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Incidence of certified need of care in the long-term care insurance system and its risk factors in the elderly of Japanese population-based cohorts: The ROAD study

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Aim: To examine the incidence of certified need of care in the national long-term care insurance (LTCI) system, and to determine its risk factors in the elderly of Japanese population-based cohorts of the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study.

Methods: Of the 3040 participants in the baseline examination of the ROAD study, we enrolled 1773 (699 men, 1074 women) aged 65 years or older who were not certified as in need of care level elderly at baseline. Participants were followed for incident certification of need of care in the LTCI system. Associated factors in the baseline examination with occurrence were determined by multivariate Cox proportional hazards regression analysis. Muscle dysfunction was defined in accordance with the European Working Group on Sarcopenia in Older People algorithm for screening sarcopenia.

Results: A total of 54 men and 115 women were certified as in need of care level elderly during the average 4.0-year follow up. The incidence was 2.0 and 2.5 per 100 person-years in men and women, respectively. Identified risk factors were region, age, body mass index <18.5 or ≥27.5 kg/m^2, grip strength, knee extension torque, usual gait speed, chair stand time and muscle dysfunction.

Conclusions: Both underweight and obesity, as well as low muscle strength and physical ability, are risk factors for certification of need of care. Considering muscle dysfunction is a risk factor for occurrence, screened individuals are recommended to receive early intervention programs regardless of muscle volume. **Geriatr Gerontol Int 2014; 14: 695–701.**

Keywords: activities of daily living, certification of need of care (*youkaigo-nintei*), disability, long-term care insurance system, prospective cohort study.

Introduction

Japan is a super-aged society experiencing an unprecedented aging of the population. The proportion of the population aged 65 years or older was 23% in 2010, and is expected to reach 30.1% in 2024 and 39% in 2051.[1] This leads to an increasing proportion of disabled elderly requiring support or long-term care, imposing enormous economic and social burdens on the country. The Japanese Government started the national long-term care insurance (LTCI) system in 2000 based on the Long-Term Care Insurance Act.[2] The aim was to certify need of care level elderly, and to provide suitable care services according to the level of care required (seven levels, including requiring support [levels 1 and 2] and requiring long-term care [levels 1–5]). The total number of certified in need of care level elderly was reported to be 5 million in 2011.[2]

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Certification of need of care in the national LTCI system is an important outcome in Japan, not only because of its massive social and economic burdens, but also because it is urgently required to reduce its risk and decrease the number of disabled elderly requiring care in their activities of daily living (ADL). For establishment of an evidence-based prevention strategy, it is critically important to accumulate epidemiological evidence including the incidence of certified need of care and identification of risk factors. However, there have been no studies to clarify the incidence of certified need of care in the LTCI system or its risk factors using large-scale, population-based cohorts.

In 2005, we started a large-scale, population-based cohort study entitled the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study with a total of 3040 participants, which aims to elucidate the environmental and genetic backgrounds of musculoskeletal diseases.[3,4] The present study investigated the incidence of certified need of care in the national LTCI system, and determined its risk factors using a database from the ROAD study.

Methods

Participants

The present analysis was based on data collected from cohorts established in 2005 for the ROAD study. Details of the cohorts have been reported elsewhere.[3,4] Briefly, we created a baseline database from 2005–2007, which included clinical and genetic information on 3040 residents of Japan (1061 men, 1979 women). Participants were recruited from resident registration listings in three communities, namely, an urban region in Itabashi, Tokyo, and rural regions in Hidakagawa and Taiji, Wakayama. Participants in the urban region in Itabashi were recruited from those of a cohort study,[5] in which participants were randomly drawn from the register database of Itabashi ward residents, with a response rate of 75.6% in the group aged >60 years. Participants in the rural regions in Hidakagawa and Taiji were recruited from resident registration lists, with response rates of 68.4% and 29.3%, respectively, in the groups aged >60 years. Inclusion criteria were the ability to: (i) walk to the survey site; (ii) report data; and (iii) understand and sign an informed consent form. For the present study, we enrolled 1773 participants (699 men, 1074 women; mean age 75.4 years) aged 65 years or older who were not certified as need of care level elderly in the national LTCI system at baseline. All participants provided written informed consent, and the study was carried out with approval from the ethics committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology.

Baseline procedures

Participants completed an interviewer-administered questionnaire containing 400 items that included lifestyle information, such as smoking habits, alcohol consumption and physical activity. At baseline, anthropometric measurements, including height and weight, were taken, and body mass index (BMI; weight [kg]/height^2 [m^2]) was estimated based on the measured height and weight. Underweight was defined as BMI <18.5 and obesity as BMI ≥27.5, according to the 2004 consensus statement from the WHO regarding appropriate BMI for Asian populations.[6] Grip strength was measured on bilateral sides using a handgrip dynamometer (TOEI LIGHT, Saitama, Japan); the higher measurement was recorded. Isometric peak knee extension torque was measured at a knee flexion angle of 90° using a dynamometer (GT-30; OG GIKEN, Okayama, Japan) twice in participants from the urban regional cohort (Itabashi, Tokyo); the higher measurement was recorded. The time taken to walk 6 m at usual walking speed in a hallway was recorded, and usual gait speed was calculated. Skeletal muscle dysfunction was defined as usual gait speed ≤0.8 m/s or grip strength <30 kg in men and <20 kg in women, according to the algorithm for screening sarcopenia recommended by the European Working Group on Sarcopenia in Older People (EWGSOP).[7,8] The time taken for five consecutive chair rises without the use of hands was recorded in the rural regional cohorts (Hidakagawa and Taiji, Wakayama). Hands were folded in front of the chest with feet flat on the floor. Timing began with the command "Go", and ended when the buttocks contacted the chair on the fifth landing.

Certification of need of care in the LTCI system

The nationally uniform criteria for long-term care need certification was established objectively by the Japanese Government, and certification of need of care level elderly is determined based on evaluation results by the Certification Committee for Long-term Care Need in municipalities in accordance with basic guidelines formulated by the Government. The process of eligibility for certification of need of care in the LTCI system was described in detail by Chen *et al.*[9] An elderly person who requires help with ADL or the caregiver contacts the municipal Government to request official certification of care needs. After the application, a trained official visits the home to assess the current physical status of the elderly person, including the presence or absence of muscle weakness or joint contracture of limbs, and difficulties in sitting-up, standing-up, maintaining sitting or standing position, transferring from one place to another, standing on one leg, walking, bathing, dressing, and other ADL. Mental status, including dementia, is also assessed. These data are analyzed to calculate a

Table 1 Baseline characteristics of population at risk for certified need of care in the long-term care insurance system

	Entire cohort		Urban cohort		Rural cohort	
	Men	Women	Men	Women	Men	Women
No. participants	699	1,074	333	486	366	588
Age (years)	75.6 (5.1)	75.2 (5.3)	77.5 (3.7)	77.3 (3.8)	73.8 (5.5)†	73.5 (5.8)†
Height (cm)	160.9 (6.0)	147.9 (6.0)*	161.0 (5.8)	148.2 (5.4)*	160.8 (6.2)	147.7 (6.5)*
Weight (kg)	59.4 (9.1)	50.0 (8.3)*	59.4 (8.2)	49.8 (7.8)*	59.4 (9.9)	50.1 (8.8)*
BMI (kg/m^2)	22.9 (2.9)	22.8 (3.4)	22.9 (2.7)	22.7 (3.3)	22.9 (3.1)	22.9 (3.5)
BMI <18.5 (%)	6.2	8.0	6.1	7.9	6.3	8.0
BMI ≥27.5 (%)	5.7	9.3**	3.9	8.5**	7.4	9.9
Grip strength (kg)	30.4 (6.8)	19.4 (4.9)*	28.6 (6.1)	18.2 (4.1)*	31.9 (7.0)†	20.3 (5.2)*†
Knee extension torque (kgm)	–	–	79.6 (27.2)	54.8 (17.0)*	–	–
Usual gait speed (m/s)	1.17 (0.31)	1.10 (0.33)*	1.27 (0.24)	1.22 (0.24)*	1.08 (0.34)†	1.00 (0.36)*†
Chair stand time (s)	–	–	–	–	10.8 (3.7)	12.2 (5.4)*
Muscle dysfunction (%)§	48.7	56.0**	52.6	60.0**	45.2	52.6**‡
Smoking (%)	21.0	3.2**	19.2	3.0**	22.6	3.4**
Alcohol consumption (%)	61.2	23.0**	61.0	28.8**	61.3	18.4**‡

Except where indicated otherwise, values are mean (SD). *$P < 0.05$ versus men in the corresponding group of the same cohort by unpaired Student's t-test. **$P < 0.05$ versus men in the corresponding group of the same cohort by χ^2-test. †$P < 0.05$ versus urban cohort in the corresponding group of the same sex by unpaired Student's t-test. ‡$P < 0.05$ versus urban cohort in the corresponding group of the same sex by χ^2-test. §Muscle dysfunction was defined as usual gait speed ≤0.8 m/s or grip strength <30 kg in men and <20 kg in women. BMI, body mass index; LTCI, long-term care insurance system.

standardized score for determination of the level of care needs (certified support, levels 1–2; or long-term care, levels 1–5). In addition, the primary physician of the applicant assesses physical and mental status, including information on diseases causing ADL disability and the extent of disabilities caused by them. Finally, the Certification Committee for Long-term Care Need reviews the data and determines the certification and its level.

Follow up and definition of incident certified need of care

After the baseline ROAD survey, participants who were not certified as need of care level elderly at baseline were followed for incident certification of need of care in the LTCI system. Incident certified need of care was defined as the incident certified 7 level, including requiring support (levels 1–2) and requiring long-term care (levels 1–5). Information on the presence or absence of certification of need of care and its date of occurrence were collected by the resident registration listings in three communities every year up to 2010, and were used for analyses in the present study.

Statistical analysis

All statistical analyses were carried out using STATA statistical software (STATA, College Station, TX, USA). Differences in the values of the parameters between two groups were tested for significance using the non-paired Student's t-test and χ^2-test. Factors associated with occurrence of certified need of care were determined using Cox proportional hazards regression analysis; hazard ratios (HR) and 95% confidence intervals (CI) were determined after adjusting for region, age, sex, and BMI.

Results

Of the 1773 participants who were not certified as in need of care level elderly at baseline, information on certification of need of care could be obtained in 1760 (99.3%) during the average 4.0-year follow up. A total of 54 men and 115 women were certified as in need of care level elderly in the national LTCI system; whereas, 1591 remained uncertified during the follow-up period. A total of 126 participants died, and eight moved away.

Table 1 shows the baseline characteristics of the population at risk for occurrence of certified need of care in the LTCI system. Although BMI was not significantly different between men and women in the entire, urban or rural cohorts, prevalence of obesity (BMI ≥27.5) was significantly higher in women than in men in the entire and urban cohorts. The prevalence of underweight was higher in women than in men in the entire,

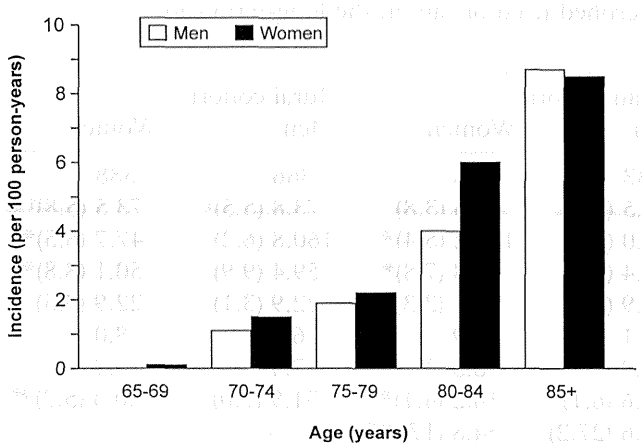

Figure 1 Incidence of certified need of care in the long-term care insurance system in men and women in each age stratum.

urban and rural cohorts; however, there was no significant difference. The prevalence of skeletal muscle dysfunction, determined by gait speed and grip strength, was significantly higher in women than in men in the entire, urban and rural cohorts.

Figure 1 shows sex- and age-distributions of the incidence of certified need of care in the LTCI system. Incidence was 2.3/100 person-years in the overall population of the entire cohort, and 2.0/100 person-years in men and 2.5/100 person-years in women. The incidence was very low in the age-stratum of 65–69 years, whereas, it tended to be markedly higher in the age-strata of 80 years and older in both sexes.

We then determined the risk factors for occurrence of certified need of care in the LTCI system. First, analysis was carried out using region, age, sex and BMI as explanatory variables in the Cox proportional hazards regression model (upper part of Table 2). Rural region and age were found to be risk factors for occurrence of certified need of care in the overall population. Sex and BMI were not significantly different. To further investigate the association between BMI and occurrence, we categorized BMI into three groups. Both underweight (BMI <18.5) and obesity (BMI ≥27.5) were found to be risk factors for occurrence of certified need of care, showing a U-shaped association. As for muscle strength and physical performance, handgrip strength, knee extension torque, usual gait speed, chair stand time and muscle dysfunction were found to be significantly associated with occurrence of certified need of care (lower part of Table 2). We carried out the same analyses in men and women separately (Table 2), and found results similar to those of the overall population.

Discussion

The present study investigated the incidence of certified need of care in the national LTCI system, and

Table 2 Hazard ratios and 95% confidence intervals for occurrence of certified need of care in the long-term care insurance system

	Overall population		Men		Women	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Region (rural *vs* urban)	1.15 (0.83–1.59)	1.61 (1.17–2.24)[b]	1.13 (0.65–1.96)	1.64 (0.94–2.86)[g]	1.15 (0.77–1.72)	1.59 (1.07–2.38)[g]
Age (+1 year)	1.17 (1.13–1.20)	1.17 (1.14–1.21)[c]	1.19 (1.12–1.26)	1.19 (1.13–1.26)[h]	1.16 (1.12–1.20)	1.16 (1.12–1.21)[h]
Sex (women *vs* men)	1.25 (0.90–1.74)	1.24 (0.89–1.73)[d]	–	–	–	–
BMI (+1 kg/m^2)	0.98 (0.93–1.03)	1.01 (0.96–1.06)[e]	0.93 (0.84–1.02)	0.96 (0.88–1.06)[i]	1.00 (0.94–1.06)	1.02 (0.97–1.08)[i]
≥18.5 or <27.5	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
BMI <18.5	2.10 (1.31–3.38)	1.77 (1.10–2.84)[e]	2.43 (1.09–5.40)	1.69 (0.75–3.82)[i]	1.93 (1.07–3.48)	1.79 (0.99–3.22)[i]
BMI ≥27.5	1.82 (1.13–2.93)	2.12 (1.32–3.43)[e]	1.39 (0.50–3.87)	1.91 (0.68–5.38)[i]	1.92 (1.12–3.29)	2.18 (1.27–3.75)[i]
Grip strength (+1 kg)	0.93 (0.91–0.95)	0.94 (0.91–0.97)[f]	0.91 (0.87–0.95)	0.94 (0.89–0.99)[j]	0.89 (0.85–0.92)	0.94 (0.89–0.98)[j]
Knee extension torque (+1 kgm)	0.97 (0.96–0.99)	0.97 (0.96–0.99)[f]	0.97 (0.95–0.99)	0.97 (0.95–0.99)[j]	0.97 (0.95–0.99)	0.97 (0.95–1.00)[j]
Usual gait speed (+0.1 m/s)	0.80 (0.77–0.85)	0.84 (0.79–0.90)[f]	0.81 (0.74–0.88)	0.83 (0.74–0.92)[j]	0.80 (0.76–0.85)	0.85 (0.78–0.92)[j]
Chair stand time (+1 s)	1.09 (1.07–1.12)	1.06 (1.03–1.10)[f]	1.18 (1.10–1.27)	1.11 (1.03–1.21)[j]	1.09 (1.06–1.11)	1.06 (1.02–1.09)[j]
Muscle dysfunction (yes *vs* no)[a]	2.91 (2.02–4.19)	1.71 (1.16–2.52)[f]	2.60 (1.45–4.68)	1.68 (0.91–3.09)[j]	3.07 (1.92–4.92)	1.72 (1.04–2.85)[j]
Smoking (yes *vs* no)	0.98 (0.58–1.68)	1.39 (0.79–2.43)[f]	1.18 (0.62–2.26)	1.54 (0.79–3.01)[j]	0.95 (0.30–2.99)	1.09 (0.35–3.47)[j]
Alcohol consumption (yes *vs* no)	0.71 (0.50–0.99)	0.83 (0.58–1.21)[f]	0.78 (0.45–1.35)	0.93 (0.53–1.61)[j]	0.70 (0.42–1.16)	0.76 (0.46–1.27)[j]

[a]Muscle dysfunction was defined as usual gait speed ≤0.8 m/s or grip strength <30 kg in men and <20 kg in women. [b]Adjusted for age, sex and body mass index (BMI). [c]Adjusted for region, sex and BMI. [d]Adjusted for region, age and BMI. [e]Adjusted for region, age and sex. [f]Adjusted for region, age, sex and BMI. [g]Adjusted for age and BMI. [h]Adjusted for region and BMI. [i]Adjusted for region and age. [j]Adjusted for region, age and BMI. Urban region and men were used as references. CI, confidence interval; HR, hazard ratio.

determined its risk factors using Japanese population-based cohorts. Identified risk factors were region, age, underweight, obesity, handgrip strength, knee extension torque, usual gait speed, chair stand time and muscle dysfunction (determined by the EWGSOP algorithm for screening sarcopenia).

In the present study, we could not obtain information on causes of certified need of care in the LTCI system. Therefore, we could not analyze the direct association of each causing condition with such factors as anthropometric and physical performance measurements. The Government of Japan reported that the top five leading causes of certified need of care were cerebral stroke, dementia, asthenia as a result of older age, joint disease and fall-related fracture, comprising 71.6% of all causes in 2010.[10] Based on these data, most of the causes of incident certification in the present study are inferred to be among the top five leading conditions.

Both low and high BMI were found to be risk factors for occurrence of certified need of care, showing an overall U-shaped association. This U-shaped association is similar to that between BMI and risk of death.[11,12] The association between risk of death from cardiovascular disease and other causes, and BMI was reported to be U-shaped in East Asians,[11] whereas the risk of all-cause mortality versus BMI was also found to have a U-shaped association in Western European and North American populations.[12] High BMI is an established risk factor for chronic diseases, including hypertension, dyslipidemia and diabetes mellitus, which increase the risk of cerebral stroke.[13] High BMI is also a major risk factor for knee osteoarthritis,[14–17] which can cause ADL disability in the elderly.[18] In contrast, low BMI is an established risk factor for osteoporosis and related fracture.[19] It also might relate to asthenia, a condition of loss or lack of bodily strength as a result of chronic wasting disease. Underweight as a result of malnutrition or sarcopenia is suggested to be included in this category.

Other identified risk factors were handgrip strength, knee extension torque, usual gait speed, chair stand time and muscle dysfunction (determined by the EWGSOP algorithm for screening sarcopenia). Previous studies have reported that low muscle strength and physical performance were predictors of subsequent ADL disability in the elderly.[20–23] The results of the present study are consistent with these previous reports. As many of the performance tests used in the present study are easy to carry out and evaluate, they can be utilized for screening elderly persons at high risk of certified need of care in the LTCI system. Those who were classified as having muscle dysfunction in the present study were at high risk of sarcopenia as well as certified need of care, regardless of muscle volume. Therefore, elderly persons screened by the EWGSOP algorithm are recommended to receive early intervention programs for prevention of ADL disability and subsequent deterioration leading to certified need of care.

The Japanese Orthopedic Association proposed the concept of "locomotive syndrome" in 2007 for the promotion of preventive health care of locomotive organs.[24–26] Locomotive syndrome refers to conditions under which the elderly have been receiving support or long-term care, or high-risk conditions under which they might soon require support or long-term care, that are caused by musculoskeletal disorders.[24–26] Functional declines in locomotive organs, including muscle strength, walking speed and balancing ability, usually progress slowly and gradually. As such, it might be difficult for people to recognize this decline in their daily life. Therefore, it is of particular importance to raise awareness of the growing risk caused by these disorders, and to take action to improve and maintain the health of locomotive organs. Population approaches, including promotion of the concept of locomotive syndrome to both younger and older generations, are important, in addition to high-risk approaches, including identifying those at risk for certified need of care and practicing intervention programs to reduce the risk of certified need of care.

There were some limitations in the present study. As we could not obtain information on causing conditions, we could not determine the risk factors for occurrence of certified need of care with respect to each causing condition. Additional studies are necessary to identify those direct associations. In the present study, the rural region was at higher risk of incident certified need of care compared with the urban region. The reasons for this could include differences in available public and private transportation or delivery services regarding meals and commodities for the elderly. In addition to these, the threshold between certified and non-certified elderly might be different among municipalities, which could lead to regional differences. Although the Certification Committee for Long-term Care Need in each municipality determines certification in accordance with guidelines formulated by the Government, the Committee also has to consider assessment by the applicant's primary physician and objective evaluation results regarding physical and mental status, which could affect the threshold of certification. Another limitation was health bias. Participants at baseline in the present study were those who could walk to the survey site, and could understand and sign an informed consent form. As those who could not were not included in the analyses, the study participants do not truly represent the general population due to health bias. Therefore, incidence of certified need of care was most likely underestimated, which should be taken into consideration when generalizing the results of the present study.

In conclusion, the present study revealed the incidence of certified need of care in the national LTCI

system, and determined its risk factors using Japanese population-based cohorts. Both underweight and obesity were found to be risk factors for certified need of care, suggesting that maintenance of intermediate BMI is important for prevention. Low muscle strength and physical ability were also shown to be risk factors for certified need of care. Physical performance measures identified as predictors can be used as screening tools to identify high-risk individuals. Considering muscle dysfunction, screened by the EWGSOP algorithm, was a risk factor for occurrence, screened individuals are recommended to receive early intervention programs regardless of muscle volume. Further studies are necessary to develop intervention programs and to test their effectiveness, along with accumulation of epidemiological evidence, to prevent certified need of care and reduce the social and economic burdens associated with this condition.

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Disclosure statement

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Serum levels of 25-hydroxyvitamin D and the occurrence of musculoskeletal diseases: a 3-year follow-up to the road study

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Abstract
Summary Assessment of serum 25-hydroxyvitamin D levels in association with the occurrence of musculoskeletal diseases using a population-based cohort study design revealed that serum 25-hydroxyvitamin D levels could predict the occurrence of osteoporosis at the femoral neck within 3 years, but not the occurrence of knee osteoarthritis or lumbar spondylosis.
Introduction The aim of this study is to clarify the association between serum 25-hydroxyvitamin D (25D) levels and occurrence of osteoporosis and osteoarthritis in the general population.
Methods The Research on Osteoarthritis/Osteoporosis Against Disability study, a large-scale population-based cohort study, was performed during 2005–2007. Serum 25D levels were measured in 1,683 participants. Of these, 1,384 individuals (81.9 %) completed a second follow-up survey 3 years later. Osteoporosis was defined according to World Health Organization criteria, in which osteoporosis is diagnosed by T-scores of bone mineral density (BMD) that are 2.5 standard deviations (SD) less than normal BMD. Knee osteoarthritis and lumbar spondylosis were defined as Kellgren–Lawrence grade ≥2, using paired X-ray films. Cumulative incidences were determined according to changes in measurements using World Health Organization criteria for osteoporosis or Kellgren–Lawrence grades for osteoarthritis between the baseline and second survey.
Results The mean (SD) serum 25D level of the 1,384 participants in both surveys was 23.4 ng/mL (6.5). The annual cumulative incidences of osteoporosis at L2–4 and the femoral neck were 0.76 and 1.83 %/year, respectively. The incidences of knee osteoarthritis and lumbar spondylosis were 3.3 and 11.4 %/year, respectively. After adjusting for potential associated factors, logistic regression analyses revealed that the odds ratio for the occurrence of femoral neck osteoporosis significantly decreased as serum 25D levels increased (+1 SD; odds ratio 0.67; 95 % confidence interval 0.49–0.92; p=0.014).
Conclusions Higher serum 25D levels may prevent the occurrence of osteoporosis at the femoral neck, but not knee osteoarthritis, lumbar spondylosis, or osteoporosis at L2–4.

Keywords 25-Hydroxyvitamin D · Epidemiology · Incidence · Osteoarthritis · Osteoporosis · Population-based cohort study

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Introduction

As the average age of the human population is rapidly increasing, the development of methods to prevent musculoskeletal disorders that impair activities of daily life (ADLs)

and quality of life (QOL) in the elderly has become an urgent need. Osteoporosis and osteoarthritis are major bone and joint health problems that cause impairment of ADL and QOL among the elderly and lead to increased morbidity and mortality in this population. The recent National Livelihood Survey performed by the Ministry of Health, Labour and Welfare in Japan [1] found that arthritis is ranked fourth, and falls and osteoporotic fractures are fifth among the diseases that cause disabilities requiring support and long-term care. Therefore, developing approaches to prevent osteoporosis and osteoarthritis could reduce the impairment of ADL and QOL and subsequent disabilities among the elderly.

Vitamin D influences bone quality and is important in maintaining bone density [2, 3]. A number of studies have reported an association between inadequate vitamin D intake and osteoporosis [4–7]. In contrast, no clear association has been found between vitamin D and osteoarthritis. An association between low levels of 25-hydroxyvitamin D (25D) and prevalent hip osteoarthritis was observed in cross-sectional studies [8, 9]. In addition, it has been shown that low serum 25D levels increased the risk of knee osteoarthritis progression [10] and incident hip joint space narrowing [11]. However, it has also been reported that serum 25D levels did not predict joint space narrowing or loss of cartilage volume of the knee [12] or clinically diagnosed knee or hip osteoarthritis [13].

In the present study, we performed a population-based cohort survey using the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study cohorts. The second ROAD survey, a 3-year follow-up survey that repeated the baseline examinations performed in the original ROAD study, has been completed. The aim of our study was to determine whether vitamin D inadequacy affects the occurrence of musculoskeletal diseases, including osteoporosis, knee osteoarthritis, and lumbar spondylosis.

Methods

Study participants

The present study was performed using the ROAD study cohorts established in 2005. The ROAD study is a national, prospective study of osteoarthritis that is made up of population-based cohorts from several communities in Japan. Details of the cohort profile have been reported elsewhere [14, 15]. In brief, between 2005 and 2007, a baseline database was created that included clinical and genetic information for 3,040 residents (1,061 men, 1,979 women; mean age, 70.3 years (SD 11.0), 71.0 years (10.7) in men, 69.9 years (11.2) in women) of Japan. The subjects were recruited from resident registration listings in three communities with different characteristics: 1,350 subjects from an urban region in Itabashi, Tokyo; 864 subjects from a mountainous region in Hidakagawa, Wakayama; and 826 subjects from a coastal region in Taiji, Wakayama. In the present study, we enrolled all 1,690 subjects (596 men, 1,094 women; mean age 65.2 years (12.0), 66.3 years (11.7) in men, 64.7 years (12.1) in women) from the mountainous and coastal regions who participated in the ROAD study. Bone mineral density (BMD) measurements and blood and urinary examinations were performed on the participants from the mountainous region and the coastal region.

The study participants provided written informed consent. The study was conducted with the approval of the ethics committees of the University of Tokyo (no. 1264 and no. 1326) and the University of Wakayama Medical University (no. 373).

Baseline assessment

Interviewer-administered questionnaire

Participants completed an interviewer-administered questionnaire that consisted of questions related to lifestyle, including occupation, smoking habits, alcohol consumption, family history, medical history, physical activity, reproductive history, and health-related QOL.

Dietary assessment

A brief diet history questionnaire (BDHQ) was administered to assess the diet of the participants, and nutrient intakes from the preceding month were determined. The BDHQ is a four-page structured questionnaire that includes questions about the frequency of consumption of 80 principal foods. The serving sizes of the foods are described as normal portions that are the standard weight and volume of servings commonly consumed by the general Japanese population. The BDHQ was modified from a comprehensive, 16-page validated self-administered diet history questionnaire [16]. A total of 141 variables, including dietary energy and nutrient intakes, were calculated using an ad hoc computer algorithm for the BDHQ. Detailed explanations accompanied each questionnaire. Well-trained interviewers clarified any unclear sections of the questionnaire, which was completed by the participants at their leisure.

Anthropometric measurements and medical history

Anthropometric measurements, including height and weight, were measured in all participants. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Handgrip strength was measured using a Toei Light handgrip dynamometer (Toei Light Co., Ltd., Saitama, Japan). Both hands were tested and the larger value used to

determine the maximum muscle strength of the subject. Experienced orthopedic surgeons collected medical information about pain, swelling, and range of motion of the knee.

Blood and urinary examinations

Samples were collected between the end of October and the middle of January from participants in the mountainous and coastal areas. All blood and urine samples were extracted between 09:00 and 15:00. After blood samples were centrifuged, the sera and urine samples were immediately placed on dry ice and transferred to a deep freezer within 24 h. Samples were stored at −80 °C until assayed.

Serum levels of 25D were measured using a radioimmunoassay with a ^{125}I-labeled tracer (DiaSorin, Stillwater, MN, USA) [17]. Intact parathyroid hormone (iPTH) levels were measured using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Manheim, Germany). Serum N-terminal propeptide of type I procollagen (PINP), a marker of bone formation, was measured using a radioimmunoassay (Orion Diagnostics, Espoo, Finland). Urinary levels of β-isomerized C-terminal telopeptide cross-links of type I collagen (β-CTX), a marker of bone resorption, were determined using an enzyme-linked immunosorbent assay (Fujirebio, Inc., Tokyo, Japan). Urinary β-CTX values were standardized to urinary creatinine concentrations.

BMD examination

Lumbar spine and proximal femur BMD values were determined using dual-energy X-ray absorptiometry (DXA; Hologic Discovery; Hologic, Waltham, MA, USA)

X-ray examination

Plain radiographs of the lumbar spine in the anteroposterior and lateral views and both knees in the anteroposterior view with weight bearing and foot map positioning were obtained.

Three-year follow-up

Between 2008 and 2010, the 1,690 participants were invited to participate in the 3-year follow-up of the ROAD survey, which repeated the baseline examinations.

Definition of osteoporosis and osteoarthritis

Osteoporosis was defined according to World Health Organization criteria; osteoporosis was diagnosed when BMD T-scores were lower than peak bone mass by 2.5 standard deviations (SD) [18]. The mean (SD) for the L2–4 BMD in young adult men and women, as measured by the Hologic DXA in Japan, is 1.011 g/cm^2 (0.119) [19]. Therefore, osteoporosis of the lumbar spine was defined as an L2–4 BMD <0.714 g/cm^2. The mean (SD) BMDs of the femoral neck in young adult men and women are 0.863 g/cm^2 (0.127) and 0.787 g/cm^2 (0.109), respectively [19]. Therefore, osteoporosis at the femoral neck in men and women was defined as a femoral neck BMD <0.546 and <0.515 g/cm^2, respectively.

Knee and lumbar radiographs were read by a single experienced orthopedist who was blinded to participants' clinical status and were categorized using the Kellgren–Lawrence grading scale [20]: grade 0, normal; grade 1, slight osteophytes; grade 2, definite osteophytes; grade 3, disk space narrowing with large osteophytes; and grade 4, bone sclerosis, disk space narrowing, and large osteophytes. In the present study, a subject with at least one knee and at least one lumbar spine with a Kellgren–Lawrence grade ≥2 was defined as having radiographic knee osteoarthritis and lumbar spondylosis, respectively. When a different grade was assigned to each knee, the participant was classified to the higher grade. To examine intra-observer variability of Kellgren–Lawrence grading, 100 randomly selected radiographs of the knee were scored by the same observer 1 month after the initial reading. To determine inter-observer variability, 100 radiographs were scored by two experienced orthopedic surgeons using the same atlas. The Kellgren–Lawrence grade (0–4) intra- and inter-variabilities were confirmed by kappa analysis to be sufficient for assessment (κ=0.86 and κ=0.80, respectively).

Incidence of osteoporosis and osteoarthritis

Cumulative incidence of osteoporosis and osteoarthritis was determined on the basis of changes in measurements between the baseline and second survey. A new case of osteoporosis was identified if an individual's BMD values at baseline were not indicative of osteoporosis, but at follow-up, BMD T-scores were lower than peak bone mass by 2.5 SD. A new case of radiographic knee osteoarthritis was identified if the Kellgren–Lawrence grade at baseline was <2 for both knees and one or both knees were assigned a grade ≥2 at follow-up. A new case of radiographic lumbar spondylosis was identified if the Kellgren–Lawrence grade at baseline was <2 for all lumbar spines and at least one spine was assigned a grade ≥2 at follow-up.

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-squared 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.

Logistic regression analysis was used to test the association between serum levels of 25D and the occurrence of osteoporosis at L2–4, osteoporosis in the femoral neck, knee osteoarthritis, and lumbar spondylosis. In the analysis, we used the occurrence of musculoskeletal diseases, such as osteoporosis, knee osteoarthritis, and lumbar spondylosis, as the objective variable and serum levels of 25D (ng/mL, +1 SD) as an explanatory variable, after adjusting for age (+1 year), sex (0, men; 1, women), BMI (+1 kg/m^2), and regional differences (0, mountainous area; 1, coastal area). In addition, we adjusted for factors associated with serum levels of 25D that were identified previously [21]: month of examination (0, October, November, or December; 1, January), smoking (0, never; 1, current), alcohol consumption (0, never; 1, current), serum levels of iPTH (0, <65 pg/mL; 1, ≥65 pg/mL), and total energy from daily amount of intake (+100 kcal/day) and vitamin D (+10 μg/day), calculated based on the BDHQ questionnaire. Furthermore, we adjusted for potential risk factors, including variables regarding exercise, past history, and pain that showed a significant ($p<0.05$) association with the occurrence of each musculoskeletal disease in the simple linear analysis.

Results

Eligible participants

Of the 1,690 study participants, 25D levels were measured at baseline in 1,683 individuals (595 men, 1,088 women; mean age 65.3 years [12.0], 66.3 years [11.7] in men, 64.7 years [12.1] in women). A total of 1,384 individuals (81.9 %; 466 men, 918 women; mean age 66.8 years [11.8], 67.8 years [11.6] in men, 66.4 years [11.8] in women) completed the second follow-up survey that included BMD measurements and X-ray radiography. A total of 251 individuals (14.9 %; 104 men, 147 women) dropped out of the follow-up study. The reasons for the dropouts were as follows: 40 individuals (27 men, 13 women) died, 97 individuals (32 men, 65 women) were ill, 16 individuals (5 men, 11 women) moved away, 8 individuals (4 men, 4 women) were absent, 51 (24 men, 27 women) declined to participate in the second survey, and 39 (12 men, 27 women) had other reasons for not participating in the second survey, including lack of response to the invitation. In addition, 55 individuals (3.3 %; 26 men, 29 women) participated in the second survey, but not all measurements were obtained.

Annual incidence of musculoskeletal diseases

In order to estimate cumulative incidence of osteoporosis and osteoarthritis, participants who had previously been diagnosed with osteoporosis and osteoarthritis at baseline were excluded from the estimation for the incidence of each musculoskeletal disease. Of the 1,384 participants who completed both the baseline and follow-up surveys, 204 individuals who had been diagnosed with osteoporosis at L2–4 or who had been prescribed medication for the treatment of osteoporosis at baseline were excluded. Thus, cumulative incidence of osteoporosis at L2–4 was estimated using data from 1,179 participants. Similarly, cumulative incidence for osteoporosis of the femoral neck, knee osteoarthritis, and lumbar spondylosis was estimated using data from 1,187; 728; and 530 participants, respectively (Table 1).

In those participants who completed both the baseline and follow-up surveys, the annual cumulative incidence of osteoporosis of the lumbar spine and femoral neck was estimated to be 0.76 and 1.83 %/year, respectively. The annual cumulative incidence of knee osteoarthritis and lumbar spondylosis was estimated as 3.3 and 11.4 %/year, respectively. The age and sex distribution of the incidence for each musculoskeletal disease is shown in Fig. 1.

Baseline characteristics of participants and occurrence of musculoskeletal diseases during 3-year follow-up periods

The measured baseline characteristics of the study participants, including serum levels of 25D; anthropometric measurements; lifestyle factors such as residence, smoking, alcohol consumption, and exercise; and medical history of fractures, hip pain, and knee pain, are shown in Table 1.

Serum 25D values categorized according to the occurrence or non-occurrence of musculoskeletal diseases are shown in Table 1. The mean levels of serum 25D were significantly lower in the subjects with femoral neck osteoporosis than those who did not develop femoral neck osteoporosis ($p=0.0088$). In contrast, serum 25D levels did not differ significantly between the groups with or without the occurrence of osteoporosis at L2–4 ($p=0.16$). Serum 25D levels were higher in subjects with knee osteoarthritis and lumbar spondylosis when compared to those who did not have knee osteoarthritis or lumbar spondylosis, although there were no significant differences (knee osteoarthritis, $p=0.15$; lumbar spondylosis, $p=0.10$).

When the osteoporosis at L2–4 occurrence group was compared to the non-occurrence group, participants in the occurrence group tended to have lower BMI ($p=0.031$), were more likely to be women ($p=0.011$), and did not exercise frequently ($p=0.017$). Serum PINP and urinary β-CTX and CTX-II levels were significantly higher in the osteoporosis at L2–4 group than in the non-occurrence group (PINP, $p=0.0001$; β-CTX, $p=0.004$; CTX-II, $p=0.006$). Serum levels

Table 1 Comparison of baseline characteristics of individuals with occurrence or non-occurrence of musculoskeletal diseases during the 3-year follow-up period

	Population at risk (n=1,179)			Population at risk (n=1,187)			Population at risk (n=728)			Population at risk (n=530)		
	Occurrence (n=27)	Non-occurrence (n=1,152)	p (Occurrence vs non-occurrence)	Occurrence (n=65)	Non-occurrence (n=1,122)	P (Occurrence vs non-occurrence)	Occurrence (n=71)	Non-occurrence (n=657)	P (Occurrence vs non-occurrence	Occurrence (n=182)	Non-occurrence (n=348)	P (Occurrence vs non-occurrence)
Means (standard deviations) of serum levels of 25D (ng/mL)	21.7 (5.3)	23.5 (6.6)	0.1556	21.4 (5.5)	23.6 (5.5)	0.0088**	24.2 (6.5)	23.0 (6.6)	0.1493	23.1 (6.5)	22.1 (6.1)	0.1033
Mean values (standard deviations) of selected characteristics												
Age (year)	66.8 (8.9)	62.4 (11.8)	0.06	70.2 (9.0)	61.9 (11.5)	<0.0001***	67.3 (8.2)	58.2 (11.8)	<0.0001***	63.2 (10.8)	56.8 (12.5)	0.0059**
Height (cm)	151.9 (7.8)	157.0 (8.6)	0.0022**	151.4 (6.7)	157.2 (8.7)	<0.0001***	153.9 (8.6)	158.8 (8.6)	<0.0001***	154.3 (9.2)	155.2 (7.9)	0.26
Weight (kg)	50.6 (7.4)	57.7 (10.3)	0.0004***	49.0 (6.4)	58.1 (10.3)	<0.0001***	56.0 (8.8)	56.8 (11.0)	0.56	54.9 (9.7)	53.6 (9.5)	0.15
BMI (kg/m^2)	22.0 (3.0)	23.4 (3.3)	0.0312*	21.5 (3.2)	23.5 (3.3)	<0.0001***	23.6 (2.9)	22.4 (3.2)	0.0035**	23.0 (3.2)	22.2 (3.3)	0.0107*
Frequency of selected characteristics (%)												
Female sex	85.2	61.0	0.011*	84.6	60.6	<0.001***	74.7	58.6	0.009**	71.4	83.1	0.002**
Residing in a coastal area	48.2	56.4	0.39	52.3	56.4	0.52	70.8	56.3	0.012*	42.3	61.5	<0.001***
Current smoking habit (more than once a month)	3.9	13.7	0.15	5.0	13.8	0.05	7.1	16.9	0.034*	14.4	9.8	0.12
Current alcohol consumption (more than once a month)	40.7	44.3	0.71	20.3	45.0	<0.001***	64.8	52.1	0.041*	61.5	60.7	0.85
Regularly walking outside (less than once a week, including job)	11.5	21.3	0.23	19.7	20.2	0.92	29.0	23.0	0.27	22.9	22.7	0.940
Regularly exercising outdoors (football, tennis, baseball, golf, etc.) after graduation from the last school	0.0	17.6	0.017*	7.7	18.1	0.032*	7.0	19.9	<0.001***	12.6	13.5	0.780
History of osteoporotic fractures (hip, spine [clinical, symptomatic], shoulder, wrist)	7.4	2.9	0.17	2.5	4.6	0.30	7.0	2.0	0.009**	5.0	2.9	0.220
Visited the doctor owing to pain in the hip	0.0	4.5	0.32	4.08	3.83	0.93	5.7	4.3	0.67	2.6	5.3	0.230
Visited the doctor owing to pain in either knee	19.1	22.9	0.68	26.4	22.4	0.50	25.9	11.7	0.002**	25.9	17.9	0.050*
Month of examination (January)	22.2	26.8	0.59	32.3	26.2	0.28	42.3	23.1	<0.001***	43.4	26.7	<0.001***
Mean values (standard deviation) of serum and urinary biochemical markers												
Serum levels of iPTH (pg/mL)	40.6 (14.5)	40.7 (31.5)	0.99	43.4 (14.9)	40.9 (38.3)	0.6	40.8 (18.3)	42.0 (46.6)	0.83	41.5 (28.4)	42.4 (49.3)	0.83
Serum levels of PINP (μg/L)	76.1 (21.9)	56.1 (25.4)	0.0001***	73.5 (28.7)	56.5 (26.1)	<0.0001***	59.0 (26.9)	56.3 (27.2)	0.43	59.0 (27.1)	59.2 (28.2)	0.94
Urinary levels of β-CTX (μg/mmol Cr)	245.1 (90.4)	176.4 (121.9)	0.0037**	269.5 (138.6)	176.9 (124.4)	<0.0001***	199.7 (130.2)	170.8 (113.0)	0.0452*	2,11.9 (157.7)	193.6 (134.7)	0.17

Table 1 (continued)

	Population at risk (n=1,179)			Population at risk (n=1,187)			Population at risk (n=728)			Population at risk (n=530)		
	Occurrence (n=27)	Non-occurrence (n=1,152)	P (Occurrence vs non-occurrence)	Occurrence (n=65)	Non-occurrence (n=1,122)	P (Occurrence vs non-occurrence)	Occurrence (n=71)	Non-occurrence (n=657)	P (Occurrence vs non-occurrence)	Occurrence (n=182)	Non-occurrence (n=348)	P (Occurrence vs non-occurrence)
Urinary levels of CTX-II (μg/mmol Cr)	327.4 (568.9)	224.8 (173.3)	0.0060**	248.9 (126.3)	223.1 (193.0)	0.29	237.5 (175.0)	189.3 (135.2)	0.0059**	207.6 (138.4)	193.6 (154.5)	0.31
Means (standard deviations) of daily nutrition intake												
Total energy (kcal/day)	1,778.1 (458.6)	1,980.9 (600.0)	0.08	1,800.2 (535.3)	1,982.5 (597.4)	0.0172*	1,963.6 (631.4)	1,964.9 (595.4)	0.99	1,945.9 (581.3)	1,815.9 (489.3)	0.0069**
Vitamin D (μg/day)	18.8 (9.3)	20.4 (12.5)	0.51	20.7 (11.0)	20.3 (12.5)	0.77	23.9 (12.3)	18.5 (11.7)	0.0003***	19.6 (11.0)	18.0 (11.3)	0.12

N number of subjects, *KL* Kellgren–Lawrence grade, *BMI* body mass index, *25D* 25-hydroxyvitamin D, *iPTH* intact parathyroid hormone, *PINP* procollagen type I N-terminal propeptide, *β-CTX* β-isomerized C-terminal telopeptide cross-links of type I collagen, *CTX-II* C-terminal cross-linked telopeptide type II collagen

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

of iPTH were not significantly associated with osteoporosis at L2–4.

When the osteoporosis at the femoral neck occurrence group was compared to the non-occurrence group, the participants who had osteoporosis at the femoral neck tended to be older (p<0.0001), tended to have lower BMI (p≤0.0001), were more likely to be female (p≤0.001), did not consume alcohol regularly (p<0.001), did not exercise regularly (p=0.032), and consumed less calories (p=0.017) than those in the non-occurrence group. Serum PINP and urinary β-CTX levels were significantly higher in the participants with osteoporosis at the femoral neck than in those who did not have osteoporosis at the femoral neck (p<0.0001). Serum levels of iPTH and urinary levels of CTX-II were not significantly associated with osteoporosis at the femoral neck.

When participants in the knee osteoarthritis occurrence group were compared to those who did not have knee osteoarthritis, those with knee osteoarthritis were older, had a higher BMI, were less likely to be female, resided in a coastal area, smoked less, consumed more alcohol, exercised less regularly, were more likely to have a history of osteoporotic fractures, and were more likely to have a history of medical visits because of knee pain. In addition, vitamin D levels were significantly higher in the participants with knee osteoarthritis than those in the non-occurrence group (p=0.0003). Although iPTH and PINP serum levels did not differ between the occurrence and non-occurrence groups, urinary β-CTX and CTX-II levels were significantly higher in the knee osteoarthritis occurrence group than those in the non-occurrence group (β-CTX, p=0.045; CTX-II, p=0.006).

Participants with lumbar spondylosis were older, had a higher BMI, were less likely to be female, and were more likely to have a history of past pain in either knee than the participants in the non-occurrence group. Although iPTH, PINP, β-CTX, and CTX-II levels were not different between those with lumbar spondylosis and those without, total daily energy intake was higher in the lumbar spondylosis group than in the non-occurrence group.

Logistic regression analysis between the occurrence of musculoskeletal disease and serum 25D levels

Logistic regression analysis was performed with the occurrence of musculoskeletal diseases, including osteoporosis, knee osteoarthritis, and lumbar spondylosis, as the objective variable and serum 25D levels (ng/mL, +1 SD) as the explanatory variable, after adjusting for age (+1 year), sex (0, men; 1, women), BMI (+1 kg/m^2), and regional differences (0, mountainous area; 1, coastal area). In addition, adjustments were made for factors previously shown to be associated with serum levels of 25D [20], including month of examination

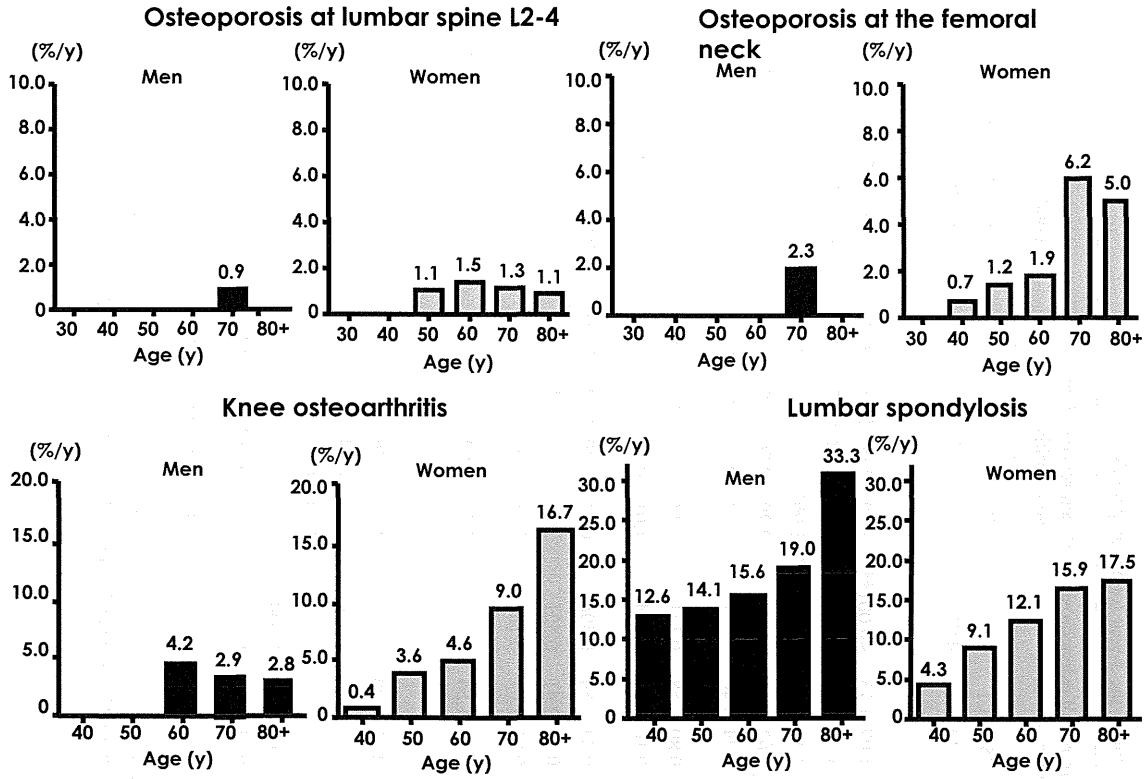

Fig. 1 Cumulative incidence (%/year) of musculoskeletal diseases (osteoporosis at the lumbar spine, osteoporosis at the femoral neck, osteoarthritis of the knee, and lumbar spondylosis) stratified by age and sex

(0, October, November, or December; 1, January), smoking (0, never; 1, current), alcohol consumption (0, never; 1, current), serum iPTH levels (0, <65 pg/mL; 1, ≥65 pg/mL), total daily energy intake (+100 kcal/day), and vitamin D (+10 μg/day) calculated according to responses on the BDHQ questionnaire. Furthermore, we adjusted for potential risk factors that showed a significant ($p<0.05$) association with the occurrence of each musculoskeletal disease in the simple linear analysis described in Table 2. Selected potential factors in each analysis were as follows: osteoporosis at L2–4, regularly exercising outdoors (0, yes; 1, no), serum levels of PINP (+1 SD), and urinary levels of β-CTX (+1 SD) and CTX-II (+1 SD); osteoporosis at femoral neck, regularly exercising outdoors (0, yes; 1, no), and urinary levels of β-CTX (+1 SD) and CTX-II (+1 SD); knee osteoarthritis, regularly exercising outdoors (0, yes; 1, no), history of osteoporotic fractures (0, no; 1, yes), history of knee pain (0, no; 1, yes), and urinary levels of β-CTX (+1 SD) and CTX-II (+1 SD); and lumbar spondylosis, history of knee pain (0, no; 1, yes).

After adjusting for potential risk factors, serum 25D levels were significantly associated with the occurrence of osteoporosis at the femoral neck (odds ratio 0.67; 95 % confidence interval 0.49–0.92; $p=0.014$). However, serum 25D levels were not significantly associated with the occurrence of knee osteoarthritis, lumbar spondylosis, or osteoporosis at L2–4.

Discussion

In the present study, using information from the population-based cohort ROAD study, we estimated the incidence of osteoporosis at L2–4 and at the femoral neck and found that higher serum 25D levels decreased the risk of future occurrence of osteoporosis at the femoral neck, but not the risk of osteoporosis at L2–4 or osteoarthritis, including knee osteoarthritis and lumbar spondylosis.

Previously, we have estimated the age–sex stratified cumulative incidence of knee osteoarthritis and lumbar spondylosis in the Japanese population, using the ROAD study of more than 2,200 subjects who participated at baseline and at the 3-year follow-up study and for whom paired radiographs and complete pain histories were obtained [22, 23]. In contrast, there are few reports estimating the incidence of osteoporosis diagnosed by BMD in the Japanese population [24, 25]. In the present study, we established the population-based cohorts of the ROAD study in identical areas to the previous studies and performed a baseline study between 2005 and 2007 and a follow-up study between 2008 and 2010. Using the data of 1,384 participants from both the baseline and follow-up studies, we estimated the annual cumulative incidence of osteoporosis at the spine L2–4 and at the femoral neck to be 0.76 and 1.83 %/year, respectively. Using the total age and sex

Table 2 Odds ratios of serum 25-hydroxyvitamin D levels influencing the occurrence of musculoskeletal diseases during the 3-year follow-up periods

		Occurrence of osteoporosis at the lumbar spine L2–4			Occurrence of osteoporosis at the femoral neck			Occurrence of knee osteoarthritis			Occurrence of lumbar spondylosis		
Explanatory variables	Reference (at the baseline)	OR	95 % CI	*p*	OR	95 % CI	*p*	OR	95 % CI	*p*	OR	95 % CI	*p*
Serum levels of 25D (ng/mL)	+1 SD	0.87	0.569–1.319	0.504	0.67	0.49–0.92	0.014*	1.23	0.90–1.69	0.198	1.01	0.81–1.28	0.900
Adjusted factors													
Age (year)	+1 year	1.05	1.00–1.09	0.043*	1.11	1.07–1.15	<0.001***	1.10	1.06–1.14	<0.001***	1.04	1.02–1.06	0.001**
Sex	0, men; 1, women	2.74	0.74–10.22	0.132	3.23	1.21–8.61	0.019*	3.24	1.24–8.45	0.016*	0.65	0.34–1.25	0.196
BMI	0, 18.5–27.5 vs 1, <18.5	3.65	0.96–14.34	0.064	8.89	3.33–23.77	<0.001***	1.00[a]	–	–	0.07	0.09–0.51	0.009**
	0, 18.5–27.5 vs 1, >27.5	0.41	0.05–3.17	0.394	0.15	0.02–1.17	0.071	2.29	0.80–6.58	0.125	2.17	1.06–4.45	0.033*
Month of examination	0, October, November, December vs 1, January	0.59	0.20–1.72	0.333	1.59	0.74–3.40	0.234	1.78	0.79–4.02	0.163	1.22	0.70–2.14	0.482
Residing region	0, mountainous area; 1, coastal area	0.71	0.28–1.81	0.467	1.69	0.80–3.58	0.171	1.18	0.53–2.64	0.688	0.71	0.42–1.20	0.197
Smoking	0, ex or never smoker; 1, current smoker	0.47	0.06–3.98	0.491	0.68	0.16–2.84	0.594	1.01	0.27–3.79	0.987	1.28	0.59–2.77	0.529
Alcohol consumption	0, ex or never drinker; 1, current drinker	1.64	0.68–3.94	0.271	0.72	0.34–1.54	0.396	0.83	0.40–1.70	0.604	0.83	0.50–1.37	0.459
Serum levels of iPTH (pg/mL)	0, <65 pg/mL; 1, ≥65 pg/mL	0.39	0.05–3.07	0.371	0.65	0.18–2.41	0.521	1.88	0.65–5.44	0.245	1.88	0.81–4.37	0.145
Total energy from daily food (kcal/day)	+100 kcal	1.00	0.90–1.11	0.991	0.93	0.86–1.01	0.101	1.01	0.94–1.08	0.768	1.04	0.98–1.10	0.179
Vitamin D from daily food (μg/day)	+10 μg	0.84	0.53–1.35	0.479	1.14	0.85–1.54	0.377	1.25	0.94–1.65	0.123	0.94	0.75–1.20	0.636
Selected adjusted factors													
Regularly exercising outdoors	0, yes; 1, no	1.00[a]	–	–	1.15	0.35–3.80	0.819	1.53	0.46–5.03	0.485	–	–	–
History of osteoporotic fractures	0, no; 1, yes	–	–	–	–	–	–	1.95	0.54–7.07	0.311	–	–	–
History of knee pain	0, no; 1, yes	–	–	–	–	–	–	1.84	0.87–3.92	0.111	1.11	0.75–1.20	0.636
Serum levels of PINP (μg/L)	+1 SD	1.51	1.00–2.26	0.040*	1.36	1.01–1.82	0.044*	–	–	–	–	–	–
Urinary levels of β-CTX (μg/mmol Cr)	+1 SD	1.05	0.69–1.61	0.802	1.18	0.91–1.51	0.206	0.76	0.512–1.13	0.176	–	–	–
Urinary levels of CTX-II (μg/mmol Cr)	+1 SD	1.09	0.83–1.44	0.528	–	–	–	1.41	0.96–2.07	0.076	–	–	–

OR odds ratio, *95 %* CI 95 % confidence interval, *25D* 25-hydroxyvitamin D, *BMI* body mass index, *iPTH* intact parathyroid hormone, *PINP* procollagen type I N-terminal propeptide, *β-CTX* β-isomerized C-terminal telopeptide cross-links of type I collagen, *CTX-II* C-terminal cross-linked telopeptide type II collagen

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

[a] Omitted from the model

population distributions from the Japanese 2010 census [26], our results indicate that approximately 450,000 people (50,000 men and 400,000 women) aged ≥40 years are affected by osteoporosis at L2–4 and that approximately 1,180,000 people (130,000 men and 1,050,000 women) aged ≥40 years are affected by osteoporosis at the femoral neck.

An association between inadequate vitamin D and osteoporosis has been reported previously. Deficiency of vitamin D results in decreased bone mineralization and secondary hyperparathyroidism and increased cortical bone loss and has been linked to the pathogenesis of osteoporosis and hip fractures [2, 3]. In addition, vitamin D supplementation may help to decrease fractures and falls [27, 28]. In a primary care cohort study of 1,470 postmenopausal Japanese women, there were trends of decreasing incidence of proximal femur and long bone fractures as serum 25D levels increased [29]. However, there are few reports that have assessed the predictive ability of serum 25D levels and the occurrence of osteoporosis itself. In the present study, we confirmed that higher serum 25D levels are associated with the prevention of osteoporosis occurrence, especially at the femoral neck.

There is conflicting information about the association of vitamin D and the occurrence of osteoarthritis. Few longitudinal studies have identified vitamin D deficiency as a risk factor for occurrence or progression of osteoarthritis. Specifically, Lane et al. reported that an increased risk of hip joint space narrowing is associated with low baseline serum 25D levels [11]. McAlindon et al. reported that an increased risk of knee osteoarthritis progression is associated with a low vitamin D intake or low serum 25D levels [10]. Bergink et al. reported that low dietary vitamin D intake increases the risk of progression of radiographic knee osteoarthritis [30]. In addition, cross-sectional studies have shown an association between low 25D levels and prevalent hip osteoarthritis [8, 9]. However, it has also been reported that low serum 25D levels do not increase the incidence of knee osteoarthritis. Felson et al. reported, using data from the Framingham Osteoarthritis Study cohort, that vitamin D status is unrelated to the risk of joint space or cartilage loss in knee osteoarthritis [12]. In addition, Kostari et al. followed a population of 805 subjects who participated in national health examination surveys held in 1978–1980 and 2000–2001 and found no significant association between serum 25D levels and the risk of incident knee or hip osteoarthritis [13]. Our study found no association between serum 25D levels and incident knee osteoarthritis. In addition, although no reports have examined the association between 25D and onset of lumbar spondylosis, we found no association between 25D and incident lumbar spondylosis.

In our previous report examining the association of vitamin D and musculoskeletal diseases at baseline [21], we found that the prevalence of osteoporosis at the L2–4 or at the femoral neck tended to be highest in the vitamin D deficiency group, followed by the vitamin D insufficiency and normal groups, although the groups did not differ significantly. The prevalence of knee osteoarthritis and lumbar spondylosis did not differ between vitamin D levels. In the present follow-up study using the same population, we found that higher levels of serum 25D prevented the occurrence of osteoporosis at the femoral neck, but not knee osteoarthritis or lumbar spondylosis, after adjusting for associated factors. This is the first study to confirm the association between 25D levels and the occurrence of musculoskeletal disorders, using the same population. Therefore, we concluded that the serum 25D levels would be useful in assessing the risk of future osteoporosis, but not the risk of future osteoarthritis.

There are several limitations to this study. First, although the ROAD study includes a large number of participants, these participants may not be representative of the general population. To address this, we compared the anthropometric measurements and smoking frequency and alcohol consumption between the study participants and the general Japanese population. No significant differences were found, with the exception that male ROAD study participants aged 70–74 years were significantly smaller than the overall Japanese population ($p<0.05$) [14]. This difference should be considered when evaluating potential risk factors for men aged 70–74 years. Second, we used Kellgren–Lawrence grade ≥2 as a criterion for the diagnosis of knee osteoarthritis and lumbar spondylosis. The Kellgren–Lawrence scale is a categorical index in which grade 2 is defined as definite osteophytes and grade 3 is defined as disk space narrowing with large osteophytes. Based on this scale, it would be difficult to evaluate osteophytosis and joint space narrowing separately. Thus, all cases of joint space narrowing, with and without the presence of osteophytosis, are categorized into the grade 3. Therefore, to evaluate the severity of knee osteoarthritis using quantitative parameters, a knee osteoarthritis computer-assisted diagnostic system [31] measuring minimum joint space width and area of osteophytosis is under development. In addition, a lumbar spondylosis computer-assisted diagnostic system is also under development. These systems will provide further accuracy in determining the association between the components of osteoarthritis including joint space and osteophytes and serum levels of 25D for early prevention of osteoarthritis. Finally, the measurement of the 25D level in the present study was measured on a single occasion. Thus, we could not exclude the effect of incidental life changes of participants, such as holidays or dietary changes that occurred around the examination date. Owing to budget and lack of manpower, we could not perform recurrent measurements of serum 25D levels to minimize fluctuations in 25D levels due to the effect of environmental factors. However, the large number of participants of the study means that the individual variance in serum 25D levels is diluted.

Importantly, the strength of the present study is that the participation rate in the follow-up survey was very high (81.9 %).

In conclusion, the present study revealed that serum 25D levels could predict the occurrence of osteoporosis at the femoral neck within 3 years, but not the occurrence of knee osteoarthritis or lumbar spondylosis. Raising serum 25D levels may be useful in the prevention of osteoporosis occurrence in the near future.

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Conflicts of interest Noriko Yoshimura, Shigeyuki Muraki, Hiroyuki Oka, Kozo Nakamura, Hiroshi Kawaguchi, Sakae Tanaka, and Toru Akune declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Association of physical activities of daily living with the incidence of certified need of care in the long-term care insurance system of Japan: the ROAD study

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Abstract
Background The present study aimed to investigate association of physical activities of daily living with the incidence of certified need of care in the national long-term care insurance (LTCI) system in elderly Japanese population-based cohorts.
Methods Of the 3,040 participants in the baseline examination, we enrolled 1,773 (699 men, 1,074 women) aged 65 years or older who were not certified as in need of care-level elderly at baseline. Participants were followed during an average of 4.0 years for incident certification of need of care in the LTCI system. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used assess function. Associated factors in the baseline examination with the occurrence were determined by multivariate Cox proportional hazards regression analysis. Receiver operating characteristic curve analysis was performed to evaluate cut-off values for discriminating between the occurrence and the non-occurrence group.
Results All 17 items in the WOMAC function domain were significantly associated with the occurrence of certified need of care in the overall population. Cut-off values of the WOMAC function score that maximized the sum of sensitivity and specificity were around 4–6 in the overall population, in men, and in women. Multivariate Cox hazards regression analysis revealed that a WOMAC function score $\geq$4 was significantly associated with occurrence with the highest hazard ratio (HR) for occurrence after adjusting for confounders in the overall population (HR [95 % confidence interval (CI)] 2.54 [1.76–3.67]) and in women [HR (95 % CI) 3.13 (1.95–5.02)]. A WOMAC function score $\geq$5 was significantly associated with the highest HR for occurrence in men [HR (95 % CI) 1.88 (1.03–3.43)].
Conclusions Physical dysfunction in daily living is a predictor of the occurrence of certified need of care. Elderly men with a WOMAC function score $\geq$5 and women with a score $\geq$4 should undergo early intervention programs to prevent subsequent deterioration.

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Introduction

Japan is a super-aged society experiencing an unprecedented aging of the population. The proportion of the population aged 65 years or older was 23 % in 2010, and is expected to reach 30.1 % in 2024 and 39 % in 2051 [1]. This leads to an increasing proportion of disabled elderly requiring support or long-term care, imposing enormous economic and social burdens on the country. The Japanese Government started the national long-term care insurance (LTCI) system in 2000 based on the Long-Term Care Insurance Act [2]. The aim was to certify need of care-level elderly and to provide suitable care services according to the level of care required [7 levels, including requiring support (levels 1 and 2) and requiring long-term care (levels 1–5)]. The total number of certified need of care-level elderly was reported to be 5 million in 2011 [2]. Certification of need of care in the national LTCI system is an important outcome in Japan not only because of its massive social and economic burdens, but also because it is urgently necessary to reduce risk and decrease the number of disabled elderly requiring care in their activities of daily living (ADLs). It is critically important to accumulate epidemiologic evidence, including identification of predictors, to establish evidence-based prevention strategies. However, no studies have determined the association of physical ADLs with the incidence of certified need of care in the national LTCI system using large-scale, population-based cohorts. The objective of the present study was to investigate the association of physical ADLs with the incidence of certified need of care in the national LTCI system and determine its predictors in elderly participants of large-scale, population-based cohorts of the research on osteoarthritis/osteoporosis against disability (ROAD) study.

Subjects and methods

Participants

The analysis was based on data collected from cohorts established in 2005 for the ROAD study. Details of the cohorts have been reported elsewhere [3, 4]. Briefly, a baseline database was created from 2005 to 2007, which included clinical and genetic information on 3,040 residents of Japan (1,061 men, 1,979 women). Participants were recruited from resident registration listings in three communities, namely, an urban region in Itabashi, Tokyo, and rural regions in Hidakagawa and Taiji, Wakayama. Participants in the urban region in Itabashi were recruited from those of a cohort study [5] in which the participants were randomly drawn from the register database of Itabashi ward residents, with a response rate in the age group >60 years of 75.6 %. Participants in the rural regions in Hidakagawa and Taiji were recruited from resident registration lists, with response rates in the groups aged >60 years of 68.4 and 29.3 %, respectively. Inclusion criteria were the ability to (1) walk to the survey site, (2) report data, and (3) understand and sign an informed consent form. For the present study, we enrolled 1,773 participants (699 men, 1,074 women; mean age 75.4 years) aged 65 years or older who were not certified as in need of care-level elderly in the national LTCI system at baseline. All participants provided written informed consent, and the study was conducted with approval from the ethics committees of the participating institutions.

Baseline procedures

Participants completed an interviewer-administered questionnaire containing 400 items that included lifestyle information, such as smoking habits, alcohol consumption, and physical activity. At baseline, anthropometric measurements, including height and weight, were taken, and body mass index (BMI) [weight (kg)/height^2 (m^2)] was estimated based on the measured height and weight.

Assessment of physical ADLs

We used the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for assessment of physical ADLs. The WOMAC is a health status instrument, consisting of three domains: pain, stiffness, and physical function. We used the WOMAC function domain to evaluate physical ADLs. It consisted of 17 items: assessing difficulties in descending stairs, ascending stairs, rising from sitting, standing, bending to floor, walking on a flat surface, getting in/out of car/bus, going shopping, putting on socks/stockings, rising from bed, taking off socks/stockings, lying in bed, getting into/out of bath, sitting, getting on/off toilet, heavy domestic duties, and light domestic duties. Each item in the domain is graded on either a 5-point Likert scale (scores of 0–4) or a 100-mm visual analog scale [6, 7]. In the present study, we used the Likert scale (version LK 3.0). Items were rated from 0 to 4; 0, no difficulty; 1, mild difficulty; 2, moderate difficulty; 3, severe difficulty; 4, extreme difficulty. The domain score ranges from 0 to 68. Japanese versions of the WOMAC have been validated [8].

Certification of need of care in the LTCI system

The nationally uniform criteria for long-term care need certification was established objectively by the Japanese Government, and certification of need of care-level elderly