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 ADLs 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 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 ADLs. Mental status, including dementia, also is assessed. These data are analyzed to calculate a 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 in 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 levels, 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 performed using STATA statistical software (STATA, College Station, TX, USA). Differences in values of the parameters between the two groups were tested for significance using the unpaired Student's t test, the Mann–Whitney's U test, and Chi-square test. We used receiver operating characteristic (ROC) curve analysis to determine a cut-off value of the WOMAC function score for discriminating two distinct groups: an occurrence and a non-occurrence group of certified need of care. Cut-off values were determined that maximized the sum of sensitivity and specificity. Factors associated with the occurrence of certified need of care were determined using Cox proportional hazards regression analysis; hazard ratios (HRs) and 95 % confidence intervals (CIs) were determined after adjusting for region, age, sex, and BMI. Smoking habit and alcohol consumption were not included as confounders because they were not significantly associated with the incidence of certified need of care.

Results

Of the 1,773 participants who were not certified as in need of care-level elderly at baseline, information on

Table 1 Baseline characteristics of population at risk for the certified need of care in the LTCI system

	Men	Women
No. of subjects	699	1,074
Age (years)	75.6 (5.1)	75.2 (5.3)
Height (cm)	160.9 (6.0)	147.9 (6.0)[b]
Weight (kg)	59.4 (9.1)	50.0 (8.3)[b]
BMI (kg/m^2)	22.9 (2.9)	22.8 (3.4)
Smoking (%)	21.0	3.2[c]
Alcohol consumption, %	61.2	23.0[c]
WOMAC function domain		
Descending stairs, pts[a]	0 (0, 0, 1, 1)	0 (0, 0, 1, 2)[d]
Ascending stairs, pts[a]	0 (0, 0, 1, 1)	0 (0, 0, 1, 2)
Rising from sitting, pts[a]	0 (0, 0, 0, 1)	0 (0, 0, 1, 1)[d]
Standing, pts[a]	0 (0, 0, 0, 1)	0 (0, 0, 1, 1)[d]
Bending to floor, pts[a]	0 (0, 0, 0, 1)	0 (0, 0, 1, 1)
Walking on a flat surface, pts[a]	0 (0, 0, 0, 1)	0 (0, 0, 0, 1)
Getting in/out of car/bus, pts[a]	0 (0, 0, 0, 1)	0 (0, 0, 1, 1)[d]
Going shopping, pts[a]	0 (0, 0, 0, 1)	0 (0, 0, 0, 1)[d]
Putting on socks/stockings, pts[a]	0 (0, 0, 0, 1)	0 (0, 0, 0, 1)[d]
Rising from bed, pts[a]	0 (0, 0, 0, 1)	0 (0, 0, 0, 1)[d]
Taking off socks/stockings, pts[a]	0 (0, 0, 0, 1)	0 (0, 0, 0, 1)[d]
Lying in bed, pts[a]	0 (0, 0, 0, 0)	0 (0, 0, 0, 1)[d]
Getting into/out of bath, pts[a]	0 (0, 0, 0, 0)	0 (0, 0, 0, 1)[d]
Sitting, pts[a]	0 (0, 0, 0, 0)	0 (0, 0, 0, 0)[d]
Getting on/off toilet, pts[a]	0 (0, 0, 0, 1)	0 (0, 0, 1, 2)[d]
Heavy domestic duties, pts[a]	0 (0, 0, 0, 1)	0 (0, 0, 0, 1)[d]
Light domestic duties, pts[a]	0 (0, 0, 0, 1)	0 (0, 0, 0, 1)[d]
Total, pts[a]	1 (0, 0, 5, 12)	2 (0, 0, 8, 17)[d]

Except where indicated otherwise, values are mean (SD)

LTCI long-term care insurance system, *BMI* body mass index, *WOMAC* the Western Ontario and McMaster Universities Arthritis Index

[a] Median (10, 25, 75, and 90 percentile)

[b] $P < 0.05$ vs men by unpaired Student's t test

[c] $P < 0.05$ vs men by Chi-square test

[d] $P < 0.05$ vs men by Mann–Whitney U test

Table 2 Association of physical activities of daily living with the occurrence of certified need of care in the LTCI system

Physical activity	Overall population		Men		Women	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
Descending stairs, pts	1.47 (1.26, 1.72)	<0.001	1.29 (0.96, 1.74)	0.089	1.56 (1.30, 1.87)	<0.001
Ascending stairs, pts	1.47 (1.25, 1.73)	<0.001	1.29 (0.93, 1.77)	0.123	1.55 (1.29, 1.86)	<0.001
Rising from sitting, pts	1.58 (1.34, 1.88)	<0.001	1.38 (0.95, 1.99)	0.092	1.67 (1.37, 2.03)	<0.001
Standing, pts	1.64 (1.41, 1.91)	<0.001	1.39 (1.02, 1.90)	0.037	1.73 (1.45, 2.06)	<0.001
Bending to floor, pts	1.57 (1.32, 1.85)	<0.001	1.61 (1.15, 2.27)	0.006	1.57 (1.29, 1.90)	<0.001
Walking on a flat surface, pts	1.57 (1.30, 1.90)	<0.001	1.25 (0.88, 1.77)	0.22	1.78 (1.41, 2.23)	<0.001
Getting in/out of car/bus, pts	1.76 (1.47, 2.10)	<0.001	1.60 (1.14, 2.26)	0.007	1.85 (1.50, 2.29)	<0.001
Going shopping, pts	1.72 (1.46, 2.03)	<0.001	1.55 (1.14, 2.11)	0.005	1.81 (1.48, 2.21)	<0.001
Putting on socks/stockings, pts	1.60 (1.33, 1.92)	<0.001	1.41 (0.98, 2.03)	0.065	1.71 (1.37, 2.12)	<0.001
Rising from bed, pts	1.68 (1.40, 2.03)	<0.001	1.41 (0.98, 2.02)	0.066	1.83 (1.47, 2.29)	<0.001
Taking off socks/stockings, pts	1.64 (1.37, 1.98)	<0.001	1.48 (1.01, 2.16)	0.046	1.72 (1.39, 2.13)	<0.001
Lying in bed, pts	1.82 (1.44, 2.30)	<0.001	1.96 (1.13, 3.40)	0.017	1.79 (1.38, 2.32)	<0.001
Getting into/out of bath, pts	1.71 (1.43, 2.04)	<0.001	1.64 (1.15, 2.33)	0.006	1.75 (1.43, 2.15)	<0.001
Sitting, pts	2.21 (1.73, 2.82)	<0.001	1.92 (1.14, 3.22)	0.014	2.32 (1.75, 3.06)	<0.001
Getting on/off toilet, pts	1.87 (1.52, 2.29)	<0.001	1.51 (1.00, 2.27)	0.05	2.09 (1.63, 2.68)	<0.001
Heavy domestic duties, pts	1.27 (1.09, 1.49)	0.003	1.20 (0.89, 1.62)	0.238	1.33 (1.10, 1.60)	0.003
Light domestic duties, pts	1.68 (1.41, 2.01)	<0.001	1.49 (1.07, 2.07)	0.019	1.80 (1.45, 2.24)	<0.001

Hazard ratios (HRs) and 95 % confidence intervals (CIs) were determined by Cox proportional hazards regression analysis after adjusting for age, sex, body mass index, and region in the overall population, and after adjusting for age, body mass index, and region in men and in women, respectively

LTCI long-term care insurance system

certification of need of care could be obtained in 1,760 (99.3 %) during the average 4.0-year follow-up. Fifty-four men and 115 women were certified as in need of care-level elderly in the national LTCI system, whereas, 1,591 remained uncertified during the follow-up period. The average period for the certification was 2.3 years. Among the above 54 men and 115 women, those who were certified as requiring long-term care level 1, 2, 3, 4, and 5 were 7, 9, 2, 4, 3 men, and 12, 17, 9, 4, 4 women, respectively. One hundred and twenty-six participants died and eight moved away. Incidence of certified need of care in the LTCI system was 2.3/100 person-years in the overall population, and 2.0/100 person-years in men and 2.5/100 person-years in women. Table 1 shows the baseline characteristics of the population at risk for occurrence of certified need of care in the LTCI system. The score of each item in the WOMAC function domain was significantly higher in women than in men in almost all items.

We then investigated association of each item in the WOMAC function domain with the occurrence of certified need of care in the LTCI system (Table 2). All 17 items in the WOMAC function domain were significantly associated with the occurrence of the certified need of care in the overall population and in women. In men, standing, bending to floor, getting in/out of car/bus, going shopping, taking off socks/stockings, lying in bed, getting into/out of bath, sitting, and light domestic duties were significantly associated with the occurrence of certified need of care, whereas other ADLs were not. In addition, the value of HR for each item in the association was higher in women than in men in 15 of 17 items.

Next we determined cut-off values of total score of the WOMAC function domain for discriminating two groups: an occurrence and a non-occurrence group of certified need of care using ROC curve analysis. The area under ROC curve was 0.70 in the overall population, 0.61 in men, and 0.74 in women (Fig. 1). The cut-off value of the WOMAC function score that maximized the sum of sensitivity and specificity was 6, 5, and 6 in the overall population, in men, and in women, respectively. In addition, the sensitivity/specificity was 57.3/75.0 % in the overall population, 45.7/75.0 % in men, and 64.4/72.6 % in women, respectively (Table 3). Furthermore, the cut-off value by which the sum was the second largest was 4 in the overall population, 4 in men, and 4 in women, and the sensitivity/specificity was 65.3/66.7 % in the overall population, 50.0/70.0 % in men, and 72.1/64.5 % in women, respectively (Table 3).

Because ROC curve analysis is a univariate analysis, we performed multivariate Cox hazards regression analysis to determine the cut-off value of the WOMAC function score for best discriminating between an occurrence and a non-

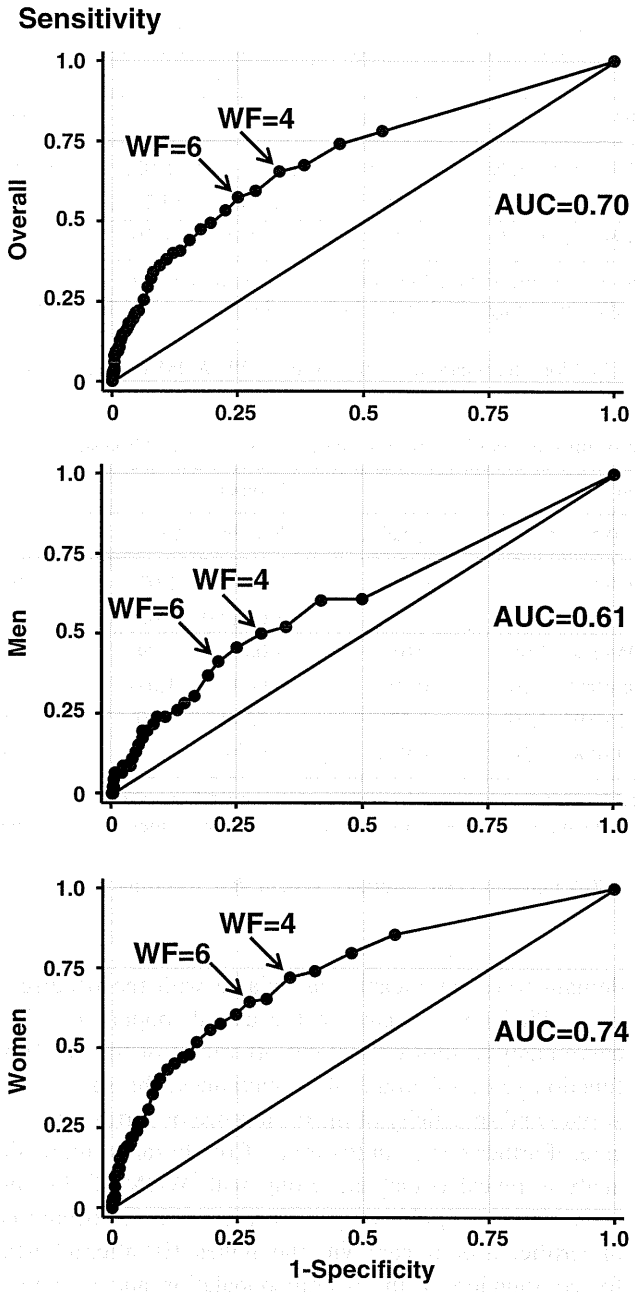

Fig. 1 Receiver operating characteristic (ROC) curve analysis for discriminating the occurrence group of certified need of care in the overall population, in men, and in women. *AUC* area under ROC curve, *WF* WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) function score

occurrence group of certified need of care after adjusting for age, sex, BMI, and region (Table 4). The group with WOMAC function score ≥4 was significantly associated with the occurrence of certified need of care compared with the group with the score <4 with the highest HR in the overall population [HR 2.54, 95 % CI (1.76–3.67)] and in women [HR 3.13, 95 % CI (1.95–5.02)]. In men, the group with WOMAC function score ≥5 was significantly

Table 3 Sensitivity and specificity of the occurrence of certified need of care determined by the cut-off point of the WOMAC function score

Cut-off point	Overall population			Men			Women		
	Sensitivity (%)	Specificity (%)	Sensitivity + specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity + specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity + specificity (%)
WF = 4pts	65.3	66.7	132.0	50.0	70.0	120.0	72.1	64.5	136.6
WF = 5pts	59.3	71.4	130.7	45.7	75.0	120.7	65.4	69.2	134.6
WF = 6pts	57.3	75.0	132.3	41.3	78.6	119.9	64.4	72.6	137.0

WOMAC the Western Ontario and McMaster Universities Arthritis Index, *WF* WOMAC function score

Table 4 Association of groups divided by the WOMAC function score with the occurrence of certified need of care in the LTCI system

	Overall population		Men		Women	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
WF ≥ 4 pts vs WF < 4 pts	2.54 (1.76, 3.67)	<0.001	1.85 (1.01, 3.39)	0.045	3.13 (1.95, 5.02)	<0.001
WF ≥ 5 pts vs WF < 5 pts	2.35 (1.64, 3.36)	<0.001	1.88 (1.03, 3.43)	0.040	2.71 (1.73, 4.27)	<0.001
WF ≥ 6 pts vs WF < 6 pts	2.50 (1.75, 3.58)	<0.001	1.84 (1.00, 3.39)	0.051	3.03 (1.93, 4.76)	<0.001

Hazard ratios (HRs) and 95 % confidence intervals (CIs) were determined by Cox proportional hazards regression analysis after adjusting for age, sex, body mass index, and region in the overall population, and after adjusting for age, body mass index, and region in men and in women, respectively

WOMAC the Western Ontario and McMaster Universities Arthritis Index, *LTCI* long-term care insurance system, *WF* WOMAC function score

Table 5 Association of the WOMAC function score with the occurrence of different certified need of care levels in the LTCI system

Outcome variable	Overall population		Men		Women	
	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value	HR (95 % CI)	*P* value
RSL1–2 and RCL 1–5	1.05 (1.03, 1.06)	<0.001	1.03 (1.01, 1.06)	0.008	1.05 (1.04, 1.07)	<0.001
RCL 1–5	1.05 (1.03, 1.07)	<0.001	1.04 (1.00, 1.07)	0.046	1.06 (1.03, 1.08)	<0.001
RCL 2–5	1.06 (1.04, 1.08)	<0.001	1.04 (1.01, 1.08)	0.015	1.06 (1.04, 1.09)	<0.001
RCL 3–5	1.05 (1.03, 1.08)	<0.001	1.05 (0.99, 1.10)	0.099	1.06 (1.02, 1.09)	0.001
RCL 4–5	1.04 (1.00, 1.08)	0.048	1.02 (0.95, 1.10)	0.501	1.05 (1.00, 1.10)	0.057
RCL 5	1.01 (0.93, 1.09)	0.830	0.99 (0.82, 1.20)	0.945	1.01 (0.93, 1.11)	0.780

Hazard ratios (HRs) and 95 % confidence intervals (CIs) were determined by Cox proportional hazards regression analysis after adjusting for age, sex, body mass index, and region in the overall population, and after adjusting for age, body mass index, and region in men and in women, respectively

WOMAC the Western Ontario and McMaster Universities Arthritis Index, *LTCI* long-term care insurance system, *RSL* requiring support level, *RCL* requiring long-term care level

associated with the occurrence of certified need of care compared with the group with a score of <5 with the highest HR [HR 1.88, 95 % CI (1.03–3.43)].

Furthermore, we examined association of the WOMAC function domain with the occurrence of different certified need of care levels in the LTCI system (Table 5). When the outcome variable of the occurrence was defined as requiring support level (RSL) 1–2 and requiring long-term care level (RCL) 1–5, RCL 1–5, and RCL 2–5, there were significant associations in the overall population, in men, and in women, respectively. When the outcome variable of the occurrence was defined as RCL 3–5, there were significant associations in the overall population and in women. When the outcome variable of the occurrence was defined as RCL 4–5, there was significant association in the overall population.

Discussion

The present study determined association of physical ADLs with the incidence of certified need of care in the national LTCI system in elderly participants of Japanese population-based cohorts. All 17 items in the WOMAC function domain were significantly associated with the occurrence of certified need of care in the overall population. ROC curve analysis showed that cut-off values of the WOMAC function score of around 4–6 maximized the sum of sensitivity and specificity of the occurrence of certified need of care. Furthermore, multivariate Cox hazards regression analysis revealed that the group with WOMAC function score ≥4 was significantly associated with the occurrence of certified need of care with the highest HR after adjusting for confounders in the overall population and in women, while the group with WOMAC function score ≥5 was significantly associated with the highest HR in men.

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 the WOMAC function domain. The Government of Japan reported that the top five leading causes of certified need of care were cerebral stroke (21.5 %), dementia (15.3 %), asthenia as a result of older age (13.7 %), joint disease (10.9 %) and fall-related fracture (10.2 %), 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. Although we could not

know the exact percentage of each causing condition, joint disease and fall-related fracture are inferred to represent approximately 20 % in total causes of incident certification in the present study, and cerebral stroke, dementia, and asthenia as a result of older age are inferred to represent approximately 50 % in total causes of incident certification.

The Government of Japan also reported that the percentage of joint disease and fall-related fracture was 16.7 % for the cause of RCL 1–5 [10]. Furthermore, it was 17.6, 19.8, 14.8, 17.4, and 9.8 % for the cause of RCL 1, 2, 3, 4, and 5, respectively [10]. Although we could not know the exact percentage of joint disease and fall-related fracture for the cause of each RCL in the present study, the percentage for the cause of RCL 1–4 is inferred to be approximately 15 % or more based on the data of the Government of Japan, which may be the reason why the WOMAC domain was significantly associated with the occurrence of certified need of care including RCLs 1–4 in the overall population.

The WOMAC physical function domain assesses difficulties in ADLs, including going up/down stairs, getting in/out of a car and bath, shopping, and household duties. Therefore, results of the present study indicate that the severity of physical dysfunction in ADLs predicts subsequent deterioration in ADLs, leading to the occurrence of certified need of care. Previous studies reported that low physical function was a predictor of subsequent ADL disability in the elderly [11, 12]. Although no previous studies have investigated the association of physical ADLs with the incidence of certified need of care in the national LTCI system in large-scale population-based cohorts, those previous findings are consistent with the present results in that low physical activity predicted subsequent deterioration in ADLs.

All 17 items in the WOMAC domain were significantly associated with the occurrence of certified need of care in women. On the other hand, 9 of 17 items were significantly associated with the occurrence of certified need of care in men. In addition, the HR for each item in the association was higher in women than in men for 15 of 17 items. The sex difference identified in this association may be due to the difference in the prevalence of knee osteoarthritis between the sexes. Muraki et al. [13] reported that prevalence of radiographic knee osteoarthritis determined by the Kellgren–Lawrence grade $\geq$2 was 47.0 % in men and 70.2 % in women, respectively, in subjects aged 60 years and older in Japanese population-based cohorts. Therefore, women are more likely than men to be affected by knee osteoarthritis and have difficulties in physical function of the lower extremities, leading to higher scores on the WOMAC function scale. Another reason for the sex differences may be the weaker muscle strength in women; muscle strength in men is higher than that in women in all decades of life [14], which may obscure the association in men, as muscle strength has been reported to be inversely associated with the WOMAC domains [15].

Functional declines in locomotive organs including physical ADLs usually progress slowly and gradually. As such, it may 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 such disorders, and to take action to improve and maintain the health of the locomotive organs. The Japanese Orthopaedic Association proposed the concept of "locomotive syndrome" in 2007 for the promotion of preventive healthcare of the locomotive organs [16–18]. Locomotive syndrome refers to conditions under which the elderly have been receiving support or long-term care, or high-risk conditions under which they may soon require support or long-term care, that are caused by musculoskeletal disorders [16–18]. 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.

Because the WOMAC function scale is a self-assessment questionnaire that is easy to conduct and evaluate, it can be used to screen elderly persons at high risk of certified need of care in the LTCI system. Multivariate Cox hazards regression analysis showed that a WOMAC function score of 5 in men and 4 in women best discriminated between the occurrence and the non-occurrence group of certified need of care in this study population. Elderly men with a WOMAC function score $\geq$5 had a 1.88-fold higher risk of occurrence of certified need of care compared with elderly men with a score <5. Elderly women with a WOMAC function score $\geq$4 had a 3.13-fold higher risk of occurrence of certified need of care compared with elderly women with a score <4. Elderly persons screened by these cut-off values should receive early intervention for the prevention of subsequent deterioration in ADLs that could lead to certified need of care. Further studies, along with the accumulation of epidemiologic evidence, are necessary to develop intervention programs that are safe and effective for elderly subjects who are at high risk of certified need of care.

There are some limitations in the present study. First, 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 measured factors, and could not determine the risk factors for occurrence of certified need of care with respect to each causing condition. The Japanese government reported that the top five leading causes of certified need of care were cerebral stroke, dementia, asthenia, osteoarthritis, 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. Additional studies are necessary to identify those direct associations. Second, 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. Since those who could not were not included in the analyses, the study participants do not truly represent the general population due to health bias, which should be taken into consideration when generalizing the results of the present study.

In conclusion, the present study determined association of physical ADLs with the occurrence of certified need of care in the LTCI system in elderly participants of Japanese population-based cohorts. The severity of physical dysfunction is a predictor of the occurrence of certified need of care. Further studies are necessary to develop intervention programs that are safe and effective for elderly individuals who are at high risk of certified need of care.

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Conflict of interest There are no conflicts of interest.

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ORIGINAL ARTICLE

Serum 25-hydroxyvitamin D below 25 ng/mL is a risk factor for long bone fracture comparable to bone mineral density in Japanese postmenopausal women

Shiro Tanaka · Tatsuhiko Kuroda · Yasushi Yamazaki · Yumiko Shiraki · Noriko Yoshimura · Masataka Shiraki

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Abstract There is emergent evidence for divergent associations between 25(OH)D levels and fractures by race and ethnicity, but data on Asian populations are sparse. We investigated this association in a primary care cohort of 1470 postmenopausal Japanese women followed for a mean period of 7.2 years and explored a potential threshold of 25(OH)D. Endpoints were incident vertebral, proximal femur, and long bone fractures. Rate ratios were estimated using multivariate Poisson regression adjusted for lumbar or femur bone mineral density (BMD) less than −2.5 SD of the young adult mean (YAM), age, weight, presence of diabetes mellitus, parathyroid hormone, estimated glomerular filtration rate, prior fracture, back pain, present medications and past medical history. Mean age was 63.7 ± 10.7 years and osteoporosis patients were 41.3 %. The background data of the present participants were almost identical to the subjects participating in the National Health and Nutrition Survey of 2003. Overall, 49.6 % of the subjects had a 25(OH)D value <20 ng/mL and 27.8 % had a 25(OH)D value from 20 to 24 ng/mL. The propensity score for exposure to 25(OH)D < 25 ng/mL in the present and independent community dwelling populations, namely the Miyama and Taiji cohorts, were not significantly different, suggesting no evidence for selection bias. The generalized additive models showed clear decreasing trends in incidence rates of proximal femur and long bone fractures at higher levels of 25(OH)D, and the annual incidence rate of proximal femur fracture was around 0.0005 in women with 25(OH)D > 25 ng/mL, probably leading to the decreasing trend in long bone fracture. Multivariate-adjusted rate ratios of 25(OH)D < 25 ng/mL were 1.01 (95 % confidence interval [CI], 0.84–1.22, $p = 0.88$) for vertebral fracture, 2.71 (95 % CI 0.94–7.83, $p = 0.07$) for proximal femur fracture, and 2.20 (95 % CI 1.37–3.53, $p < 0.01$) for long bone fracture. The respective rate ratios of a BMD level lower than −2.5 SD of the YAM were 1.61 (95 % CI 1.33–1.94, $p < 0.01$), 1.52 (95 % CI 0.67–3.45, $p = 0.32$), and 1.54 (95 % CI 1.02–2.33, $p = 0.04$). In conclusion, 25(OH)D is a leading risk factor for long bone fracture comparable to BMD in Japanese postmenopausal women. The contribution of 25(OH)D to fracture risks is substantial even below 25 ng/mL and is possibly site-specific. We recommend measuring the serum 25(OH)D level in primary care settings.

Keywords Cohort study · Osteoporosis · Proximal femur fracture · Vitamin

S. Tanaka
Division of Clinical Trial, Design and Management, Translational Research Center, Kyoto University, Kyoto, Japan

T. Kuroda
Public Health Research Foundation, Tokyo, Japan

Y. Yamazaki
Department of Laboratory Medicine, Research Institute and Practice for Involutional Diseases, 1610-1, Meisei, Misato, Azumino, Nagano 399-8101, Japan

Y. Shiraki
Department of Gynecology and Obstetrics, Research Institute and Practice for Involutional Diseases, 1610-1, Meisei, Misato, Azumino, Nagano 399-8101, Japan

N. Yoshimura
Department of Joint Disease Research, 22nd Century Medical and Research Center, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

M. Shiraki (✉)
Research Institute and Practice for Involutional Diseases, 1610-1, Meisei, Misato, Azumino, Nagano 399-8101, Japan
e-mail: ripid@fc4.so-net.ne.jp

Introduction

Vitamin D is an essential determinant of bone health [1]. The global increase in the prevalence of vitamin D deficiency is of great concern in public health [2], leading to several proposals for nutrition policy including interventions targeting vitamin D [3]. Vitamin D deficiency and insufficiency are defined as <20 ng/mL (<50 nmol/L) and from 20 to 29 ng/mL (50–74 nmol/L), respectively, in guidelines in many countries [4–7]. To date, vitamin D deficiency and insufficiency are not defined explicitly in guidelines in Japan, although members of the Japanese Society for Bone and Mineral Research suggested 28 ng/mL as a threshold for insufficiency [8]. These definitions are mainly based on the level associated with maximal parathyroid hormone (PTH) suppression, but concerning the most important endpoint, which is fractures, a consensus on the threshold of 25(OH)D has not been reached.

It is well-known that the prevalence of low 25(OH)D is highly variable across countries [9, 10]. Furthermore, there is emergent evidence for divergent associations between 25(OH)D and fracture by race and ethnicity. The Women's Health Initiative reported that higher 25(OH)D levels were associated with a lower risk of fracture in white women, but a higher risk of fracture in black or Asian women and that there were no associations in Hispanics or Native Americans [11]. Similarly, positive associations with bone mineral density (BMD) and geometry were observed in Caucasians but not in those of African ancestry in the Osteoporotic Fractures in Men Study [12]. The evidence for the association between 25(OH)D and fracture is particularly sparse for Asians [13]. Suzuki et al. [14] reported higher prevalence of experience of falls in community-dwelling elderly having a 25(OH)D level less than 20 ng/mL.

The threshold of 25(OH)D for fracture remains unclear in Asians. We, therefore, sought to investigate the associations between 25(OH)D and vertebral, proximal femur, and long bone fractures in a primary care cohort of Japanese postmenopausal women. Furthermore, the potential selection bias in this cohort was evaluated by the comparison of the baseline data with the National Health and Nutrition Survey (NHNS) and with community dwelling cohort studies using a propensity score method.

Materials and methods

Subjects

The Nagano Cohort Study is an ongoing cohort study of outpatients at a primary care institute in Nagano Prefecture, Japan [15]. Study participants were postmenopausal ambulatory volunteers over 50 years of age who were recruited among patients who visited this institute and who were assessed for eligibility by two practitioners (MS and YS). Between April 1993 and August 2011, 3212 postmenopausal women were enrolled. The patients with critical illness, chronic alcoholism, severe psychological disorders who could not decide for themselves whether to participate in the study, and bed bound conditions were not registered in the Nagano cohort study. The exclusion criteria for the current analysis were secondary osteoporosis (e.g., osteopenia with hyperparathyroidism, hyperthyroidism, chronic kidney disease, or osteomalacia) and previous or current use of glucocorticoids, warfarin or anti-cancer drugs. Although some drugs were known to affect bone metabolism, those patients treated with proton pump inhibitor or with statins, were not excluded. Women with premature menopause and osteoporosis patients treated by medications such as active vitamin D_3, vitamin K_2, selective estrogen receptor modulators (SERMs), or bisphosphonates were not excluded. A total of 1470 individuals were included in this analysis after exclusion of 245 cases of secondary osteoporosis and the patients treated with warfarin or anti-cancer drugs, 1098 individuals who were not followed for more than 1 year, and 399 individuals in whom 25(OH)D was not measured. The ethics committee of the Research Institute and Practice for Involutional Diseases approved the Nagano cohort study protocol. We obtained comprehensive written informed consent from all subjects.

Baseline data collection

At baseline, anthropometric indices including body weight and body height were measured. Subjects were also interviewed about lifestyle factors (smoking habit, alcohol consumption, past and present occupation) and medical history (age at menopause, presence of pain and comorbidities, such as diabetes mellitus, hypertension, dyslipidemia and past history of cancer).

The diagnosis of osteoporosis was made in accordance with the WHO criteria in which osteoporosis was defined as BMD less than 2.5 SD of the YAM. The BMD of the lumbar spine was measured at baseline using dual-energy X-ray absorptiometry (Lunar DPX-L or DPX-IQ or Prodigy; GE Lunar Corporation, Madison, WI), and a quality assurance test was performed on every measurement to detect machine drift. The inter-assay variance of the lumbar BMD measurement in our laboratory was 0.5 ± 0.5 % (CV ± SD) [15]. A major osteoporotic fracture was defined as a clinical vertebral fracture or fractures at the proximal femur, distal forearm, or proximal humerus.

Serum 25-OHVD was measured using a competitive protein-binding assay after extraction and purification of the samples using HPLC at Teijin Bio Science Laboratories (Tokyo, Japan) and Mitsubishi Chemical Medience (Tokyo,

Japan) [16]. Serum level of PTH was measured by the intact PTH CLEIA kit (Mitsubishi Chemical Medience Corporation, Tokyo, Japan). Underweight, overweight, and obesity were defined by a body mass index (BMI) of less than 18.5 kg/m^2, between 25 and 29 kg/m^2, or 30 kg/m^2 or more, respectively. Participants with a HbA_{1C} value of 6.5 % (Japan Diabetes Society value) or more or who were receiving antihyperglycemic treatment were considered to have Type 2 diabetes. Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease formula: eGFR (mL/min/1.73 m^2) = $186.3 \times Cr^{-1.154} \times Age^{-0.203} \times 0.742 \times 0.881$. Back pain was defined as any symptom of pain in the back trunk area regardless of the degree or consistency of the pain [17].

Endpoints

Endpoints were the incidence of vertebral fracture, proximal femur fracture, and long bone fracture using the person-year method of analysis. Incident vertebral fractures include both new clinical and morphometric fractures. Morphometric vertebral fractures were evaluated based on radiographs by the semi-quantitative visual method [18]. A validation analysis of our semi-quantitative method for analyzing incident vertebral fracture was reported elsewhere [19]. Radiographs were taken at baseline, during the follow-up period annually, and when a patient complained of fracture-related symptoms. Proximal femur and long bone fractures were identified from medical records or confirmed by additional radiographs. The accumulation of person-years at risk began at the registration of each patient and ended at the date of death the date of confirmation of incident fracture, date of lost to follow-up, date of the transfer the patients to the other hospital because of worsening of present illness or date of last visit before August, 2011. During follow-up, we asked participants to visit the institute regularly. We attempted to contact participants by telephone or letter when it became evident that they were at risk for becoming lost to follow-up.

Statistical analysis

Baseline characteristics and laboratory measurements were described by mean ± SD or as a percentage and were compared between groups with cutoff values of 25(OH)D (20 and 25 ng/mL) by trend tests using general linear models or logistic regression models. The distribution of 25(OH)D was depicted by box and whisker plots. The range and middle bar of the box and whisker plots represents third/first quartile and median, the size of the box is proportional to the number of patients, the whiskers are drawn to the most extreme points in the group that lie within the box plus or minus 1.5 times the inter-quartile range, and outliers are identified with squares. Rate ratios with 95 % confidence intervals (CI) were estimated by multivariate Poisson regression models with the following adjustment variables throughout: lumbar or femur BMD < -2.5 SD of the YAM, age, weight, diabetes mellitus, PTH, eGFR, prior fracture, presence of back pain, and treatments by bisphosphonates, SERMs, and active vitamin D_3. To explore potential nonlinear relationships, we estimated the spline function and 95 % CI of the association between 25(OH)D and incidence rates of fractures using multivariate-adjusted generalized additive models. Missing data were treated by the multiple imputation method using the adjustment variables. All reported p values are two-tailed, and $p < 0.05$ was taken to indicate statistical significance. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

Baseline characteristics of the 1470 Japanese postmenopausal women are summarized in Tables 1 and 2. We initially compared the baseline data with those of community dwelling Japanese women from the National Health and Nutritional Survey (NHNS) to assess the generalizability of the present study. We used NHNS data in 2003 since 2003 is the median year of registration in the present study. There were no notable differences in the numerical data between the NHNS and the Nagano cohort (Table 1). However, the percentages of comorbidity such as hypertension and dyslipidemia were different between these two populations. These discrepancies may be attributable to the differences in diagnostic criteria. Since the reference value of BMD was not available in the NHNS, we utilized the Z scores for each bone sites, which were installed in the machine by the manufacturer. The Z scores of both lumbar BMD and total femur were within ±0.5, suggesting that the BMD in each site was nearly equal to the reference population at each decade. Furthermore, we compared the baseline data with independent community dwelling populations, namely the Miyama and Taiji cohorts [20, 21], in terms of propensity score, the probability of exposure to 25(OH)D <25 ng/mL conditional on age, height, weight, prior fracture, back pain, lumbar BMD, rheumatoid arthritis and smoking status. The mean ± SD of propensity score in the Nagano cohort was 0.77 ± 0.03, while 0.76 ± 0.03 in the Miyama and Taiji cohorts ($p = 0.10$), suggesting no evidence for selection bias. As shown in Table 2, 49.6 % of the participants had a 25(OH)D value of less than 20 ng/mL and 27.8 % had a 25(OH)D value of 20–24 ng/mL. As expected, a lower 25(OH)D value correlated significantly with elevated PTH

Table 1 Baseline characteristics of the 1470 postmenopausal women in comparison with the National Health and Nutritional Survey in 2003

Age category		Total	40–49 years	50–59 years	60–69 years	≥70 years
Height (cm)	Reference	153.0 ± 7.1[a]	156.2 ± 5.1	153.7 ± 5.6	150.5 ± 5.2	146.2 ± 6.5
	(N)	(3190)	(476)	(662)	(690)	(656)
	Nagano	150.8 ± 6.5	156.1 ± 5.5	153.6 ± 5.2	151.1 ± 5.6	146.7 ± 6.2
	(N)	(1470)	(136)	(392)	(447)	(492)
Weight (kg)	Reference	52.8 ± 8.9	55.2 ± 8.8	54.3 ± 8.6	53.3 ± 8.3	49.6 ± 8.7
	Nagano	51.2 ± 8.0	53.8 ± 8.2	53.4 ± 8.3	52.1 ± 7.7	47.9 ± 8.1
BMI (kg/m^2)	Reference	22.6 ± 3.6	22.6 ± 3.5	23.0 ± 3.4	23.6 ± 3.5	23.2 ± 3.6
	Nagano	22.5 ± 3.2	22.1 ± 3.1	22.6 ± 3.3	22.8 ± 3.1	22.2 ± 3.3
SBP (mmHg)	Reference	128.7 ± 21.3	122.2 ± 16.0	130.8 ± 18.5	138.8 ± 20.1	142.6 ± 18.9
	Nagano	142.0 ± 24.5	128.7 ± 20.0	134.0 ± 22.3	140.2 ± 22.6	151.8 ± 24.9
DBP (mmHg)	Reference	76.5 ± 11.8	76.2 ± 10.6	80.2 ± 14.7	81.1 ± 10.9	78.1 ± 11.8
	Nagano	83.0 ± 13.4	81.0 ± 13.7	81.6 ± 13.5	82.5 ± 12.4	84.8 ± 14.1
HbA_{1C} (%, NGSP)	Reference	5.70 ± 0.78	5.59 ± 0.66	5.78 ± 0.89	5.93 ± 0.80	5.97 ± 0.91
	Nagano	5.90 ± 1.04	5.59 ± 0.56	5.92 ± 0.78	6.02 ± 1.01	5.99 ± 1.28
Triglycerides (mg/dL)	Reference	123.9 ± 89.4	122.5 ± 32.1	131.7 ± 88.8	148.9 ± 81.2	132.1 ± 9.1
	Nagano	142.2 ± 80.6	133.2 ± 90.9	149.6 ± 87.5	143.0 ± 78.5	138.2 ± 73.6
Total cholesterol (mg/dL)	Reference	206.3 ± 31.5	199.7 ± 34.7	219.5 ± 34.3	218.2 ± 34.6	207.8 ± 31.3
	Nagano	191.1 ± 32.9	204.6 ± 35.1	202.7 ± 37.0	197.8 ± 37.0	200.4 ± 36.7
Hypertension	Reference	44.6 %	12.7 %	36.3 %	60.0 %	73.2 %
	Nagano	42.8 %	16.1 %	28.4 %	40.3 %	63.7 %
Dyslipidemia	Reference	34.1 %	16.8 %	37.6 %	50.6 %	44.1 %
	Nagano	28.0 %	22.6 %	32.0 %	31.4 %	23.4 %
Z score	Lumbar	−0.13 ± 1.47	0.07 ± 1.41	−0.36 ± 1.43	−0.17 ± 1.37	0.04 ± 1.58
For BMD[b]	Femur total	0.32 ± 1.01	−0.01 ± 1.30	0.37 ± 0.98	0.43 ± 0.87	0.28 ± 1.04

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMD* bone mineral density

[a] The National Health and Nutritional Survey includes people 20 years old or over, while Nagano cohort consisted of subjects aged over 40 years

[b] *Z* score for BMD was obtained from the manufacture's reference value, which was calculated in over 20,000 Japanese women

levels, but there were no significant associations between 25(OH)D values and the other baseline characteristics. Accordingly, distributions of 25(OH)D were similar across weight and osteoporosis categories but there was a non-monotonic association with age (Fig. 1, box and whisker plots). In contrast, the average 25(OH)D level in cases with incident proximal femur fracture or long bone fracture was significantly lower than in non-cases (Fig. 1).

Types of incident fractures according to 25(OH)D status

Over a mean follow-up period of 7.2 years, a total of 287 clinical and 351 morphometric vertebral fractures and 158 long bone fractures (47 forearm, 43 proximal femur, 11 rib, 5 humerus, and 52 other sites) were observed over a total of 10567.0 person-years. A total of 1050 patients were followed until August, 2011 or for 3 years or more, and of the remaining 420 patients, 33 patients died and 387 patients were lost to follow-up. Multiple vertebral fractures occurred in 156 subjects. The types of incident fractures according to 25(OH)D status are shown in Table 3. Crude incidence rates of vertebral fractures, proximal femur fractures, and long bone fractures per 1000 person-years were 60.4 (95 %CI: 55.9–65.3), 4.1 (95 %CI: 3.0–5.5), and 15.0 (95 %CI: 12.8–17.5), respectively.

Contribution of 25(OH)D to incident fractures

To explore potentially non-linear relationships between the 25(OH)D level and incident fractures, we fitted the generalized additive models adjusted for confounding factors (Fig. 2). As shown graphically, clear decreasing trends according to higher values for 25(OH)D were shown only by the curves for the proximal femur and long bone fractures, with the relationships appearing to be non-linear. Notably, the incidence rate of proximal femur fracture was very low in women with 25(OH)D over 25 ng/mL, probably leading to the decreasing trend in long bone fractures. We also fitted multivariate Poisson regression models with

Table 2 Baseline characteristics of the 1470 postmenopausal women according to 25(OH)D status

	<20 ng/mL ($N = 729$)		20–24 ng/mL ($N = 409$)		≥25 ng/mL ($N = 332$)		p*
	Mean	SD	Mean	SD	Mean	SD	
25(OH)D (ng/mL)	15.4	3.1	22.0	1.4	29.4	4.4	<0.01
Age (years)	63.9	11.5	63.5	10.5	63.6	9.2	0.56
BMI (kg/m^2)	22.5	3.4	22.6	3.0	22.5	3.1	0.85
<18.5 kg/m^2 (%)	10.4 %		6.8 %		8.7 %		0.21
25-29 kg/m^2 (%)	18.0 %		18.6 %		17.5 %		0.90
≥30 kg/m^2 (%)	1.7 %		1.2 %		1.2 %		0.96
Prior fracture (%)	21.4 %		23.2 %		20.8 %		0.73
Prior vertebral fracture (%)	19.5 %		19.1 %		19.3 %		0.92
Prior proximal femur fracture (%)	0.6 %		0.7 %		0.6 %		0.86
Other prior fracture (%)	1.4 %		3.7 %		1.2 %		0.67
Back pain (%)	29.6 %		30.6 %		31.9 %		0.45
Lumbar BMD (T score)	−1.83	1.52	−1.85	1.31	−1.94	1.35	0.27
Femur BMD (T score)	−1.54	1.18	−1.43	1.16	−1.43	1.11	0.26
Osteoporosis (%)	35.5 %		32.0 %		35.5 %		0.80
Bisphosphonates (%)	10.3 %		12.0 %		12.0 %		0.34
SERM (%)	2.3 %		2.4 %		2.1 %		0.86
Active vitamin D_3 (%)	14.7 %		15.9 %		14.2 %		0.94
Rheumatoid arthritis (%)	12.0 %		13.5 %		11.2 %		0.87
Diabetes mellitus (%)	6.9 %		8.3 %		9.6 %		0.11
Smoker (%)	2.5 %		1.7 %		2.1 %		0.58
PTH (pg/mL)	40.3	17.1	36.3	13.3	35.0	12.8	<0.01
eGFR (mL/min/1.73 m^2)	63.9	20.1	65.0	23.1	63.3	20.0	0.83
Pentosidine (pmol/mgCr)	46.3	25.9	44.7	17.5	45.0	21.7	0.44
Homocysteine (nmol/mL)	9.1	3.3	9.2	3.6	8.7	2.9	0.25
BAP (IU)	32.2	13.4	32.2	11.8	31.7	10.6	0.68
NTX (nM/mMCr)	53.1	29.4	53.3	27.1	53.1	23.8	0.99
Osteocalcin (ng/mL)	8.0	5.7	7.9	3.7	7.7	3.4	0.42
ucOC (ng/mL)	4.69	3.03	5.07	3.69	4.37	2.97	0.53

BMI body mass index, *BMD* bone mineral density, *SERM* selective estrogen receptor modulator, *PTH* parathyroid hormone, *eGFR* estimated glomerular filtration rate, *BAP* bone alkaline phosphatase, *NTX* N-terminal telopeptide, *ucOC* undercarboxylated osteocalcin

* Trend tests

various cutoff values of 25(OH)D, yielding the largest rate ratios for proximal femur and long bone fractures were observed at 24 and 25 ng/mL, respectively, suggesting a potential threshold of 25(OH)D at 25 ng/mL (Table 4).

Table 5 shows rate ratios for vertebral, proximal femur, and long bone fractures according to 25(OH)D status classified as either below 25 ng/mL, at 25 ng/mL, or above. As shown, incidence rates of vertebral fracture were not different between the two 25(OH)D groups. In contrast, incidence rates of proximal femur and long bone fractures in the low 25(OH)D group were higher than in the high 25(OH)D group by 2.71 (95 %CI: 0.94–7.83, $p = 0.07$) and 2.20 (95 %CI: 1.37–3.53, $p < 0.01$), respectively, and the rate ratios were substantially higher than the rate ratios of a BMD level lower than −2.5 SD of the YAM (1.52 for proximal femur fracture and 1.54 for long bone fracture). The association between 25(OH)D and long bone fracture remained significant ($p < 0.01$) if we excluded women with past history of proximal femur fracture ($N = 9$). The association between 25(OH)D and long bone fracture remained significant if we did not adjust for BMD and PTH (rate ratio: 2.24, 95 %CI: 1.40–3.59, $p < 0.01$), if we excluded 9 women with past history of proximal femur fracture (rate ratio: 2.22, 95 %CI: 1.38–3.57, $p < 0.01$), or if we excluded 219 women treated by active vitamin D_3 (rate ratio: 2.64, 95 %CI: 1.50–4.64, $p < 0.01$).

Discussion

There is emergent evidence for ethnic differences in the associations between vitamin D deficiency and fractures

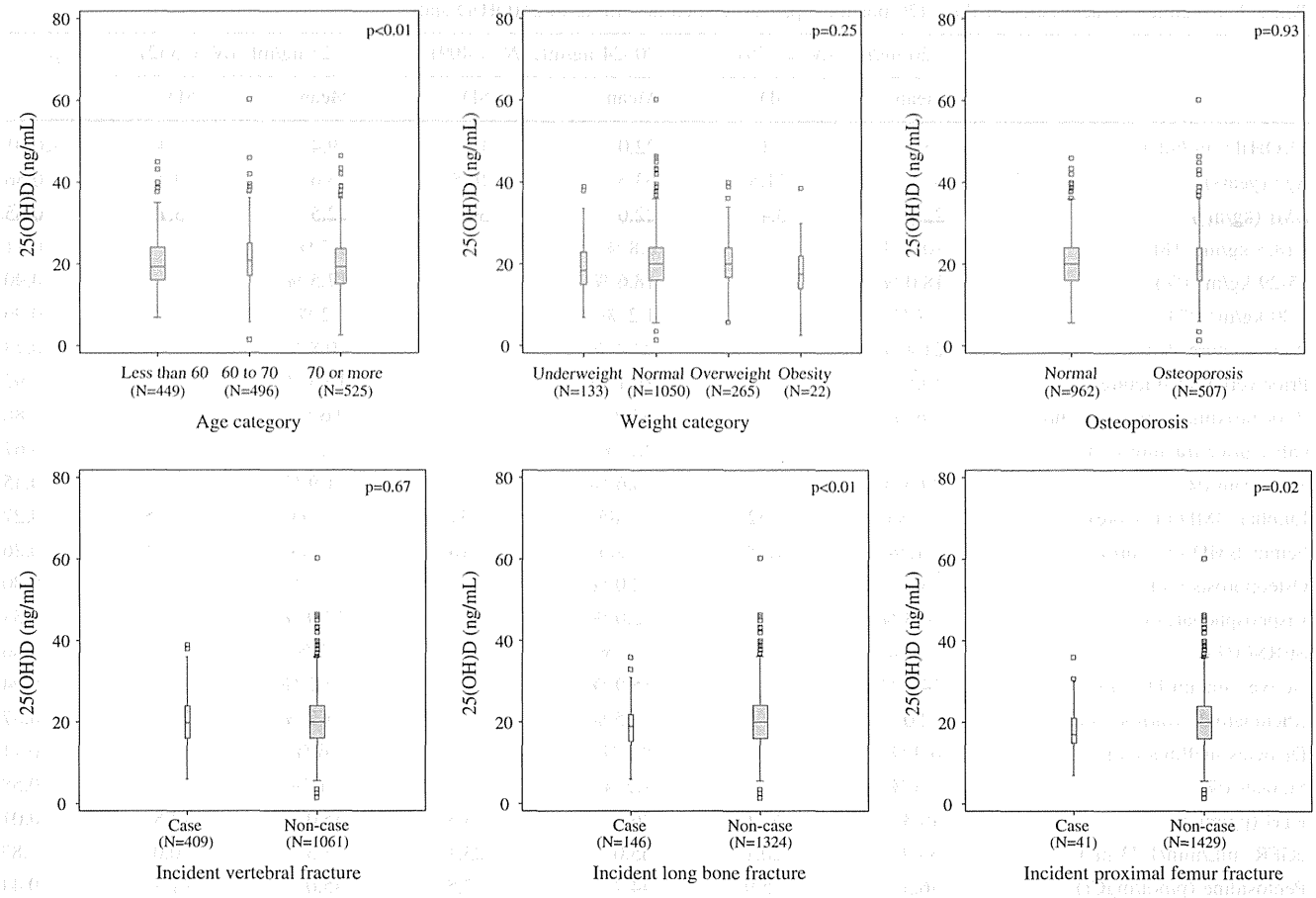

Fig. 1 Box and whisker plots of 25(OH)D according to (**a**) age, (**b**) weight, and (**c**) osteoporosis, (**d**) incident cases and non-cases of vertebral fracture, (**e**) incident cases and non-cases of long bone fracture, and (**d**) incident cases and non-cases of proximal femur fracture. Distributions of 25(OH)D were similar across weight and osteoporosis categories but there was a non-monotonic association with age. The average in cases with incident proximal femur fracture or long bone fracture was significantly lower than in non-cases. The *range* and *middle bar* of the *box* and *whisker plots* represents third/first quartile and median, the size of box is proportional to the number of patients, the whiskers are drawn to the most extreme points in the group that lie within the box plus or minus 1.5 times the inter-quartile range, and outliers are identified with *squares*

Table 3 Type of incident fracture in the 1470 postmenopausal women according to 25(OH)D status

	<20 ng/mL (N = 729)		20–24 ng/mL (N = 409)		≥25 ng/mL (N = 332)	
	Frequency	Proportion (%)	Frequency	Proportion (%)	Frequency	Proportion (%)
Vertebral fracture	316	43.3	162	39.6	160	48.2
Clinical vertebral fracture	139	19.1	81	19.8	67	20.2
Major osteoporotic fracture	191	26.2	109	26.7	82	24.7
Long bone fracture	85	11.7	53	13.0	20	6.0
Forearm fracture	24	3.3	14	3.4	9	2.7
Proximal femur fracture	28	3.8	11	2.7	4	1.2
Rib fracture	8	1.1	2	0.5	1	0.3
Humerus fracture	0	0.0	3	0.7	2	0.6

[11, 12], but data on Asian populations are sparse [13], making the most reliable assessment of vitamin D status, serum 25(OH)D, underused, at the least, in Japan. This cohort study of 1470 Japanese postmenopausal women in a primary care setting revealed that the increase in incidence rate of long bone fracture caused by low 25(OH)D level is 2-fold even at values below 25 ng/mL, which is slightly higher than the threshold for vitamin D insufficiency previously proposed in Japan [8].

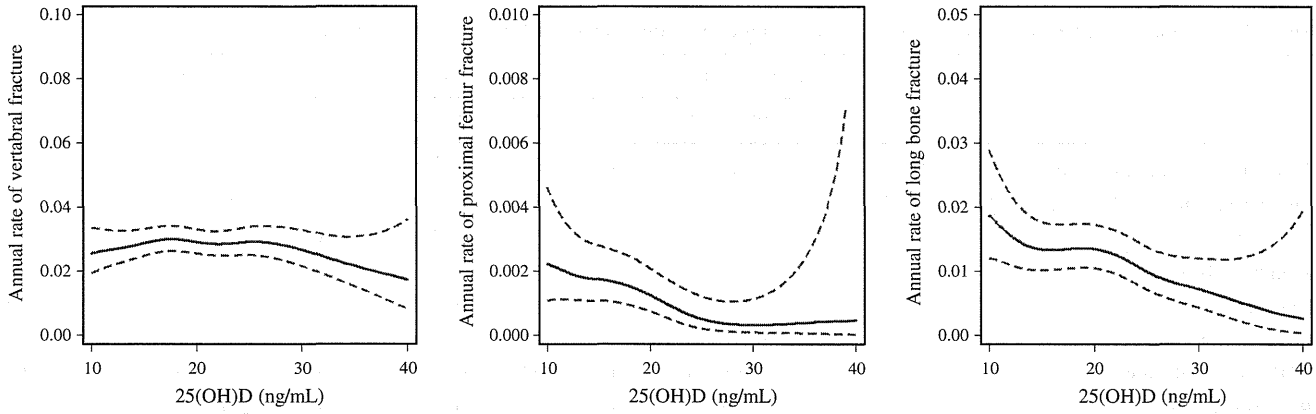

Fig. 2 Annual incidence rates (*solid line*) and 95 % confidence interval (*broken line*) of vertebral (*left*), proximal femur (*middle*) and long bone (*right*) fractures in relation to 25(OH)D level estimated by multivariate generalized additive models. Clear decreasing trends according to higher values for 25(OH)D were shown only by the curves for proximal femur and long bone fractures, with the relationships appearing to be non-linear

Table 4 Rate ratios of 25(OH)D with various cutoff values for vertebral, proximal femur and long bone fractures

	Vertebral fracture			Proximal femur fracture			Long bone fracture		
	RR	95 % CI	*p*	RR	95 % CI	*p*	RR	95 % CI	*p*
25(OH)D < 21 ng/mL (816 [55.5 %])†	1.13	(0.96–1.33)	0.13	2.17	(1.06–4.43)	0.03	1.49	(1.07–2.08)	0.02
25(OH)D < 22 ng/mL (901 [61.3 %])†	1.13	(0.96–1.33)	0.15	2.01	(0.94–4.29)	0.07	1.47	(1.05–2.08)	0.03
25(OH)D < 23 ng/mL (1011 [68.8 %])†	1.04	(0.88–1.23)	0.67	2.98	(1.15–7.73)	0.02	1.58	(1.09–2.30)	0.02
25(OH)D < 24 ng/mL (1069 [72.7 %])†	1.01	(0.85–1.20)	0.93	3.41	(1.19–9.73)	0.02	2.07	(1.36–3.17)	<0.01
25(OH)D < 25 ng/mL (1138 [77.4 %])†	1.01	(0.84–1.22)	0.88	2.71	(0.94–7.83)	0.07	2.20	(1.37–3.53)	<0.01
25(OH)D < 26 ng/mL (1190 [81.0 %])†	1.13	(0.93–1.38)	0.22	2.30	(0.79–6.67)	0.12	1.87	(1.15–3.03)	0.01
25(OH)D < 27 ng/mL (1247 [84.8 %])†	1.18	(0.95–1.47)	0.13	2.06	(0.71–6.01)	0.19	1.93	(1.13–3.30)	0.02
25(OH)D < 28 ng/mL (1291 [87.8 %])†	1.18	(0.93–1.50)	0.17	1.64	(0.56–4.81)	0.37	1.73	(0.97–3.07)	0.06
25(OH)D < 29 ng/mL (1324 [90.1 %])†	1.18	(0.91–1.53)	0.21	1.99	(0.58–6.89)	0.27	1.70	(0.92–3.16)	0.09
25(OH)D < 30 ng/mL (1350 [91.8 %])†	1.23	(0.93–1.64)	0.15	1.77	(0.50–6.20)	0.37	1.56	(0.81–2.98)	0.18

RR rate ratio, *CI* confidence interval

* Estimated by separate multivariate Poisson regression models including lumbar bone mineral density for vertebral fracture and proximal femur bone mineral density for femur and long bone fracture

† Numbers and proportions of subjects below the cutoff values

The associations between 25(OH)D and fractures were significant only for long bone fracture and similar site-specific relationships were found in past studies. In a clinical trial of Japanese women with osteoporosis, a 25(OH)D level less than 20 ng/mL was significantly associated with a three-fold increase in non-vertebral weight-bearing bone fractures but not with bone fractures at other sites [22]. A recent pooled analysis suggested the effect of vitamin D supplementation is slightly different between hip and non-vertebral fractures [23]. The mechanism of these findings would be explained by the pleiotropic effects of vitamin D. Vitamin D is not only associated with calcium metabolism but is also involved in the correct renewal and mineralization of bone [24] and has a direct stimulatory effect on muscle tissue and neurological control of balance/neuromuscular function [25], both of which contribute to falls [14], sarcopenia [26], and mortality [27]. In fact, supplementation of vitamin D has been shown to reduce the risks of falls and incident non-vertebral fractures [23, 28–33]. Furthermore, Asian women are known to have high risks of hip fracture [34]. The site-specific associations in this study may be, therefore, attributable to the effects on muscular weakness, which can result in increase in long bone fracture. On the other hand, a nested case–control study in the Women's Health Initiative reported a positive association between higher 25(OH)D levels and self-reported fractures in a subset of Asian women [11]. This discrepancy with our results may be attributable to unadjusted BMD. In the nested case–control study, women with 25(OH)D below 20 ng/mL had a relatively high BMI, which was reported to be positively associated with femoral neck BMD [35]. In other words,

Table 5 Rate ratios of 25(OH)D below 25 ng/mL for vertebral, proximal femur and long bone fractures adjusted for risk factors of fracture

	Vertebral fracture			Proximal femur fracture			Long bone fracture		
	RR	95 % CI	*p*	RR	95 % CI	*p*	RR	95 % CI	*p*
25(OH)D < 25 ng/mL, yes/no	1.01	(0.84–1.22)	0.88	2.71	(0.94–7.83)	0.07	2.20	(1.37–3.53)	<0.01
Lumbar or femur BMD < -2.5 SD of the YAM	1.61	(1.33–1.94)	<0.01	1.52	(0.67–3.45)	0.32	1.54	(1.02–2.33)	0.04
Age, +10 years	1.78	(1.61–1.97)	<0.01	3.96	(2.45–6.38)	<0.01	1.43	(1.18–1.74)	<0.01
Weight, +10 kg	1.20	(1.07–1.33)	<0.01	0.88	(0.56–1.36)	0.55	0.94	(0.75–1.17)	0.56
Diabetes mellitus, yes/no	0.88	(0.65–1.20)	0.42	2.38	(0.96–5.93)	0.06	1.54	(0.93–2.56)	0.09
PTH, +10 pg/mL	0.96	(0.91–1.01)	0.15	1.07	(0.90–1.28)	0.43	1.04	(0.94–1.15)	0.46
eGFR, +10 mL/min/1.73 m^2	1.02	(0.98–1.06)	0.24	0.98	(0.82–1.16)	0.77	1.03	(0.96–1.12)	0.39
Prior fracture, yes/no	1.86	(1.53–2.25)	<0.01	1.69	(0.84–3.43)	0.14	2.02	(1.37–2.98)	<0.01
Back pain, yes/no	1.41	(1.19–1.66)	<0.01	1.59	(0.84–3.01)	0.15	0.88	(0.62–1.24)	0.47
Treated by bisphosphonates, yes/no	0.91	(0.72–1.15)	0.45	0.39	(0.11–1.30)	0.13	0.90	(0.55–1.47)	0.68
Treated by SERM, yes/no	1.05	(0.63–1.74)	0.86	0.93	(0.12–7.14)	0.94	0.32	(0.04–2.28)	0.25
Treated by active vitamin D_3, yes/no	1.16	(0.95–1.40)	0.14	1.03	(0.48–2.24)	0.93	0.95	(0.62–1.45)	0.80

femoral neck BMD may be a potential confounding factor in the causal pathway from 25(OH)D to fracture.

The prevalence of 25(OH)D levels below 20 ng/mL in this cohort was 49.6 %, an estimate that is comparable to that in an international epidemiological study (47.0 %) [9]. The latitude of the residents of this cohort was 36°N, which is approximately in central Japan (26–43°N), where the duration of sunshine during the year is average in Japan; therefore, the present population would be expected to have 25(OH)D levels around the average for Japan. Previous studies in other regions of Japan reported estimates of a prevalence of 25(OH)D levels below 20 ng/mL of 21.6 % in Tokyo [14], 75.7 % in Chiba [8], and 80.7 % in Shimane [36]. The prevalence of such low levels of 25(OH)D in this cohort was not higher than in the other parts of Japan (Chiba or Shimane) with the exception of Tokyo. The prevalence of low 25(OH)D can be variable due not only to latitude but also to age, gender, genetic traits, skin pigmentation, cultural behavior (clothing, nutrition intake, outdoor activity), degree of affluence, and season [2, 9, 10]. In fact, a multinational study of 18 countries reported that the prevalence of low 25(OH)D was 41.2 % in Europe, 73.3 % in the Middle East, 55.2 % in Asia, 37.4 % in Latin America, and 44.1 % in Australia, but the prevalence in this cohort, 49.6 %, was close to the estimate for Asia. We suggested a potential threshold of 25(OH)D at 25 ng/mL as the value that yields the largest rate ratios for proximal femur and long bone fractures (Table 4), but it is notable that this value is not universally appropriate. For example, in a setting of screening women requiring lifestyle intervention, this value may be too high given that 77 % of subjects had 25(OH)D values lower than 25 ng/dL. Further research is warranted for cutoff values suitable for specific objectives.

Our findings should be interpreted in the context of study limitations. First, serum for measurements was collected without regard to specific seasons although seasonal variations in 25(OH)D concentration are well-known. Season-specific targets for 25(OH)D concentration may be more appropriate [37] and worthy of further research. Second, our study population consisted of women in one area in Japan, limiting the ability for comparisons among general populations or patient populations comprising different ethnicities. Third, the duration of registration ranged from 1993 to 2011, leading to inclusions of subjects with a variety of past dietary habits and with birth cohort effects. Bias caused by the second and third issues is expected to be small, however, since the baseline data in the present population were not different far from the NHNS population and the Miyana and Taiji cohorts. Fourth, we did not assess falls although a fall is an important outcome. Finally, our analysis was likely to be influenced by several other sources of bias, such as selection bias, informative censoring, and bias caused by treatment for osteoporosis initiated or switched during follow-up. Unfortunately reasons for being lost to follow-up were not available for some patients.

In conclusion, the 25(OH)D value is a leading factor indicating the degree of risk for long bone fracture comparable to BMD in Japanese postmenopausal women. The contribution of 25(OH)D to risk of fracture is substantial even below 25 ng/mL and is possibly site-specific. We recommend measuring the serum 25(OH)D level in primary care settings.

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Conflict of interest All of the authors state that they have no conflicts of interest.

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ORIGINAL ARTICLE

Mutual associations among musculoskeletal diseases and metabolic syndrome components: A 3-year follow-up of the ROAD study

Noriko Yoshimura[1], Shigeyuki Muraki[2], Hiroyuki Oka[1], Sakae Tanaka[3], Hiroshi Kawaguchi[4], Kozo Nakamura[5], and Toru Akune[2]

[1]*Department of Joint Disease Research, 22nd Century Medical and Research Center, University of Tokyo, Tokyo, Japan,* [2]*Department of Clinical Motor System Medicine, 22nd Century Medical and Research Center, University of Tokyo, Tokyo, Japan,* [3]*Department of Orthopaedic Surgery, Sensory and Motor System Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan,* [4]*JCHO Tokyo Shinjuku Medical Center, Shinjyuku-ku, Tokyo, Japan, and* [5]*National Rehabilitation Center for Persons with Disabilities, Saitama, Japan*

Abstract

Objective. This study aimed to assess the mutual associations between musculoskeletal diseases (knee osteoarthritis [KOA], lumbar spondylosis [LS], osteoporosis [OP]) and metabolic syndrome components (obesity [OB], hypertension [HT], dyslipidemia [DL], impaired glucose tolerance [IGT]).

Methods. Of the 1,690 participants (596 men, 1,094 women) at baseline, 1,384 individuals (81.9%; 466 men, 918 women) had complete data at the first follow-up in 2008. Logistic regression analysis included the occurrence or nonoccurrence of the musculoskeletal diseases or metabolic components as the outcome variable and the remaining musculoskeletal diseases and metabolic components at baseline as explanatory variables, adjusted for age, sex, residential region, smoking, and alcohol consumption.

Results. The risk of KOA occurring increased significantly with HT (odds ratio [OR], 2.57; 95% confidence interval [CI], 1.22–5.42; $p = 0.013$) and IGT (OR, 1.99; 95%CI, 1.07–3.70; $p = 0.029$). The risk of OP occurring at the lumbar spine increased with OP at the femoral neck (OR, 4.21; 95%CI 1.46–12.1; $p = 0.008$), and vice versa (OR, 2.19; 95%CI, 1.01–479; $p = 0.047$). KOA increased the risk of HT (Kellgren–Lawrence [KL] grade = 0, 1 vs. KL = 2: OR, 1.84; 95%CI, 1.09–3.12; $p = 0.024$) and DL (KL = 0, 1 vs. KL ≥ 3: OR, 1.66; 95%CI, 1.05–2.61; $p = 0.029$) occurring. Reciprocal relationships existed between the presence of metabolic components and the occurrence of the other metabolic components.

Conclusion. Mutual relationships existed between the occurrence and presence of musculoskeletal diseases, particularly KOA, and metabolic syndrome components.

Keywords

Incidence, Knee osteoarthritis, Lumbar spondylosis, Metabolic risk factor, Osteoporosis

History

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Introduction

The rapid aging of the Japanese society has increased the number of disabled elderly individuals requiring support or long-term care. The leading cause of disability is cardiovascular disease (21.5%), followed by dementia (15.3%), senility (13.7%), osteoarthritis (OA) (10.9%), and falls/osteoporotic fractures (10.2%) [1]. Owing to the similarity between the rate for cardiovascular disease and that for the combined contribution of musculoskeletal diseases (OA and osteoporosis [OP]), prevention for these diseases should be as important as that for cardiovascular disease, in order to reduce disability.

Most patients with cardiovascular disease have multiple risk factors for cardiovascular disease [2]; the presence of a specific combination of these risk factors (obesity [OB], hypertension [HT], dyslipidemia [DL], and impaired glucose tolerance [IGT] [3]) leads to metabolic syndrome—a condition that predisposes the affected individual to cardiovascular disease-associated morbidity and mortality.

It has been suggested that a significant relationship may exist between the components of metabolic syndrome and musculoskeletal diseases. Several studies have reported that OB or increased body mass index (BMI) increases the risk of the onset of knee osteoarthritis (KOA) [4–9]. We have previously confirmed that the presence of HT and IGT are risk factors for the occurrence of KOA, independent of OB [10]. In contrast, there have been few reports regarding a significant relationship between DL and musculoskeletal diseases.

Compared to the number of reports regarding the association between metabolic syndrome components and KOA, there have been relatively few reports regarding the relationship between metabolic syndrome components and lumbar spondylosis (LS), while we have previously reported a significant association between BMI and the incidence of LS [11].

Regarding the metabolic syndrome components and OP, a meta-analysis showed that high BMI is a protective factor for most osteoporotic fracture sites [12]. A review of cardiovascular medications used for HT reported that the medications were

Correspondence to: Noriko Yoshimura, MD, PhD, Department of Joint Disease Research, 22nd Century Medical and Research Center, Graduate School of Medicine, University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-8655, Japan. Phone: +81-3-5800-9178. Fax: +81-3-5800-9179. E-mail: yoshimuran-ort@h.u-tokyo.ac.jp

associated with increased bone mineral density (BMD) and/or a reduction in osteoporotic fractures [13]. A systematic review indicated that type 2 diabetes mellitus increases the risk of osteoporotic fractures [14]. However, the influence of high-density lipoprotein cholesterol (HDL-cho) levels on OP remains controversial [15,16].

Regarding mutual relationships between the presence and occurrence of musculoskeletal diseases, we have previously reported that the presence of OP in women appears to reduce the occurrence of OA at the lumbar spine [17].

However, to the best of our knowledge, there have been no reports regarding mutual relationships between the presence and occurrence of the musculoskeletal diseases (KOA, LS, and OP) and metabolic components (OB, HT, DL, and IGT). The present study aimed to estimate the cumulative incidence of each of the musculoskeletal diseases and metabolic syndrome components and to clarify their mutual causalities and interactions, using a large-scale, population-based cohort entitled the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study.

Patients and methods

Participants

The present study included the cohort established in 2005 for the ROAD study. Details of the cohort profile have been reported elsewhere [18,19]. In brief, from 2005 to 2007, we developed a baseline database that included clinical and genetic information on 3,040 Japanese residents (1,061 men, 1,979 women) who were recruited from resident registration listings in 3 communities with different characteristics: 1,350 subjects (465 men, 885 women) from an urban region in Itabashi, Tokyo; 864 (319 men, 545 women) from a mountainous region in Hidakagawa, Wakayama; and 826 (277 men, 549 women) from a coastal region in Taiji, Wakayama.

Of the total sample, the BMD measurement was performed only on subjects from the mountainous and coastal regions, who also underwent blood and urinary examinations. Therefore, the present study included data of those 1,690 subjects (596 men, 1,094 women).

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

Procedures in the baseline study

1) Questionnaire survey

All participants completed an interviewer-administered questionnaire modified from the Osteoporotic Fractures in Men Study [20] that contained 400 items. Lifestyle-related questions were asked regarding smoking habits, alcohol consumption, family medical history, physical activity, reproductive variables, health-related quality of life, and prescription medication use.

2) Radiographic assessment

Participants also underwent radiographic examination of both knees and the lumbar spine using anteroposterior and lateral views with weight-bearing and foot-map positioning. The radiographic severity of OA was determined according to the Kellgren–Lawrence (KL) grade: KL0, normal; KL1, slight osteophytes; KL2, definite osteophytes; KL3, joint or intervertebral space narrowing with large osteophytes; and KL4, bone sclerosis, joint or intervertebral space narrowing, and large osteophytes [21].

Radiographs of each site (vertebrae or knees) were examined by a single experienced orthopedic surgeon (SM) who was masked to the clinical status. In the present study, the maximum grade, diagnosed in at least one intervertebral level of the lumbar spine or at least one knee joint, was regarded as the subjects' KL grades. A participant with a KL grade ≥ 2 was defined as having radiographic OA.

3) Measurement of BMD

BMD was measured at the lumbar spine (L2–4) and proximal femur using dual-energy X-ray absorptiometry (DXA) (Hologic Discovery; Hologic, Waltham, MA, USA) on the same DXA equipment, and the same spine phantom was scanned daily to monitor the machine's performance in study populations from different regions. BMD of the phantom was adjusted to 1.032 (0.016) g/cm^2 ($\pm$ 1.5%) during all examinations.

OP was defined based on the World Health Organization (WHO) criteria, in which OP is diagnosed when BMD T-scores are lower than peak bone mass by -2.5 SDs [22]. The mean BMD of L2–4, measured using the Hologic DXA in Japan, was reported to be 1.011 (0.119) g/cm^2 for both young adult men and women. Therefore, we defined OP of the lumbar spine as L2–4 BMD < 0.714 g/cm^2. Further, the mean BMD of the femoral neck in young adult men and women was reported to be 0.863 (0.127) g/cm^2 and 0.787 (0.109) g/cm^2, respectively [23]. Therefore, we defined OP of the femoral neck as BMD < 0.546 g/cm^2 (men) and < 0.515 g/cm^2 (women).

4) Measurement of metabolic syndrome components

An experienced public health nurse measured systolic and diastolic blood pressures (BPs) using a mercury sphygmomanometer in addition to the anthropometric measurements (height, weight, and BMI). Hemoglobin A1c (HbA1c), blood glucose, HDL-cho, total cholesterol, and triglyceride levels were also measured between 09:00 and 15:00. All analyses were performed at the same laboratory within 24 h of extraction (Osaka Kessei Research Laboratories, Inc., Osaka, Japan).

In this study, definitions of metabolic syndrome components were based on criteria defined by the Examination Committee of Criteria for Metabolic Syndrome in Japan [24] and the Japan Society for the Study of Obesity [25]. However, because not all blood samples were obtained under fasting conditions, we also used indices from the National Health and Nutrition Survey in Japan, which were adopted as metabolic syndrome criteria in a previous national screening study due to the difficulty in collecting samples under fasting conditions [26]. The following definitions were used: OB, BMI > 27.5 kg/m [2,27]; HT, systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg; DL, serum HDL-cho level < 40 mg/dL; and IGT, serum HbA1c level $\geq 5.5\%$ (measured according to the Japan Diabetes Society definition, and $\geq 5.9\%$ defined by the National Glycohemoglobin Standardization Program [28]). Furthermore, subjects taking medications for HT, DL, or diabetes mellitus were regarded as having HT, DL, or IGT, respectively.

Three-year follow-up

From 2008 to 2010, the 1,690 participants were invited to attend a 3-year follow-up of the second ROAD survey, involving repetition of the baseline examinations. The same experienced orthopedic surgeon (SM), while masked to the participants' clinical status, evaluated the knee and spine radiographs and categorized them using the KL grading scale.

A new case of OA of each joint was defined as a baseline KL grade < 2 for joints and a follow-up grade ≥ 2 for at least 1 joint. A new case of OP was diagnosed when an individual who did not show OP at baseline was determined to have OP at follow-up.

New cases of OB, HT, DL, and IGT were determined in a similar manner: individuals lacking the respective status at baseline but exhibiting the status at follow-up. Furthermore, subjects being treated with medication for HT, DL, or diabetes mellitus at baseline and follow-up were regarded as having HT, DL, or IGT, respectively.

Statistical analyses

Statistical analyses were performed using STATA statistical software (STATA Corp, College Station, TX). Differences in proportions were compared using the Chi-square test. Differences in continuous variables were tested for significance using analysis of variance for multiple groups or Scheffé's least significant difference test for pairs of groups. All p values and 95% confidence intervals (CIs) of two-sided analysis are presented.

To test the associations between musculoskeletal diseases and metabolic syndrome components, we performed multivariate logistic regression analyses. Occurrence or nonoccurrence of KOA over the 3 years (0, nonoccurrence; 1, occurrence) was used as the outcome variable, and the presence of LS classified using the KL grade (0, KL grades 0 and 1; 1, KL grade 2; 2, KL grades 3 and 4), OP at L2–4, OB, HT, DL, and IGT at baseline were used as explanatory variables after adjusting for age, sex, regional differences, smoking, and alcohol consumption. Regarding LS, occurrence over the 3 years (0, absence; 1, presence) was used as the outcome variable, and the presence of KOA classified by the KL grade, OP at L2–4, OB, HT, DL, and IGT at baseline were used as explanatory variables after adjusting for the variables mentioned above. OP at L2–4 was then replaced with OP of the femoral neck, and the analyses were run again. Regarding OP of the lumbar spine L2–4, occurrence was used as the outcome variable, and KOA, LS, OP of the femoral neck, OB, HT, DL, and IGT at baseline were used as explanatory variables after adjusting for the variables mentioned above. Regarding OP of the femoral neck, occurrence was analyzed separately as the outcome variable, and KOA, LS, OP at L2–4, OB, HT, DL, and IGT at baseline were used as explanatory variables after adjusting for the variables mentioned above.

Next, the occurrence of each metabolic component (OB, HT, DL, and IGT) was analyzed as the outcome variable, while KOA, LS, OP of L2–4 or the femoral neck, and the metabolic components not used as the outcome variable at baseline were used as explanatory variables after adjusting for age, sex, residing region, smoking, and alcohol consumption. Following the multivariate logistic regression analyses, the odds ratios (ORs) were evaluated.

Results

Eligible participants

Of the 1,690 participants in the baseline survey that was performed in mountainous and coastal regions, we analyzed the data of the 1,384 subjects (81.9%; 466 men, 918 women) who completed all of the examinations at both baseline and follow-up.

Table 1 shows the baseline characteristics of the subjects who participated in both the baseline and second surveys. Regarding the musculoskeletal diseases, the prevalence of each of radiographic

Table 1. Baseline characteristics of the subjects who participated in both baseline and second surveys in the Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study.

	Total $n = 1,384$	Men $n = 466$	Women $n = 918$	p value (men vs. women)
Age, n (%)				
≤ 39 y	39 (2.8)	10 (2.1)	29 (3.2)	0.23
40–49 y	135 (9.8)	40 (8.6)	95 (10.3)	
50–59 y	298 (21.5)	99 (21.2)	199 (21.7)	
60–69 y	413 (29.8)	131 (28.1)	282 (30.7)	
70–79 y	404 (29.2)	155 (33.3)	249 (27.1)	
≥ 80 y	95 (6.9)	31 (6.7)	64 (7.0)	
Total	1,384 (100.0)	466 (100.0)	918 (100.0)	
Selected characteristics, mean (SD)				
Age, y	63.9 (11.8)	64.9 (11.6)	63.4 (11.9)	0.0246*
Height, cm	155.6 (9.0)	164.0 (7.0)	151.3 (6.7)	<0.001***
Weight, kg	56.0 (10.7)	62.1 (10.7)	52.5 (8.7)	<0.001***
Prevalence of selected characteristics, %				
Residing in a coastal area	54.1	51.9	55.2	0.245
Current smoking habit (more than once a month)	12.3	29.4	3.5	<0.001***
Current alcohol consumption (more than once a month)	40.6	68.2	26.6	<0.001***
KL grade and BMD, mean (SD)				
KL grade of the knee (worst site)	1.48 (1.12)	1.24 (1.09)	1.61 (1.12)	<0.0001***
KL grade of the knee (worst site)	2.12 (1.11)	2.29 (1.01)	2.03 (1.14)	0.002**
BMD of the lumbar spine (L2–4)	0.94 (0.20)	1.05 (0.19)	0.88 (0.18)	<0.0001***
BMD of the femoral neck	0.68 (0.14)	0.75 (0.13)	0.64 (0.13)	<0.0001***
Prevalence of musculoskeletal diseases, %				
Knee osteoarthritis (KL grade ≥ 2)	46.8	37.3	51.6	<0.001***
Lumbar spondylosis (KL grade ≥ 2)	61.6	76.2	54.3	<0.001***
Osteoporosis of the lumbar spine L2–4 (WHO criteria)	12.0	2.2	17.0	<0.001***
Osteoporosis of the femoral neck (WHO criteria)	10.8	2.6	15.0	<0.001***
Metabolic syndrome components, mean (SD)				
BMI, kg/m^2	23.1 (3.4)	23.4 (3.2)	22.9 (3.4)	0.0089**
Systolic blood pressure, mmHg	134.1 (20.4)	136.6 (18.3)	132.9 (21.4)	0.0015**
Diastolic blood pressure, mmHg	74.2 (11.4)	77.0 (11.5)	72.8 (11.0)	<0.0001***
Serum HDL-cho level, mg/dL	61.2 (15.9)	55.8 (16.1)	64.0 (15.0)	<0.0001***
Serum HbA1c level (Japan Diabetes Society), %	5.19 (0.73)	5.23 (0.85)	5.17 (0.67)	0.19
Prevalence of metabolic syndrome components, %				
Obesity	10.4	11.6	9.8	0.307
Hypertension	67.2	72.7	64.4	0.002**
Dyslipidemia	13.0	15.2	11.9	0.079
Impaired glucose tolerance	21.1	24.7	19.3	0.020*

BMD bone mineral density, *BMI* body mass index, *HbA1C* hemoglobin A1c, *HDL-cho* high-density lipoprotein cholesterol, *KL* Kellgren-Lawrence, *WHO* World Health Organization
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

KOA, OP of L2–4, and OP of the femoral neck was significantly higher in women than in men ($p < 0.001$). In contrast, the prevalence of radiographic LS was significantly higher in men than in women ($p < 0.001$). Regarding the metabolic syndrome components, the prevalence of HT and IGT was significantly higher in men than in women ($p < 0.05$).

Cumulative incidence of each musculoskeletal disease and comparison of the baseline metabolic syndrome component characteristics

Because we previously reported the age-sex distribution of the cumulative incidence of musculoskeletal diseases of the same subjects as in the present study [9,11], we report only the cumulative incidence for the total population at risk for KOA, LS, OP at L2–4, and OP at the femoral neck: 3.25%/year, 11.4%/year, 0.76%/year, and 1.83%/year, respectively.

Table 2 compares the baseline characteristics between the occurrence and nonoccurrence of the musculoskeletal diseases. The prevalence of each of LS, HT, and IGT at baseline was significantly higher with the occurrence of KOA than without (LS, $p = 0.009$; HT, $p < 0.001$; IGT, $p < 0.001$). The proportions of KOA and HT at baseline were significantly higher with the occurrence of LS than without (KOA, $p = 0.001$; HT, $p = 0.003$). The prevalence of OP of the femoral neck at baseline was significantly higher with the occurrence of OP of L2–4 than without ($p < 0.001$). Similarly, the prevalence of OP of L2–4 at baseline was significantly higher with the occurrence of OP of the femoral neck than without ($p < 0.001$). In addition, the prevalence of each of OB and HT at baseline was significantly lower with the occurrence of OP of the femoral neck than without (OB, $p = 0.031$; HT, $p = 0.009$).

Cumulative incidence of each metabolic syndrome component and comparison of baseline musculoskeletal disease characteristics

The cumulative incidence of each of OB, HT, DL, and IGT was 1.21%/year, 15.8%/year, 6.53%/year, and 4.56%/year, respectively. Table 3 compares the baseline characteristics between the occurrence and nonoccurrence of the above-mentioned metabolic components. The prevalence of DL was significantly higher with the occurrence of OB than without ($p = 0.013$), while the prevalence of OP at the femoral neck was significantly lower with the occurrence of OB than without ($p = 0.013$). The prevalence of each of KOA, OP of the lumbar spine L2–4, and OB was significantly higher with the occurrence of HT than without (KOA, $p < 0.001$; OP at L2–4, $p = 0.038$; OB, $p = 0.045$). Similarly, the prevalence of each of KOA, OP of the femoral neck, HT, and IGT were significantly higher with the occurrence of DL than without (KOA, $p = 0.005$; OP at femoral neck, $p = 0.003$; HT, $p = 0.008$; IGT, $p = 0.001$). The prevalence of OB was significantly higher with the occurrence of IGT than without ($p = 0.010$).

Mutual associations among musculoskeletal diseases and metabolic syndrome components during the 3-year follow-up

Regarding the musculoskeletal diseases, the risk of the occurrence of KOA increased significantly with the presence of HT ($p = 0.013$) and IGT ($p = 0.029$) (Table 4). Although the other metabolic syndrome components did not significantly influence the occurrence of musculoskeletal diseases, the presence of OB tended to increase the risk of the occurrence of LS ($p = 0.053$). The risk of the occurrence of OP at L2–4 was increased by the presence of OP at the femoral neck ($p = 0.008$), and the risk of the occurrence of OP at the femoral neck was increased by the presence of OP at L2–4 ($p = 0.047$) (Table 4). The presence of OP at lumbar L2–4 tended to decrease the risk of the occurrence of KOA, and the presence of LS tended to decrease the risk of the occurrence of OP at the femoral neck, although both of these associations were not statistically significant.

Table 5 shows the ORs associated with the presence of musculoskeletal diseases and metabolic syndrome components for the occurrence of the metabolic syndrome components. The presence of KOA increased the risk of the occurrence of HT and DL (HT, $p = 0.024$ and DL, $p = 0.029$); however, the other musculoskeletal diseases did not significantly influence the occurrence of the other metabolic syndrome components. In contrast, there was a mutual association between the occurrence of the metabolic syndrome components and the presence of the other metabolic syndrome components. The presence of HT significantly increased the risk of the occurrence of OB ($p = 0.007$), and, inversely, the presence of OB significantly increased the risk of the occurrence of HT ($p = 0.016$). The presence of OB also increased the risk of the occurrence of IGT ($p = 0.023$). Finally, the presence of IGT increased the risk of the occurrence of DL ($p = 0.004$).

Finally, Figure 1 summarizes the above-mentioned mutual associations between each factor for the musculoskeletal diseases and metabolic syndrome components (Figure 1).

Discussion

In the present study, using the data from a population-based cohort with a high participation rate (81.9%) over a period of 3 years, we observed that the risk of the occurrence of KOA was increased by the presence of HT and IGT, and, inversely, the presence of KOA increased the risk of the occurrence of HT and DL. The occurrence of LS tended to be influenced by the presence of OB. A reciprocal relationship existed between OP of the lumbar spine and OP of the femoral neck. Within the metabolic components, the presence of IGT increased the risk of the occurrence of DL, and there was a reciprocal relationship between OB and HT in addition to that between OB and IGT. However, the risk of OP occurring was not influenced by the presence of the metabolic syndrome components. Further, there was no significant association between HT and DL.

The influence of the metabolic components was the strongest with KOA, followed by LS; however, they did not appear to influence OP. Therefore, the results of the present study might indicate that the metabolic syndrome components influence the onset of osteoproliferative changes, such as those with OA, but not bone loss, such as that in OP.

The present findings regarding the relationship between the occurrence of KOA and the presence of HT or IGT support those that we previously reported [10]. At the same time, the risk of the occurrence of HT and DL was increased by the presence of KOA, independent of the presence of OB. Using the same individuals' data, confounding factors, such as bicycling, regular exercise, and a history of knee injuries, were all significantly associated with KOA in a previous study [29]; therefore, these factors could have influenced the relationships in the present study. With the addition of variables for regular cycling, regular exercise, and the history of injury to either knee at baseline to the logistic regression analysis in the present study, the adjusted ORs for HT and IGT, with the outcome as the occurrence of KOA, remained unchanged.

In addition, OB was not a significant risk factor for the occurrence of KOA in the present study. However, when the variable OB was replaced with the actual BMI values in the same model, the logistic regression analysis showed that greater BMIs significantly increased the risk of the occurrence of KOA (lumbar spine OP as an explanatory factor for OP, BMI + 1 kg/m^2; OR, 1.15; 95% CI, 1.05–4.73; $p = 0.038$; femoral neck OP as an explanatory factor for OP, BMI + 1 kg/m^2; OR, 1.15; 95% CI, 1.04–1.27; $p = 0.005$), indicating that the occurrence of KOA is associated with greater body composition, although the effect of OB, as defined by BMI,