.03	0.918	0.98	0.87–1.11	0.776
Vitamin D (μg/day)	+10 μg	0.91	0.81–1.03	0.138	0.48	0.24–0.93	0.031*

RRR, relative risk ratios; 95 % CI, 95 % confidence interval

BMI body mass index, *iPTH* intact parathyroid hormone, β-*CTX* β-isomerized C-terminal cross-linking telopeptide of type I collagen, *BMD* bone mineral density, *L2–4* lumbar spine L2–L4

*p <0.05; **p <0.01; ***p <0.001

deficiency was associated with lower lung function and a more rapid decline in lung function in smokers over 20 years in their longitudinal cohort, which consisted of 626 elderly men [29]. In the present study, smoking remained a strongly associated factor for vitamin D deficiency after adjustment for gender and other potentially confounding factors (Table 4). In addition, after an identical multinominal logistic analysis performed only in women, smoking was still associated with vitamin D deficiency (vs. non- or ex- smoking: 9.82, 1.35–71.5, p=0.024), which suggests that vitamin D deficiency in both men and women may be influenced by smoking. In the present study, we could not confirm the effect of smoking on lung function because of the lack of information. Hence, future studies are required to confirm the relationship between vitamin D status, smoking, and lung function. In regards to the walking habit and 25D status, the lower sun exposure caused by less outside walking might be associated with lower levels of 25D. Our results showed outside walking and the above-mentioned dietary intake of vitamin D might prevent vitamin D deficiency, which are consistent with statements or recommendations [10].

Besides bone and mineral diseases such as rickets [30], osteomalacia [30], OP [1, 3], osteoporotic fractures [4] and falls [5], a number of studies have reported an association between inadequate vitamin D and other chronic diseases, such as cardiovascular disease [31], diabetes [32], cancer [33–35], and autoimmune diseases such as multiple sclerosis [36]. In the present study, we clarified the association between 25D status and various coexisting disorders including hyperparathyroidism, OP, osteoarthritis, hypertension, dyslipidaemia, impaired glucose tolerance, and chronic kidney disease. We found that vitamin D deficiency was significantly associated with hyperparathyroidism, although no significant relationship was observed for the presence of other diseases after the adjustment for confounding factors. However, to clarify whether vitamin D inadequacy might cause the occurrence or the progression of the above-mentioned diseases, we have already been prepared to perform a follow-up of our cohorts, so that we can report the effect of vitamin D inadequacy on health dysfunction in the general population as a next step.

This study has several limitations. First, although the ROAD study includes a large number of participants, these participants may not truly be representative of the general population. To address this, we compared the anthropometric measurements and the frequencies of smoking and alcohol consumption between the entire group of study participants and the general Japanese population. No significant differences were found, with the exception that the male ROAD study participants aged 70–74 years were