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

Medical information

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

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

Radiography and radiographic assessment

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

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

BMD measurement

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

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

Statistical analysis

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

Results

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

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

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

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

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

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

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

Values are represented as mean (standard deviation)

BMI body mass index

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

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

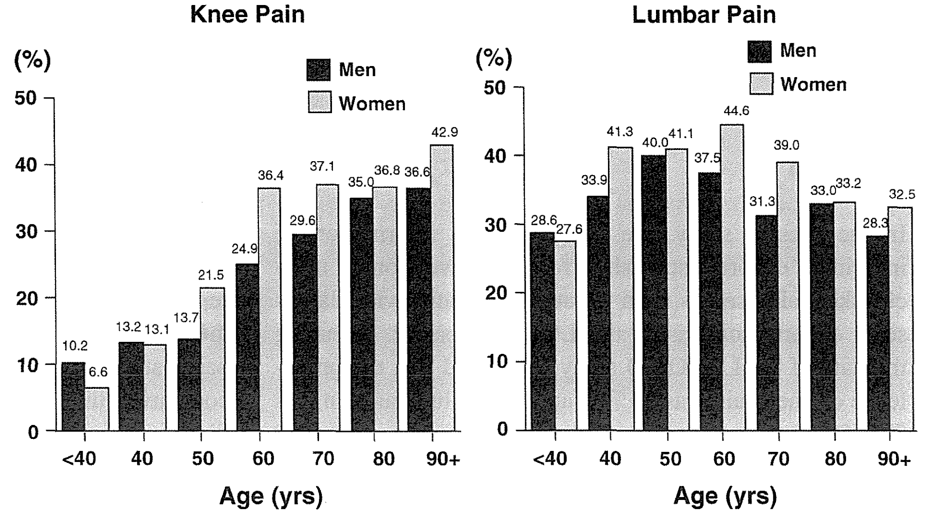

Fig. 3 Prevalence of knee pain and lumbar pain according to age and gender

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

Acknowledgments This work was supported by grants from Grant-in-Aid for H17-Men-eki-009 (Director, Kozo Nakamura), H20-Chou-jyu-009 (Director, Noriko Yoshimura), H23-Choujyu-002 (Director, Toru Akune), and H-25-Chojyu-007 (Director, Noriko Yoshimura) of the Ministry of Health, Labour and Welfare; and Scientific Research B23390172, B20390182, and Challenging Exploratory Research 24659317 to Noriko Yoshimura, B23390357 and C20591737 to Toru Akune, and B23390356 and C20591774, Challenging Exploratory Research 23659580 to Shigeyuki Muraki, Challenging Exploratory Research 24659666, 21659349 and Young Scientists A18689031 to Hiroyuki Oka, and Collaborating Research with NSF 08033011-00262 (Director, Noriko Yoshimura) from the Ministry of Education, Culture, Sports, Science and Technology in Japan. The sponsors did not contribute to the study design, data collection, data analysis, data interpretation, or the writing of the report.

Conflict of interest The authors wish to thank Ms. Kyoko Yoshimura, Mrs. Toki Sakurai, and Mrs. Saeko Sahara for their assistance with data reduction and administration.

References

1. Ministry of Health, Labour and Welfare. Outline of the results of National Livelihood Survey 2010. http://www.mhlw.go.jp/toukei/saikin/hw/k-tyosa/k-tyosa10/4-2.html
2. Muraki S, Yamamoto S, Ishibashi H, Nakamura K (2006) Factors associated with mortality following hip fracture in Japan. J Bone Miner Metab 24:100–104
3. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-Yo Y, Yoshida M, Saika A, Yoshida H, Suzuki T, Yamamoto S, Ishibashi H, Kawaguchi H, Nakamura K, Akune T (2009) Prevalence of knee osteoarthritis, LS and osteoporosis in Japanese men and women: the Research on Osteoarthritis/Osteoporosis Against Disability study. J Bone Miner Metab 27:620–628
4. Yoshimura N, Nakamura K, Akune T, Fujiwara S, Shimizu Y, Yoshida H, Omori G, Sudo A, Nishiwaki Y, Yoshida M, Shimokata H (2013) The longitudinal cohorts of motor system organ (LOCOMO) study (In Japanese). Nippon Rinsho 71:642–645
5. Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, Lewis C, Cawthon PM, Marcus R, Marshall LM, McGowan J, Phipps K, Sherman S, Stefanick ML, Stone K (2005) Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study: a large observational study of the determinants of fracture in older men. Contemp Clin Trials 26:569–585
6. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW (1998) Validation study of WOMAC. A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheum 15:1833–1840
7. Johnson JA, Coons SJ, Ergo A, Szava-Kovats G (1998) Valuation of EuroQOL (EQ-5D) health states in an adult US sample. Pharmacoeconomics 13:421–433
8. Fukuhara S, Suzukao Y (2004) Manual of the SF-8 Japanese version. Institute for Health Outcomes & Process Evaluation Research, Kyoto
9. Teng EL, Chui HC (1987) The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 48:314–318
10. Kellgren JH, Lawrence LS (1957) Radiological assessment of osteoarthrosis. Ann Rheum Dis 16:494–502
11. World Health Organization (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO Technical Report Series 843, Geneva
12. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, Kushida K, Miyamoto S, Soen S, Nishimura J, Oh-Hashi Y, Hosoi T, Gorai I, Tanaka H, Igai T, Kishimoto H, Osteoporosis Diagnostic Criteria Review Committee: Japanese Society for Bone and Mineral Research (2001) Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 19:331–337
13. Portal site of Official Statistics of Japan. Population Census 2010. http://www.e-stat.go.jp/SG1/estat/GL08020103.do?_toGL08020103_&tclassID=000001034991&cycleCode=0&requestSender=search
14. Soni A, Kiran A, Hart DJ, Leyland KM, Goulston L, Cooper C, Javaid MK, Spector TD, Arden NK (2012) Prevalence of reported knee pain over twelve years in a community-based cohort. Arthritis Rheum 64:1145–1152
15. Muraki S, Oka H, Akune T, Mabuchi A, En-yo Y, Yoshida M, Saika A, Suzuki T, Yoshida H, Ishibashi H, Yamamoto S, Nakamura K, Kawaguchi H, Yoshimura N (2009) Prevalence of radiographic knee osteoarthritis and its association with knee pain in the elderly of Japanese population-based cohorts: the ROAD study. Osteoarthr Cartil 17:1137–1143
16. Verhaak PF, Kerssens JJ, Dekker J, Sorbi MJ, Bensing JM (1998) Prevalence of chronic benign pain disorder among adults: a review of the literature. Pain 77:231–239
17. Coggon D, Ntani G, Palmer KT, Felli VE, Harari R et al (2013) Disabling musculoskeletal pain in working populations: is it the job, the person, or the culture? Pain 154:856–863
18. Muraki S, Akune T, Oka H, Mabuchi A, En-yo Y, Yoshida M, Saika A, Nakamura K, Kawaguchi H, Yoshimura N (2009) Association of occupational activity with radiographic knee osteoarthritis and LS in elderly patients of population-based cohorts: a large-scale population-based study. Arthr Rheum 61:779–786
19. Coggon D, Croft P, Kellingray S, Barrett D, McLaren M, Cooper C (2000) Occupational physical activities and osteoarthritis of the knee. Arthr Rheum 43:1443–1449

20. Felson DT (2004) An update on the pathogenesis and epidemiology of osteoarthritis. Radiol Clin North Am 42:1–9
21. Jensen LK (2008) Knee osteoarthritis: influence of work involving heavy lifting, kneeling, climbing stairs or ladders, or kneeling/squatting combined with heavy lifting. J Occup Environ Med 65:72–89
22. Duncan R, Peat G, Thomas E, Hay E, McCall I, Croft P (2007) Symptoms and radiographic osteoarthritis: not as discordant as they are made out to be? Ann Rheum Dis 66:86–91
23. Smith BH, Elliott AM, Hannaford PC, Royal College of General Practitioners' Oral Contraception Study (2004) Is chronic pain a distinct diagnosis in primary care? Evidence arising from the Royal College of General Practitioners' Oral Contraception Study. Fam Pract 21:66–74

Osteoporos Int
DOI 10.1007/s00198-013-2372-z

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

N. Yoshimura · S. Muraki · H. Oka · M. Morita · H. Yamada · S. Tanaka · H. Kawaguchi · K. Nakamura · T. Akune

Received: 13 September 2012 / Accepted: 9 April 2013

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

Electronic supplementary material The online version of this article (doi:10.1007/s00198-013-2372-z) contains supplementary material, which is available to authorized users.

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

S. Muraki · T. Akune
Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113–8655, Japan

M. Morita · H. Yamada
Department of Orthopaedic Surgery, Fujita Health University, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan

S. Tanaka · H. Kawaguchi
Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

K. Nakamura
Rehabilitation Services Bureau, National Rehabilitation Center for Persons with Disabilities, 1, Namiki 4-chome, Tokorozawa City, Saitama Prefecture 359-8555, Japan

Published online: 15 May 2013

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.

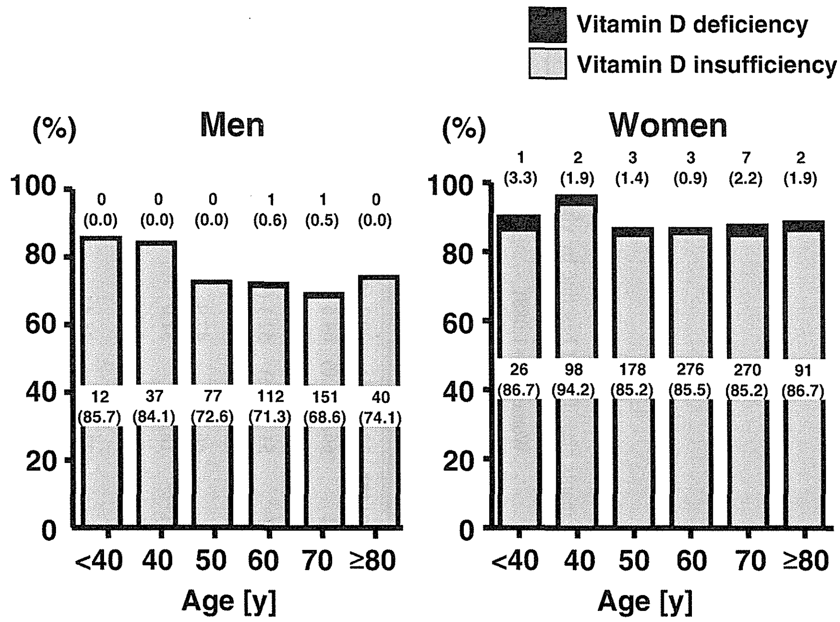

Fig. 1 The number of individuals (prevalence, %) with vitamin D insufficiency and deficiency as classified by gender. The numbers along the middle line indicate the number of individuals (prevalence, %) with vitamin D insufficiency for each bar, while those along the upper line indicate the number of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

Table 5 Prevalence (%) of coexisting disorders, such as hyperparathyroidism, osteoporosis, osteoarthritis, metabolic risk factors, and renal dysfunction, among 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
Hyperparathyroidism (iPTH >65 pg/mL)	6.8	8.0	45.0	<0.001*	6.1	8.2	50.0	0.057	7.6	7.9	44.4	<0.001*
Osteoporosis (L2–4)	11.5	14.1	10.0	0.442	2.4	3.7	0.0	0.712	22.9	18.9	11.1	0.376
Osteoporosis (femoral neck)	10.2	13.0	25.0	0.109	4.9	3.3	0.0	0.623	17.1	17.4	27.8	0.514
Osteoporosis (L2–4 or femoral neck)	14.6	20.5	25.0	0.057	4.9	6.3	0.0	0.758	26.9	27.1	27.8	0.997
Knee osteoarthritis (KL >=3)	19.4	20.0	35.0	0.238	15.3	14.5	0.0	0.813	24.4	22.5	38.9	0.243
Lumbar spondylosis (KL >=3)	42.7	35.9	30.0	0.072	45.1	34.5	50.0	0.054	38.7	36.5	27.8	0.568
Hypertension	67.9	70.2	60.0	0.473	71.2	76,0	100.0	0.344	63.9	67.6	55.6	0.411
Dyslipidaemia	11.5	12.5	10.0	0.855	9.8	15.6	0.0	0.156	13.7	11.1	11.1	0.667
Impaired glucose tolerance	21.3	21.5	30.0	0.653	23.2	24.7	50.0	0.648	19.1	20.0	27.8	0.688
Chronic kidney disease	43.7	42.9	40.0	0.932	46.3	42.7	0.0	0.333	40.5	43.2	44.4	0.847

iPTH intact parathyroid hormone, *L2–4* lumbar spine L2–L4, *KL* Kellgren–Lawerence grade, *BMI* body mass index

*p <0.001

significantly smaller in terms of body structure than the overall Japanese population (p <0.05) [13]. This difference should be considered when evaluating potential risk factors for men aged 70–74 years; factors such as body build, particularly greater weight, are known to be associated with metabolic risk factors and knee osteoarthritis. Therefore, our results may represent an underestimate of the prevalence of these conditions. Second, in the present study, this study was only the data of the baseline study. Thus, we were not able to confirm the causal relationship between vitamin D status and other associated factors. However, we have already completed a 3-year after follow-up study, so that we can clarify the causal relationship between vitamin D status and the above-mentioned factors in the following reports after the baseline profile of vitamin D status described in the present study. Third, the total number of individuals in the vitamin D deficiency group was very small (n=20), which could make the results pertaining to vitamin D deficiency somewhat less credible than those relating to vitamin D insufficiency. To address this limitation, we performed a multiple regression analysis using the serum levels of vitamin D as the objective variable and the identical explanatory variables as used in the multinominal regression analysis shown in Table 4. The explanatory variables were as follows: 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), and the values of the baseline BMD at the lumbar spine (+1 SD). Supplementary Table 1 shows the lower serum levels of vitamin D were characterised by younger age, female sex, residing in a mountainous area, measurements performed in January, smoking habit, non- or ex-drinking, higher serum iPTH, and a low intake of vitamin D. This tendency was almost similar to the characteristics of vitamin D insufficiency and deficiency, with the exception that alcohol drinking was also significantly associated with lower serum levels of vitamin D. However, as shown in Table 1, the frequency of alcohol drinking was confirmed to be significantly different according to the 25D status. Thus, the results of the multinominal logistic regression did not differ substantially from those of the multiple regression analysis using continuous values for vitamin D. Rather, these results may support the characteristics of each 25D status as clarified in the present study. Finally, the nutrition survey in the present study was performed using a questionnaire with a multiple-choice style for each meal. Although this questionnaire is widely used in Japanese studies, it might raise the possibility of recall bias. In fact, the mean dietary intake of vitamin D per day calculated in the present study tended to be high from the adequate intake (5 μg/day) published by the Ministry of Health and Welfare in Japan [37]. However, the Ministry of Health, Labour and Welfare in Japan also commented that the adequate intake had been determined as an index without enough scientific evidence. Simultaneously, this agency provided another index in which the tolerable upper intake level of vitamin D was 50 μg/day. Based on these issues regarding the estimation of vitamin D intake, we believe our results regarding the intake of vitamin D are not beyond the world consensus. Instead, the mean intake estimated in the present study could indicate that people in Japan have a much higher daily intake of vitamin D than those in most regions worldwide. Nonetheless, we were unable to conclude whether the total intake of vitamin D calculated in the present study represented actual values or was overestimated by using the questionnaire. In the other cohort from the urban area investigated in the ROAD study, we should be able to confirm the consistency of the estimation of vitamin D using the BDHQ questionnaire.

Acknowledgments This work was supported by Grants-in-Aid for Scientific Research B23390172 and B20390182 to NY, C20591737 to TA, and C20591774 to SM, for Young Scientists A18689031 to HO, and Collaborating Research with NSF 08033011–00262 (Director, NY) from the Ministry of Education, Culture, Sports, Science and Technology; and H17-Men-eki-009 (Director, KN), H18-Choujyu-037 (Director, TN), H20-Choujyu-009 (Director, NY), and H23-Chojyu-002 (Director, TA) from the Ministry of Health, Labour and Welfare in Japan. This study was also supported by grants from the Japan Osteoporosis Society (NY, SM, HO, and TA), and research aid from the Japanese Orthopaedic Association (JOA-Subsidised Science Project Research 2006–1 and 2010–2, Director, HK). The authors wish to thank Dr. Takako Nojiri and Mr. Kazuhiro Hatanaka of the Gobo Public Health Centre; Dr. Naoki Hirabayashi of the Kawakami Clinic, Hidakagawa Town; Mrs. Tomoko Takijiri, Mrs. Kumiko Shinou, Mrs. Rie Takiguchi, Mrs. Kyoko Maeda, Ms. Ikuyo Ueyama, Mrs. Michiko Mori, Mrs. Hisayo Sugimoto, and other members of the public office in Hidakagawa Town; Dr. Shinji Matsuda of the Shingu Public Health Centre; and Mrs. Tamako Tsutsumi, Mrs. Kanami Maeda, Mr. Shoichi Shimoichi, Mrs. Megumi Takino, Mrs. Shuko Okada, Mrs. Kazuyo Setoh, Mrs. Chise Ryouno, Mrs. Miki Shimosaki, Mrs. Chika Yamaguchi, Mrs. Yuki Shimoji, and other members of the public office in Taiji Town for their assistance in locating and scheduling participants for examinations. We also thank Ms. Kyoko Yoshimura, Mrs. Toki Sakurai, and Mrs. Saeko Sahara for their assistance with data reduction and administration.

Conflicts of interest None.

References

1. Lips P (2001) Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev 22:477–501
2. Bischoff-Ferrari HA, Zhang Y, Kiel DP, Felson DT (2005) Positive association between serum 25-hydroxyvitamin D level and bone density in osteoarthritis. Arthritis Rheum 53:821–826
3. Rizzoli R, Bonjour JP (2004) Dietary protein and bone health. J Bone Miner Res 19:527–531
4. Bischoff-Ferrari HA, Willett WC, Orav EJ et al (2012) A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med 367:40–49
5. Bischoff-Ferrari HA, Willett WC, Orav JE, Kiel DP, Dawson-Hughes B (2011) Fall prevention with vitamin D. BMJ 342:d2608
6. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, El-Hajj Fuleihan G, Josse RG, Lips P, Morales-Torres J; IOF Committee of Scientific Advisors (CSA) Nutrition Working Group (2009) Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int 20:1807–1820
7. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, Josse RG, Lips P, Morales-Torres J, Yoshimura N (2010) IOF position statement: vitamin D recommendations for older adults. Osteoporos Int 21:1151–1154
8. Lim SK, Kung AW, Sompongse S, Soontrapa S, Tsai KS (2008) Vitamin D inadequacy in postmenopausal women in eastern Asia. Curr Med Res Opin 24:99–106
9. Lips P, Hosking D, Lippuner K, Norquist JM, Wehren L, Maalouf G, Ragi-Eis S, Chandler J (2006) The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. J Intern Med 260:245–254
10. Nakamura K, Tsugawa N, Saito T, Ishikawa M, Tsuchiya Y, Hyodo K, Maruyama K, Oshiki R, Kobayashi R, Nashimoto M, Yoshihara A, Ozaki R, Okano T, Yamamoto M (2008) Vitamin D status, bone mass, and bone metabolism in home-dwelling postmenopausal Japanese women: Yokogoshi Study. Bone 42:271–277
11. Suzuki T, Kwon J, Kim H, Shimada H, Yoshida Y, Iwasa H, Yoshida H (2008) Low serum 25-hydroxyvitamin D levels associated with falls among Japanese community-dwelling elderly. J Bone Miner Res 23:1309–1317
12. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T (2010) Cohort Profile: research on osteoarthritis/osteoporosis against disability (ROAD) study. Int J Epidemiol 39:988–995
13. Yoshimura N, Muraki S, Oka H, Mabuchi A, En-yo Y, Yoshida M, Saika A, Yoshida H, Suzuki T, Yamamoto S, Ishibashi H, Kawaguchi H, Nakamura K, Akune T (2009) Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. J Bone Miner Metab 27:620–628
14. Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, Lewis C, Cawthon PM, Marcus R, Marshall LM, McGowan J, Phipps K, Sherman S, Stefanick ML, Stone K (2005) Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study: a large observational study of the determinants of fracture in older men. Contemp Clin Trials 26:569–585
15. Sasaki S, Yanagibori R, Amano K (1998) Self-administered diet history questionnaire developed for health education: a relative validation of the test-version by comparison with 3-day diet record in women. J Epidemiol 8:203–215
16. Hollis BW, Kamerud JQ, Selvaag SR, Lorenz JD, Napoli JL (1993) Determination of vitamin D status by radioimmunoassay with an 125I-labeled tracer. Clin Chem 39:529–533
17. Wahl DA, Cooper C, Ebeling PR, Eggersdorfer M, Hilger J, Hoffmann K, Josse R, Kanis JA, Mithal A, Pierroz DD, Stenmark J, Stöcklin E, Dawson-Hughes B (2012) A global representation of vitamin D status in healthy populations. Arch Osteoporo 7:155–172
18. Kellgren JH, Lawrence LS (1957) Radiological assessment of osteo-arthrosis. Ann Rheum Dis 16:494–502
19. World Health Organization (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO Technical Report Series 843. WHO, Geneva

20. Orimo H, Hayashi Y, Fukunaga M, Sone T, Fujiwara S, Shiraki M, Kushida K, Miyamoto S, Soen S, Nishimura J, Oh-Hashi Y, Hosoi T, Gorai I, Tanaka H, Igai T, Kishimoto H, Osteoporosis Diagnostic Criteria Review Committee: Japanese Society for Bone and Mineral Research (2001) Diagnostic criteria for primary osteoporosis: year 2000 revision. J Bone Miner Metab 19(6):331–337
21. The Examination Committee of Criteria for Metabolic Syndrome (2005) The definition and criteria of metabolic syndrome. J Jpn Soc Intern Med 94:794–809, in Japanese
22. Ministry of Health, Labour and Welfare (2010) The outline of the results of National Health and Nutrition Survey 2010. http://www.mhlw.go.jp/stf/houdou/2r98520000020qbb-att/2r98520000021c0o.pdf (in Japanese). Accessed 28th Feb 2013
23. Japan Society of Nephrology (2009) Evidence-based practice guideline for the treatment of CKD. Clin Exp Nephrol 13:537–566
24. Greene-Finestone LS, Berger C, de Groh M, Hanley DA, Hidiroglou N, Sarafin K, Poliquin S, Krieger J, Richards JB, Goltzman D, CaMos Research Group (2011) 25-Hydroxyvitamin D in Canadian adults: biological, environmental, and behavioral correlates. Osteoporos Int 22(5):1389–1399. doi:10.1007/s00198-010-1362-7, Epub 2010 Aug 21
25. Japan Meteorological Agency (2012) http://www.data.jma.go.jp/obd/stats/etrn/view/nml_amd_ym.php?prec_no=65&block_no=1089&year=2012&month=&day=&view= and http://www.data.jma.go.jp/obd/stats/etrn/view/nml_sfc_ym.php?prec_no=65&block_no=47778&year=2012&month=&day=&view= (in Japanese). Accessed 28th Feb 2013
26. Krall EA, Sahyoun N, Tannenbaum S, Dallal GE, Dawson-Hughes B (1989) Effect of vitamin D intake on seasonal variations in parathyroid hormone secretion in postmenopausal women. N Engl J Med 321:1777–1783
27. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357:266–281
28. Nashimoto M, Nakamura K, Matsuyama S, Hatakeyama M, Yamamoto M (2002) Hypovitaminosis D and hyperparathyroidism in physically inactive elderly Japanese living in nursing homes: relationship with age, sunlight exposure and activities of daily living. Aging Clin Exp Res 1:5–12
29. Lange NE, Sparrow D, Vokonas P, Litonjua AA (2012) Vitamin D deficiency, smoking, and lung function in the normative aging study. Am J Respir Crit Care Med 186(7):616–621. doi:10.1164/rccm.201110-1868OC, Epub 2012 Jul 19
30. Balsan S, Garabédian M (1991) Rickets, osteomalacia, and osteopetrosis. Curr Opin Rheumatol 3:496–502
31. Krause R, Bühring M, Hopfenmüller W, Holick MF, Sharma AM (1998) Ultraviolet B and blood pressure. Lancet 352:709–710
32. Mathieu C, Gysemans C, Giulietti A, Bouillon R (2005) Vitamin D and diabetes. Diabetologia 48:1247–1257
33. Gorham ED, Garland CF, Garland FC, Grant WB, Mohr SB, Lipkin M, Newmark HL, Giovannucci E, Wei M, Holick MF (2007) Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. Am J Prev Med 32:210–216
34. Garland CF, Mohr SB, Gorham ED, Grant WB, Garland FC (2006) Role of ultraviolet B irradiance and vitamin D in prevention of ovarian cancer. Am J Prev Med 31:512–514
35. Holick MF (2006) Calcium plus vitamin D and the risk of colorectal cancer. N Engl J Med 354:2287–2288
36. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A (2006) Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. JAMA 296:2832–2838
37. Ministry of Health, Labour and Welfare (2009) Dietary Reference Intakes in Japan 2009. http://www.mhlw.go.jp/shingi/2009/05/s0529-4.html. Assessed on 28th Feb 2013

Osteoporos Int (2014) 25:1089–1098
DOI 10.1007/s00198-013-2489-0

ORIGINAL ARTICLE

Prevalence and progression of radiographic ossification of the posterior longitudinal ligament and associated factors in the Japanese population: a 3-year follow-up of the ROAD study

N. Yoshimura · K. Nagata · S. Muraki · H. Oka · M. Yoshida · Y. Enyo · R. Kagotani · H. Hashizume · H. Yamada · Y. Ishimoto · M. Teraguchi · S. Tanaka · H. Kawaguchi · Y. Toyama · K. Nakamura · T. Akune

Received: 14 May 2013 / Accepted: 5 August 2013 / Published online: 22 August 2013

Abstract

Summary The prevalence of radiographic cervical ossification of the posterior longitudinal ligament (OPLL) in 1,562 Japanese from a population-based cohort was 1.9 %. The presence of OPLL showed a significant association with the femoral neck bone mineral density (BMD), presence of diffuse idiopathic skeletal hyperostosis (DISH) and plasma pentosidine levels. Only one new case of radiographic OPLL was detected, but OPLL progressed in all affected subjects.

Introduction The purpose of this study was to clarify the prevalence and progression of radiographic OPLL and the associated factors, using the population-based cohort Research on Osteoarthritis/osteoporosis Against Disability (ROAD).

Methods In the ROAD study, 1,690 participants underwent X-ray examination of the entire spine and both knees. Radiographic OPLL, lumbar spondylosis, knee osteoarthritis and DISH were diagnosed by a single, well-experienced orthopaedic surgeon. An interviewer-administered questionnaire and tests for anthropometric measurements were administered, and the BMDs of the lumbar spine and proximal femur were determined. A new OPLL case was considered if heterotopic ossification in the posterior longitudinal ligament was absent at baseline but present during follow-up. Progression was defined as an increase in the maximum length or width of the ossification at follow-up over that at baseline.

Results Radiographic OPLL was detected in 30 (17 men, 13 women) of 1,562 individuals who underwent X-ray examination of the cervical spine (prevalence=1.9 %). Its prevalence was significantly higher in men than in women (p =0.007), but no association with age was observed. In a logistic regression analysis, OPLL showed a significant association with the femoral neck BMD, presence of DISH and plasma pentosidine levels. Only one new case of radiographic OPLL was detected, but OPLL progressed in all affected subjects.

Conclusion This population-based study clarified the prevalence of radiographic OPLL in the Japanese population as well as its progression. OPLL showed significant association with plasma pentosidine levels, BMD and DISH.

Keywords Bone mineral density · Diffuse idiopathic skeletal hyperostosis · Ossification of posterior longitudinal ligament of cervical spine · Plasma pentosidine · Prevalence · Progression

Electronic supplementary material The online version of this article (doi:10.1007/s00198-013-2489-0) contains supplementary material, which is available to authorized users.

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

K. Nagata · M. Yoshida · Y. Enyo · R. Kagotani · H. Hashizume · H. Yamada · Y. Ishimoto · M. Teraguchi
Department of Orthopedic Surgery, Wakayama Medical University, 811-1 Kimidera, Wakayama, Wakayama 641-8509, Japan

S. Muraki · T. Akune
Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

S. Tanaka · H. Kawaguchi
Department of Orthopaedic Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Y. Toyama
Department of Orthopaedic Surgery, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

K. Nakamura
National Rehabilitation Center for Persons with Disabilities, 1, Namiki 4-chome, Tokorozawa, Saitama 359-8555, Japan