Table IV
OPA according to occupational activity

	Occupational activity		Crude regression coefficient (95% CI)	P value	Adjusted regression coefficient* (95% CI)	P value
	No	Yes				
Sitting on a chair ≥2 h/day	3.5 ± 8.8	2.4 ± 6.7	−1.06 (−1.89 to −0.22)	0.013	−0.39 (−1.19 to 0.41)	0.339
Kneeling ≥1 h/day	2.5 ± 6.9	4.8 ± 10.9	2.25 (1.22 to 3.29)	<0.0001	1.62 (0.65–2.60)	0.0011
Squatting ≥1 h/day	2.5 ± 6.8	4.3 ± 10.5	1.72 (0.78 to 2.66)	0.0004	1.03 (0.13–1.92)	0.025
Standing ≥2 h/day	2.1 ± 5.6	3.2 ± 8.3	1.02 (−0.12 to 2.16)	0.079	0.25 (−0.84 to 1.33)	0.657
Walking ≥3 km/day	3.0 ± 8.7	3.0 ± 7.0	0.05(−0.79 to 0.88)	0.912	−0.56 (−1.37 to −0.24)	0.170
Climbing ≥1 h/day	3.1 ± 8.4	2.7 ± 6.2	−0.39 (−1.38 to 0.59)	0.434	−0.78 (−1.76 to 0.20)	0.119
Lifting weights ≥10 kg ≥ once/week	3.0 ± 8.1	3.0 ± 7.8	0.04 (−0.79 to 0.88)	0.920	0.20 (−0.60 to 1.00)	0.624

Values are mean ± SD.
* Adjusted regression coefficient was calculated using multiple regression analysis after adjustment for age, gender, and BMI.

(regression coefficient −0.055, 95% CI −0.164 to 0.054, $P = 0.32$). Further, when we analyzed the independent associations of occupational activities with mJSW in women in the same way, kneeling was independently associated with mJSW (regression coefficient −0.20, 95% CI −0.36 to −0.03, $P = 0.02$), and walking tended to be independently associated with mJSW (regression coefficient −0.13, 95% CI −0.27 to 0.005, $P = 0.058$), but lifting weights were not (regression coefficient −0.09, 95% CI −0.23 to 0.05, $P = 0.22$).

Discussion

The present study is the first epidemiologic study using a large-scale, population-based cohort to determine the association of job title and occupational activity with joint space narrowing and osteophytosis separately. These variables were estimated not by categorical grade but by continuous values such as mJSW and OPA at the knee. In the present study, kneeling, squatting, walking, and heavy lifting were significantly associated with mJSW. For OPA, kneeling and squatting were significantly associated with higher OPA, whereas other activities were not.

Although agricultural, forestry, and fishery workers have been historically among the first to be identified in relation to knee OA in Caucasians[34,35], no studies have focused on mJSW or OPA separately. The present study is the first to examine the association of characteristic features of knee OA such as mJSW and OPA separately with job title, and clarified that, among women, agricultural, forestry, and fishery workers had significantly lower mJSW compared with clerical workers and technical experts. As other authors have hypothesized, the combination of intense exposure to heavy labor of varied nature and repeated local stresses, especially at a young age, could contribute to some systemic mechanism in the development of OA[36]. This argument would support the implementation of preventive measures as a priority to reduce the intensity of physical labor in this sector—particularly for young female farm workers. In contrast, there were no associations between job titles and mJSW in men. Because men are known to have greater muscle strength than women at all ages[37], and muscle strength has a protective effect on knee OA[38,39], it might be that the greater muscle strength obscures the harmful effects of agricultural, forestry, and fishery work, leading to lower risk for knee OA in men.

For kneeling and squatting, studies in Caucasians have suggested that these occupational activities, and job titles that require them, are associated with knee OA[19–24], whereas our previous study showed that these activities were significantly associated with severe knee OA. However, in all previous studies, knee OA was diagnosed by KL grade or whether subjects had undergone total knee arthroplasty. The present study was the first to clarify the association of kneeling and squatting with joint space narrowing and osteophytosis separately. In addition, these variables were not estimated using a categorical method but rather with continuous values such as mJSW and OPA. This study clarified that kneeling and squatting were significantly associated with decreased mJSW as well as increased OPA. There were no occupational activities associated with both joint space narrowing and osteophytosis except for kneeling and squatting; in addition, kneeling had a larger impact on mJSW than lifting weights. Thus, these occupational activities must be strongly associated with knee OA.

Walking and lifting weights were associated with joint space narrowing but not with osteophytosis in the present study. This discrepancy may be partly explained by the high prevalence of osteophytosis in Japan. In fact, our previous study[4] showed that KL = 2 OA, which consists of definite osteophytosis but no definite joint space narrowing, was high in subjects in Japan compared with studies in Caucasians[40,41], whereas KL = 3 OA, which consists of definite joint space narrowing, did not differ significantly between these two ethnic groups. The higher prevalence of osteophytosis in Japan could be due to lifestyle factors, because the Japanese traditional lifestyle includes sitting on the heels on a mat and using Japanese-style lavatories; these positions may cause mechanical stress to the knee joint and possibly lead to acceleration of osteophytosis. The burden on the knee associated with walking and lifting weights may be weaker compared with the burden associated with kneeling and squatting; thus, the association between osteophytosis and occupational activities of walking and lifting weights may be obscured by the traditional Japanese lifestyle. In addition, the separate associations of walking and lifting weights with joint space narrowing and osteophytosis suggest that these two features of knee OA may have distinct etiological mechanisms. In fact, a recent cross-sectional study has shown that osteophytosis was unrelated not only to joint space narrowing on plain radiographs, but also to cartilage loss measured by quantitative magnetic resonance imaging[27]. The present study also showed that mJSW and OPA were significantly correlated, but each predicted only 21% of the variation in the other. Furthermore, our study on an experimental mouse model for OA has identified a cartilage-specific molecule, carminerin, that regulates osteophytosis without affecting joint cartilage destruction during OA progression[28,29].

In the present study, we found gender differences regarding the association of occupational activities with mJSW. In women, kneeling, squatting, walking, and lifting weights were significantly associated with mJSW, whereas in men, only squatting was significantly associated with mJSW. This difference may be partly explained by muscle strength in men. Because men are known to have greater muscle strength than women at all ages, and muscle strength has a protective effect on knee OA[37–39], it might be that the greater muscle strength obscures the harmful effects of occupational activities on knees in men.

Our technique to measure mJSW is a little different from many other methods (Ref) in that the tibia margin is defined using both the tibial plateau (bright band) and the rim, whereas other methods use the tibial plateau alone[42,43]. However, our preparatory examination showed higher reproducibility in "the middle line between

the anterior and posterior margins of the tibial plateau"[32]. In fact, in our previous study[32], to decide the ideal algorithms for the measurements, we initially evaluated the reproducibility of "the tibial plateau alone" and "'the middle line between the anterior and posterior margins of the tibial plateau" by an intraclass coefficient of correlation (ICC) on radiographs of 20 individuals taken at a 2-week intervals with various knee flexion angles (0, 10, 20, and 30°) and X-ray beam angulations (0, 5, 10, and 15°). Results showed higher reproducibility in "the middle line between the anterior and posterior margins of the tibial plateau" at each condition.

There were several limitations to the present study. First, this is a cross-sectional study on factors associated with knee OA, so a causal association with occupational activity could not be determined. However, information collected included a lifetime occupational history and details of specific workplace physical activities; therefore, ample evidence on the background of joint space narrowing and osteophytosis at the knee could be obtained. Second, a rotation of the knee could cause a large error, especially in OPA, which could hide associations of independent variables with this metric. However, the patella was centralized over the lower end of the femur with the aid of fluoroscopy when we took X-rays; thus the rotational error is likely to be small and have minimal effects on the results of the present study.

In conclusion, the present cross-sectional study using a large-scale population from the ROAD study revealed distinct risk factors of occupational activities for joint space narrowing and osteophytosis in Japanese subjects. Other occupational activities of kneeling and squatting were associated with joint space narrowing as well as osteophytosis. Walking and heavy lifting were associated with joint space narrowing, but not with osteophytosis. Further studies, along with longitudinal data from the ROAD study, will elucidate the environmental background of OA and help clarify clinical evidence for the development of disease-modifying treatments.

Author contributions

All authors have made substantial contributions to all three of sections (1), (2) and (3) below;

(1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data

(2) drafting the article or revising it critically for important intellectual content

(3) final approval of the version to be submitted.

Competing interest

There are no competing interest.

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Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.joca.2011.03.008.

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Spine

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EPIDEMIOLOGY

Health-Related Quality of Life in Subjects With Low Back Pain and Knee Pain in a Population-Based Cohort Study of Japanese Men

The Research on Osteoarthritis Against Disability Study

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Study Design. Cross-sectional surveys of health-related quality of life (QOL) in subjects with low back pain and knee pain using a population-based cohort.

Objective. The purpose of the present study was to clarify the impact of low back pain and knee pain on QOL in men. In addition, we analyzed the impacts of vertebral fracture (VFx), lumbar spondylosis, and knee osteoarthritis (OA) on the magnitude of QOL loss in men with low back pain and knee pain.

Summary of Background Data. Low back pain and knee pain are major public health issues causing disability among the elderly men, but there were no population-based studies to compare the impact of low back pain on QOL with that of knee pain in Japanese men.

Methods. From 3040 participants in the Research on Osteoarthritis Against Disability study, data from 767 men older than 40 years who completed questionnaires (mean age = 69.7 years) were examined. To carry out the QOL assessment, the Medical Outcomes Study Short Form 8 (SF-8) and EuroQol (EQ-5D) were used. We examined the association of low back pain and knee pain with QOL. Furthermore, we also examined the presence of VFx and the severity of lumbar spondylosis and knee OA with the magnitude of QOL loss in men with low back pain and knee pain, respectively.

Results. The impact of low back pain on QOL was larger than that of knee pain. In men with low back pain, there were few associations between Kellgren-Lawrence grade and QOL, whereas VFx was associated with physical QOL. For men with knee pain, Kellgren-Lawrence grade equal to 4 knee OA was associated with QOL.

Conclusion. This study revealed that low back pain has a larger impact than knee pain on QOL. Furthermore, low back pain with VFx is strongly associated with physical QOL loss.

Key words: knee pain, low back pain, osteoarthritis, quality of life, vertebral fracture. **Spine 2011;36:1312–1319**

Low back pain and knee pain are major public health issues causing disability among the elderly in most developed countries.[1–3] The prevalence of low back pain and knee pain is high in the elderly in Japan, ranging from 25% to 30%.[2,3] According to the recent National Livelihood Survey of the Ministry of Health, Labour, and Welfare in Japan, low back pain is rated first among symptoms that send men to the hospital.[4] Thus, it is important to clarify the impact of low back pain and knee pain on quality of life (QOL). Several studies have focused on the association of low back pain with

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The manuscript submitted does not contain information about medical device(s)/drug(s).

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The present study was conducted with the approval of ethical committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology.

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All authors have no conflicts of interest.

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QOL in whites,[5–8] but for knee pain, there are few studies regarding its association with QOL.[9] Furthermore, to the best of our knowledge, there are no population-based studies that examine the impact of low back pain and knee pain on QOL in the same population using the same tool, although low back pain and knee pain may not be independent. Furthermore, the presence of pain at both sites may have more impact on QOL than pain at a single site. One of the main causes of low back pain in the elderly is vertebral fracture (VFx).[10] Low back pain is also believed to be one of the principal clinical symptoms of lumbar spondylosis, although the magnitude of the impact of lumbar spondylosis on low back pain is not as strong as one would expect.[2,11,12] A significant part of knee pain is caused by knee osteoarthritis (OA),[13,14] and the prevalence of knee pain increases as knee OA becomes more severe.[3] Thus, the impact of pain on QOL may differ on the basis of the cause and severity of the underlying disease. However, to the best of our knowledge, there are no population-based studies that examine the association of pain with QOL according to the cause or severity of the underlying disease.

Furthermore, sex differences have been observed in low back pain and knee pain. The prevalence of low back pain and knee pain differs between men and women,[2,3] and low back pain is rated as the first symptom that sends men to the hospital, although it is rated as the second symptom for women.[4] Thus, the impact of this pain on QOL may be stronger in men than in women. Although studies have examined the association of low back pain[5–8] or knee pain[9] with QOL, neither men nor women were analyzed separately[5,6,9] or the studies focused only on women.[7,8] There are no large-scale population-based studies examining the impact of low back pain or knee pain on QOL in men alone.

The objective of the present study was to clarify the independent association of low back pain and knee pain with QOL among 767 men using cohorts from Research on Osteoarthritis Against Disability (ROAD). We also examined whether the presence of both low back pain and knee pain had a larger impact on QOL than pain at only one site. Furthermore, we analyzed the impact of VFx, lumbar spondylosis, and knee OA on the magnitude of loss of QOL in men with low back pain and knee pain.

MATERIALS AND METHODS

Subjects

The ROAD study is a nationwide prospective study for bone and joint diseases (with OA and osteoporosis as the representative bone and joint diseases) consisting of population-based cohorts established in several communities in Japan. As detailed profile of the ROAD study has been described elsewhere,[15,16] and only a brief summary is provided here. To date, we have completed the creation of a baseline database including clinical and genetic information of 3040 inhabitants (1061 men and 1979 women) aged 23 to 95 years (mean = 70.6 years), who were recruited from listings of resident registrations in three communities: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a seacoast region in Taiji, Wakayama. All participants provided written informed consent, and the study was conducted with the approval of ethical committees of the University of Tokyo and the Tokyo Metropolitan Institute of Gerontology. Participants completed an interviewer-administered questionnaire of 400 items that included lifestyle information such as smoking habits, alcohol consumption, family history, and health-related QOL. We also examined the presence of cerebral stroke, diabetes mellitus, cardiac disease, and hypertension using an interviewer-administered questionnaire, as QOL may be affected by these comorbidities. Furthermore, because a lower level of physical activity may affect the association of pain with QOL, we obtained a history of leisure physical activity, including information on participation in sports and the frequency and duration of other leisure activities such as walking, jogging, swimming, playing tennis, playing baseball, playing golf, and muscle strength training. Anthropometric measurements included height and weight, and body mass index (BMI; weight [kg]/height^2 [m^2]) was calculated. All subjects were interviewed by experienced orthopedists regarding low back pain and knee pain and were asked, "Have you experienced low back pain on most days in the past month, in addition to now?" and "Have you experienced knee pain on most days in the past month, in addition to now?," respectively. Those who answered yes were defined as having pain. From the baseline data of the overall participants, the present study analyzed 767 men aged 40 years or older who completed a questionnaire of the Medical Outcomes Study Short Form 8 (SF-8) and the EuroQol (EQ-5D).

Radiographic Assessment

All participants underwent radiographic examination of the lumbar spine including intervertebral levels L1–L2 to L5–S with anteroposterior and lateral views, and both knees using anteroposterior and lateral views with weight-bearing and foot map positioning. Lumbar spine and knee radiographs were read without knowledge of participant clinical status by a single experienced orthopedist (S. M.). VFx was assessed by lateral radiographs of the lumbar spine (L1–L5) in terms of a wedge, biconcave, or crush appearance according to the Japanese Society of Bone and Mineral Research criteria[17] (Figure 1). Lumbar spondylosis and knee OA were assessed using the Kellgren-Lawrence (KL) radiographic atlas, and the

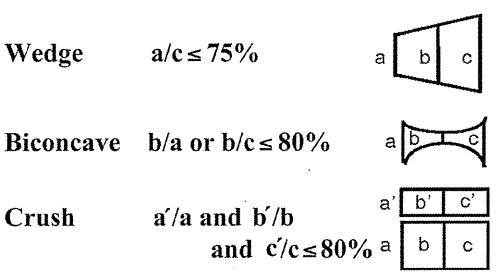

Figure 1. Diagnostic criteria for vertebral fractures according to the Japanese Society for Bone and Mineral Research.

severity was determined by KL grading.[18] We defined lumbar spondylosis and knee OA as KL 2 or more in at least one knee and one intervertebral level, respectively.

Instruments

The SF-8 scale was used for the QOL assessment. The SF-8 was constructed to provide a shorter alternative to the SF-36,[19] the most widely used patient-based health status survey, for use in large population-based surveys of general and specific populations. The SF-8 measures eight concepts: general health (GH), physical function (PF), role physical (RP), bodily pain (BP), vitality (VT), social function (SF), mental health (MH), and role emotional (RE). The SF-8 was scored by assigning the mean SF-36 scale score from the 2002 general Japanese population to each response category of the SF-8 measuring the same concept, and then weighting each SF-8 item to compute aggregate physical component scores (PCS) and mental component scores (MCS) summary scale measures. The SF-8 can be scored using a published algorithm for Japanese versions of the SF-8, which have been well-validated.[20] We also used the EuroQol (EQ-5D) questionnaire,[21] which was translated into Japanese.[22] The five-dimensional health care classification includes questions on the status of morbidity, self-care, usual activities, pain/discomfort, and anxiety/depression. Participants were asked to indicate current health status by choosing the most appropriate of the three statements about each of the five QOL dimensions. Each statement represents an increasing degree of severity. These results were coded and converted to a score of utility using a table of values.[22]

Statistical Analysis

We used the nonpaired student *t* test to examine differences between subjects with and without low back pain and knee pain. To determine the independent impact of low back pain and knee pain on QOL, multiple regression analysis was used with age, BMI, low back pain, and knee pain as independent variables. Furthermore, to examine the impact of the presence of both low back pain and knee pain on QOL, QOL scores in subjects with both low back pain and knee pain, with low back pain only, with knee pain only, and without these conditions were compared using the Tukey Honestly Significant Difference (HSD) test after adjustment for age and BMI. We further examined the association of KL grade at the lumbar spine and knee with the magnitude of QOL loss in subjects with low back pain and knee pain, respectively, using the Tukey HSD test after adjustment for age and BMI. If a subject had pain in both knees, the more severe KL grade was used for that subject. For the lumbar spine, the most severe KL grade among all intervertebral spaces was used. We also examined the association of the presence of VFx with the magnitude of QOL loss in subjects with low back pain using multiple regression analysis after adjustment for age, BMI, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension. The association of physical activity with the magnitude of QOL loss in subjects with low back pain and in those with knee pain was determined using multiple regression analysis after adjustment for age, BMI, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension. Data analyses were performed using SAS version 9.0 (SAS Institute Inc., Cary, NC).

RESULTS

Characteristics of the 767 participants aged 40 years and older in the ROAD study are shown in Table 1. The prevalence of low back pain and knee pain was approximately 15% and 21%, respectively. The prevalence of lumbar spondylosis and knee OA was 80% and 42%, respectively, which was high compared with that of VFx.

TABLE 1. Characteristics of Participants

N	767
Age, yr	69.7 ± 10.5
Height, cm	162.8 ± 6.7
Weight, kg	61.5 ± 10.8
BMI, kg/m^2	23.1 ± 3.4
Low back pain, %	15.4
Knee pain, %	20.6
Vertebral fracture, %	11.6
Lumbar spondylosis, %	80.0
Knee osteoarthritis, %	42.1
Comorbidities, %	
Cerebral stroke	5.8
Diabetes mellitus	13.8
Cardiac disease	13.4
Hypertension	41.1
Medical Outcomes Study Short Form 8	
GH	50.2 ± 5.5
PF	49.9 ± 6.2
RP	50.2 ± 6.7
BP	50.4 ± 9.2
VT	50.4 ± 6.3
SF	52.4 ± 5.5
MH	54.4 ± 5.3
RE	52.0 ± 5.2
PCS	47.4 ± 6.8
MCS	53.4 ± 5.3
EQ-5D	0.91 ± 0.14

Values are mean ± SD unless otherwise indicated.

BMI indicates body mass index; BP, bodily pain; EQ-5D, EuroQol; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical function; RE, role emotional; RP, role physical; SF, social function; VT, vitality;

TABLE 2. Mean (SD) Scores of All Domains, PCS, and MCS in the SF-8 and EQ-5D in Men with and Without Low Back Pain and Knee Pain

	Low Back Pain			Knee Pain		
	No	Yes	Adjusted Beta*	No	Yes	Adjusted Beta*
Medical Outcomes Study Short Form 8						
GH	50.5 (5.4)	48.3† (5.6)	−0.105‡	50.5 (5.4)	49.1† (5.5)	−0.100‡
PF	50.5 (5.8)	47.0† (7.5)	−0.135‡	50.4 (5.7)	48.2† (7.6)	−0.085‡
RP	50.7 (6.4)	47.4† (7.7)	−0.102‡	50.7 (6.2)	48.7† (7.9)	−0.073‡
BP	51.4 (9.2)	44.6† (7.2)	−0.235‡	51.1 (9.2)	47.6† (8.7)	−0.119‡
VT	50.8 (6.3)	48.4† (5.8)	−0.110‡	50.8 (6.1)	49.0† 6.5)	−0.109‡
SF	52.8 (5.0)	50.5† (7.5)	−0.100‡	52.5 (5.3)	52.4 (5.8)	0.028
MH	54.6 (5.1)	53.1† (6.0)	−0.078‡	54.4 (5.2)	54.6 (5.3)	0.034
RE	52.3 (4.9)	50.6† (5.5)	−0.087‡	52.1 (4.9)	51.9 6.2)	−0.0001
PCS	48.2 (6.5)	43.3† (7.2)	−0.191‡	48.1 (6.5)	44.8† (7.2)	−0.147‡
MCS	53.4 (5.1)	53.1 (6.3)	−0.010	53.2 (5.2)	54.2 (5.6)	0.076‡
EQ-5D	0.93 (0.13)	0.83† (0.17)	−0.180‡	0.92 (0.13)	0.87† (0.16)	−0.099‡

Values are mean (SD) unless otherwise indicated.

**The adjusted beta values are shown using multiple regression analysis after adjustment for age, body mass index, the other pain, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension.*

†P < 0.05 versus subjects without the corresponding pain by nonpaired student t test.

‡P < 0.05 by multiple regression analysis.

BP indicates bodily pain; EQ-5D, EuroQol; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical function; RE, role emotional; RP, role physical; SF, social function; SF-8, 8-Item Short Form Health Survey; VT, vitality.

Table 2 shows the scores for all domains in the SF-8 and the EQ-5D utility score by the presence of low back pain and knee pain. We further examined the independent association of low back pain and knee pain with QOL using multiple regression analysis after adjustment for age, BMI, cerebral stroke, diabetes mellitus, cardiac disease, hypertension, and the other pain. Low back pain was significantly associated with lower QOL scores in all the domains of the SF-8 except for MCS, and in the EQ-5D utility scores, whereas knee pain was associated with lower scores of GH, PF, RP, BP, VT, and PCS in the SF-8 and the EQ-5D utility score, but not with SF, MH, and RE. For the MCS, knee pain was associated with higher scores. The adjusted beta values of low back pain were larger than those of knee pain in almost all QOL domains.

To examine the impact of the presence of both low back pain and knee pain on QOL, we next compared the QOL scores in the subjects with both low back pain and knee pain, only low back pain, only knee pain, and without any pain (Table 3). The Tukey HSD test after adjustment for age, BMI, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension showed that the scores for almost all physical domains in the SF-8 were significantly lower in subjects with both low back pain and knee pain, only low back pain, and only knee pain than in those without pain. The EQ-5D utility score was also significantly lower in subjects with both low back pain and knee pain, those with only low back pain, and those with only knee pain than in those without pain. There were no significant differences in any domains between subjects with both low back pain and knee pain and those with only low back pain. Some domains tended to be lower in subjects with pain in both sites than in those with only knee pain, but differences were not significant.

Next, to clarify the impact of VFx and lumbar spondylosis on the magnitude of QOL loss in men with low back pain, we examined the association of KL grade of lumbar spine and the presence of VFx with QOL in the subjects with low back pain (Table 4). In men with low back pain, there were no associations of KL grade with any domain of the SF-8 and the EQ-5D utility scores, whereas the RP and PCS scores were significantly lower in subjects with VFx than in those without fracture.

Likewise, we examined the association of KL grade of knee with QOL in the subjects with knee pain (Table 5). After adjustment for age and BMI, the Tukey HSD test showed that the PCS in the SF-8 was significantly lower in men with KL 4 knee OA than in those with KL 0 or 1.

We next analyzed the association of physical activity with QOL in subjects with low back pain and in those with knee pain (see Table, Supplemental Digital Content 1, http://links.lww.com/BRS/A519). Multiple regression analysis

TABLE 3. Mean (SD) Scores of All Domains, PCS, and MCS in the SF-8 and EQ-5D in Men by the Combination of Low Back Pain and Knee Pain

	Low Back Pain and Knee Pain	Only Low Back Pain	Only Knee Pain	No Low Back Pain or Knee Pain
Prevalence, %	**5.2**	**9.8**	**15.5**	**69.6**
Medical Outcomes Study Short Form 8				
GH	48.2* (5.4)	48.7* (5.7)	49.3* (5.5)	50.8 (5.3)
PF	47.7* (6.2)	46.8* (8.2)	48.4* (8.1)	50.9 (5.0)
RP	48.0 (6.9)	47.6* (8.0)	49.0* (8.3)	51.1 (5.8)
BP	45.3* (7.7)	44.6* (6.9)	48.4* (8.9)	52.1 (9.1)
VT	47.9* (6.1)	48.8* (5.7)	49.3* (6.6)	51.1 (6.1)
SF	51.1 (6.5)	50.7 (7.9)	52.8 (5.5)	52.8 (4.8)
MH	54.4 (4.8)	52.7* (6.4)	54.7 (5.4)	54.6 (5.0)
RE	51.6 (5.0)	50.4* (7.2)	52.0 (6.5)	52.3 (4.4)
PCS	43.4* (6.5)	43.5* (7.5)	45.3* (7.4)	48.8 (6.1)
MCS	54.1 (5.6)	53.0 (6.7)	54.3 (5.5)	53.2 (5.0)
EQ-5D	0.82* (0.17)	0.84* (0.16)	0.88* (0.15)	0.94 (0.12)

Values are mean (SD) unless otherwise indicated.

**Significantly lower than that of subjects with no low back pain or knee pain by the Tukey Honestly Significant Difference test after adjustment for age, body mass index, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension.*

BP indicates bodily pain; EQ-5D, EuroQol; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical function; RE, role emotional; RP, role physical; SF, social function; SF-8, 8-Item Short Form Health Survey; VT, vitality.

after adjustment for age, BMI, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension showed that physical activity was not associated with any QOL parameter in subjects with low back pain or in those with knee pain.

DISCUSSION

This is the first large-scale, population-based cohort study in Japanese men that examined the impact of low back pain and knee pain on QOL measured by the SF-8 as well as the EQ-5D. In the present study, low back pain and knee pain were significantly associated with QOL in men, and multiple regression analysis showed that the adjusted beta values of low back pain were larger than that of knee pain in almost all QOL domains. Furthermore, in men with low back pain, VFx was significantly associated with QOL loss. For men with knee pain, KL 4 knee OA was strongly associated with magnitude of QOL loss compared with KL 0 or 1.

Previous studies showed that low back pain was associated with QOL,[5–8] but no studies focused on men, although sex differences were found in low back pain.[2,4] In addition, although low back pain and knee pain may not be independent, and the presence of pain at both sites may have more impact on QOL loss than pain at one site, no studies have examined the impact of low back pain and knee pain on QOL simultaneously in the same population. In the present study, low back pain and knee pain were significantly associated with lower QOL scores in men. The adjusted beta values of low back pain were higher than that of knee pain in almost all QOL domains, suggesting that low back pain had more impact on QOL loss than knee pain, although we did not evaluate the pain severity of low back pain and knee pain. Furthermore, the pain thresholds and pain onset in daily living in low back pain are not the same as in knee pain, so strict comparisons between low back pain and knee pain are limited, even though we examined the association of low back pain and knee pain with QOL in the same populations using the same method. The presence of both low back pain and knee pain was also significantly associated with QOL loss compared with no low back pain or knee pain, whereas there were no differences in QOL parameters between subjects with both low back pain and knee pain and those with only low back pain. These findings suggest that when both low back pain and knee pain exist, the combination may not result in any additional impact on QOL than pain in single site; it is possible that the impact of knee pain on QOL may be obscured by low back pain, because the impact of low back pain on QOL was larger than that of knee pain.

Previous clinical studies showed that strong impacts of clinical VFx on QOL were observed.[23,24] The present study also clarified that VFx had significant associations with the magnitude of QOL loss measured by RP and PCS of the SF-8 in subjects with low back pain, indicating that low back pain with VFx has a more severe impact on physical QOL than low back pain without VFx in men. This means that VFx may not

TABLE 4. Mean (SD) Scores on the SF-8 and EQ-5D by Vertebral Fracture and Kellgren-Lawrence Grade in Subjects with Low Back Pain

	Vertebral Fracture			Lumbar Spondylosis		
	No	Yes	KL 0,1	KL 2	KL 3	KL 4
Prevalence, %	**18.6**	**81.4**	**16.2**	**35.0**	**28.2**	**20.5**
Medical Outcomes Study Short Form 8						
GH	48.6 (5.6)	47.2 (5.9)	46.8 (6.8)	49.9 (5.3)	47.8 (5.4)	47.4 (5.3)
PF	47.5 (7.6)	44.8 (7.0)	48.6 (5.7)	49.4 (5.7)	43.6 (9.6)	46.3 (6.7)
RP	48.1 (7.3)	44.3* (8.7)	49.1 (6.9)	49.3 (6.9)	45.5 (8.5)	45.5 (8.2)
BP	44.9 (7.4)	43.2 (6.2)	42.3 (4.9)	46.2 (7.6)	45.2 (6.8)	43.2 (8.2)
VT	48.7 (6.0)	47.0 (5.0)	47.6 (7.7)	48.8 (5.3)	47.9 (5.5)	48.9 (5.6)
SF	50.4 (7.8)	51.2 (6.2)	49.4 (8.8)	52.6 (4.9)	49.6 (8.4)	49.0 (8.4)
MH	52.5 (6.1)	55.4 (4.5)	51.7 (7.6)	55.3 (4.0)	51.6 (6.1)	52.0 (6.4)
RE	50.2 (6.9)	52.2 (3.6)	49.0 (8.3)	52.6 (3.3)	49.1 (8.3)	50.5 (5.6)
PCS	44.2 (6.6)	39.4* (8.2)	44.0 (5.0)	44.9 (7.1)	41.9 (8.0)	42.0 (7.5)
MCS	52.4 (6.2)	56.4 (5.8)	51.0 (8.5)	54.9 (4.5)	52.2 (6.1)	52.8 (6.7)
EQ-5D	0.82 (0.17)	0.85 (0.16)	0.86 (0.15)	0.87 (0.14)	0.78 (0.17)	0.80 (0.19)

Values are mean (SD) unless otherwise indicated.

**P < 0.05 versus no vertebral fracture by the Tukey Honestly Significant Difference test after adjustment for age, body mass index, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension.*

BP indicates bodily pain; EQ-5D, EuroQOL; GH, general health; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical function; RE, role emotional; RP, role physical; SF, social function; SF-8, 8-Item Short Form Health Survey; VT, vitality.

only be a cause of low back pain but also worsen the severity of low back pain. Meanwhile, the severity of lumbar spondylosis was not significantly associated with magnitude of QOL loss in subjects with low back pain. This finding may be partly explained by the weak association between lumbar spondylosis and low back pain reported by us and others.[2,11,12] Indeed, disc degeneration was reported to be detected by magnetic resonance imaging in at least one lumbar level in all but one asymptomatic volunteer in a group with volunteers aged 60 to 80 years.[25] Regarding the knee, the adjusted beta values of knee pain on QOL were weak compared with low back pain, whereas the KL 4 knee OA was significantly associated with magnitude of PCS loss in subjects with knee pain compared with KL 0 or 1. The PCS in subjects with KL 2 knee OA were similar to those with KL 0 or 1. Considering the definition of the KL grade, this may also mean that osteophytosis and joint space narrowing, which are representative features of knee OA, have a different impact on QOL; that is, osteophytosis may have a weak impact on QOL, whereas joint space narrowing may have a strong impact.

As measured by MCS of the SF-8, low back pain was not significantly associated with lower scores in the present study, whereas knee pain was significantly associated with higher scores on MCS, and significantly lower PCS scores. Several factors may contribute to the dissociation between MCS and PCS for low back pain and knee pain. First, MCS questions within the SF-8 include generic questions about energy levels, feelings of being "downhearted and blue," and interference in daily activities as a result of emotional problems. These questions are less sensitive to the presence of mental health issues than disease-specific scales such as the Kessler psychological distress scale.[26] In fact, Hill et al[27] showed that psychological distress has been shown to be significantly more frequent in those with arthritis than those without, although scores on MCS were not significantly different between these two groups. Second, the dissociation may be due to a disability paradox,[28] which suggests that people with chronic disabilities report serious limitations in Activities of Daily Living (ADL) and problems in performing social roles, yet state that they have excellent or good QOL. Low back pain and knee pain lead to functional impairment. This may be associated with lower PCS scores, but the individual may not feel that the impairment of social activity or ADL was due to mental factors. Particularly in elderly individuals, pain may be considered a natural consequence of being elderly and thus may not lead to lower MCS.

There are several limitations to the present study. First, this is a large-scale population-based study, but a cross-sectional study of baseline data, so a causal relationship could not be determined. The ROAD study is a longitudinal survey, so further progress will elucidate any causal relationships. Second, among the 1047 men 40 years or older in the ROAD

TABLE 5. Mean (SD) Scores of the SF-8 and EQ-5D by KL Grade in Subjects with Knee Pain

	KL 0,1	KL 2	KL 3	KL 4
Prevalence, %	**57.9**	**30.1**	**7.8**	**4.2**
Medical Outcomes Study Short Form 8				
GH	48.8 (5.2)	50.0 (4.8)	49.2 (6.5)	47.3 (6.9)
PF	49.4 (6.1)	48.9 (7.2)	47.0 (10.1)	43.6 (9.3)
RP	49.6 (7.5)	49.5 (6.9)	46.2 (12.0)	46.2 (6.7)
BP	47.5 (8.2)	50.1 (8.6)	43.8 (8.2)	44.8 (9.5)
VT	49.8 (5.7)	49.6 (7.1)	47.1 (7.4)	46.2 (6.3)
SF	53.5 (4.2)	51.2 (6.8)	51.9 (7.2)	52.3 (6.0)
MH	54.9 (5.1)	54.2 (5.0)	54.2 (6.6)	55.4 (5.5)
RE	52.7 (3.9)	51.3 (6.6)	50.9 (9.9)	51.6 (7.0)
PCS	45.4 (6.6)	46.7 (6.3)	42.2 (9.6)	40.3* (6.8)
MCS	54.8 (4.7)	52.9 (5.2)	54.4 (7.3)	55.8 (6.8)
EQ-5D	0.90 (0.15)	0.88 (0.16)	0.81 (0.20)	0.80 (0.17)

Values are mean (SD) unless otherwise indicated.

**P < 0.05 versus KL 0,1 by the Tukey Honestly Significant Difference test after adjustment for age, body mass index, cerebral stroke, diabetes mellitus, cardiac disease, and hypertension.*

BP indicates bodily pain; EQ-5D, EuroQol; GH, general health; KL, Kellgren-Lawrence; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical function; RE, role emotional; RP, role physical; SF, social function; SF-8, 8-Item Short Form Health Survey; VT, vitality.

study, 767 men had completed questionnaires for both the SF-8 and the EQ-5D, so the response rate was 73.7%. Subjects who completed questionnaires may have had better QOL than those who did not, so our results regarding QOL may have represented overestimations. Third, we did not include the onset of VFx in the analysis, although the severity of low back pain often appears to be associated with the interval from onset of VFx. In terms of clinical fractures, we examined the history of fracture, including VFx, in the ROAD study by self-report, and no clinical VFx occurred within the 1 month before baseline examination. However, we could not compare radiographs of the lumbar spine at baseline examination with those before the examination, as subjects had not undergone radiography of the lumbar spine before that examination. We were therefore unable to assess the incidence of subclinical fracture within the 1 month before baseline examination, although clinical and subclinical fractures are associated with lower QOL in women.[29] However, the association between severity of low back pain and the interval from onset of subclinical VFx may be weaker than that for clinical VFx, so the absence of data on the incidence of subclinical VFx may not strongly affect the present results.

In conclusion, the present study revealed that the impact of low back pain was larger than that of knee pain in almost all QOL domains. In men with low back pain, VFx had some association with physical QOL loss. In men with knee pain, KL 4 knee OA was strongly associated with QOL loss. Further progress will elucidate the backgrounds of low back pain and knee pain.

➢ Key Points

- ❑ Low back pain and knee pain are major public health issues causing disability among the elderly men, but there were no population-based studies to compare the impact of low back pain on QOL with that of knee pain in Japanese men.
- ❑ The objective of the present study was to clarify the independent association of low back pain and knee pain with QOL among 767 men using cohorts from ROAD.
- ❑ The impact of low back pain on QOL was larger than that of knee pain. In men with low back pain, there were few associations between KL grade and QOL, whereas VFx was associated with physical QOL, indicating that low back pain with VFx is strongly associated with physical QOL loss.

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ORIGINAL ARTICLE

Changes in serum levels of biochemical markers of bone turnover during 10 years among Japanese men and women: associated factors and birth-cohort effect. The Taiji Study

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Abstract We aimed to clarify changes in biochemical markers of bone turnover (BTMs) over 10 years, associations with changes in bone mineral density (BMD), and birth-cohort effects in a Japanese community. We randomly selected 400 individuals (age, 40–79 years; 50 of each gender and age stratum) from a list of registered residents in 1993. We measured BMD of the spine and hip, and serum concentrations of total osteocalcin (OC), beta-C-terminal cross-linking telopeptide of type I collagen (beta-CTX), and N-terminal cross-linking telopeptide of type I collagen (NTX), in 1993 and 2003. Of the 400 subjects, 322 (153 men, 169 women) completed the 10-year follow-up. Mean change rates (standard deviation) for serum total OC, beta-CTX, and NTX over 10 years were −1.00 (3.74)%/year, 5.10 (22.48)%/year, and 0.40 (3.41)%/year, respectively, in men, and 0.02 (5.32)%/year, 5.53 (14.54)%/year, and 0.62 (3.26)%/year, respectively, in women. Change rates of BTMs were higher for women in their forties than for women in their fifties to seventies ($P < 0.05$), and higher in the menstrual transition group than in pre- and postmenopausal groups ($P < 0.001$). Changes in levels of BTMs over 10 years in women were significantly associated with change rates of BMDs at L2–L4 and total hip after adjusting for potential confounders. A significant birth-cohort effect was observed among women in their fifties. We concluded that change rates of BTMs during the 10 years were influenced by menstrual transition, age, and sex and associated with bone loss at L2–L4 and total hip.

Keywords Biochemical markers of bone turnover · Bone loss · Menstrual transition · Birth-cohort effect

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Introduction

In Japan, about 10 million patients are estimated to have osteoporosis (OP) [1], and osteoporotic fractures are ranked fifth among the diseases responsible for causing disabilities requiring support [2]. Moreover, the number of cases of hip fracture has increased steeply in the past 20 years with the rapid aging of the population [3]. Early detection of OP to reduce the risk of osteoporotic fractures is therefore an urgent issue in terms of maintenance of quality of life in the elderly and containment of medical costs required for their care.

Biochemical markers of bone turnover (BTMs) are widely used in clinical situations to evaluate the efficacy of treatments for OP [4–6]. Several epidemiological studies have shown that BTMs can predict bone loss in women [7–10], but few reports appear to have examined trends in BTMs during more than one decade. In addition, few reports have clarified associations between changes in levels of BTMs and bone loss, particularly in men [11, 12].

Moreover, observation over the course of a decade enables comparison of values at the same age strata among different birth cohorts. We have already identified a birth-cohort effect in values of bone mineral density (BMD) using data from 1990 and 2000 in another cohort established in Wakayama Prefecture, a mountainous area in Japan [13]. In that study, values of bone mineral density (BMD) for women in their fifties and for men in their sixties were significantly higher for the younger than for the older birth cohort [13].

We established a cohort comprising men and women in a rural area in Japan and followed this cohort for 10 years. The present study was performed for the purpose of clarifying three issues: (1) changes in BTMs over 10 years in men and women as classified by age and menstrual transition; (2) associations between increases in BTMs and bone loss over 10 years in both men and women; and (3) effects of birth cohort on BTMs among general inhabitants, namely, whether differences in BTMs exist between birth cohorts for a given age stratum in both men and women.

Materials and methods

Cohort profile and eligible participants

The survey was performed in the Japanese town of Taiji. The Taiji cohort has been profiled in detail elsewhere [14–16] and so is only described briefly here. Taiji is located in the southern coastal area of Wakayama Prefecture, Japan. A list of all inhabitants born between 1913 and 1952, and therefore between 40 and 79 years old in 1993, was compiled on the basis of resident registrations as of the end of 1992. A cohort of 2,261 inhabitants (1,028 men, 1,233 women) was identified, and all members of the cohort completed a self-administered, 125-item questionnaire addressing lifestyle factors such as dietary habits, smoking habits, alcohol consumption, and physical exercise (whole cohort).

From this total cohort, 50 men and 50 women from each of four age groups (total, 400 participants) between 40 and 79 years by decade of birth year (1913–1922, 1923–1932, 1933–1942, and 1943–1952) were selected randomly and underwent BMD measurement in 1993. At this time, blood samples were taken from all participants (BMD cohort, baseline study). Background data including physical characteristics and mean BMD values for all 400 participants at baseline are shown in Table 1.

Among the 400 participants, 21 individuals (4 men, 17 women) had been diagnosed with osteoporosis in the past, but none had been treated using bisphosphonates, raloxifene, or calcitonin. Among the female participants, of 100 female participants in their forties and fifties at baseline, 41 women (41.0%) were premenopausal with regular periods, 14 (14.0%) were premenopausal with irregular periods, and the remaining 45 (45.0%) were postmenopausal.

Among the 400 participants at baseline, 322 (80.5%; 153 men, 169 women) participated in the examination held after 10 years. Loss of 78 participants at the 10-year follow-up was explained as follows: 52 participants had died (33 men, 19 women); 14 participants had moved (6 men, 8 women); 6 participants were ill (4 men, 2 women); 3 participants refused to participate (2 men, 1 woman); and 3 participants were away from the area at the time of follow-up (2 men, 1 woman).

During the 10 years, 37 new fragile fractures (10 men, 27 women), including 5 spinal fractures (1 man, 4 women), were reported in the interviewer-administered questionnaire surveys.

All examinations were performed with the full consent of participants. These study protocols were approved by the ethics committees of both Wakayama Medical University and the University of Tokyo.

BMD measurements

Baseline BMD was measured in 1993 using dual-energy X-ray absorptiometry (DXA) (QDR 1000; Hologic, Bedford, MA, USA). At baseline, all 400 participants (200 men, 200 women) underwent measurement of BMD from anteroposterior images of lumbar vertebrae L2–L4 and the proximal femur (femoral neck, Ward's triangle, trochanter, and total hip). These measurements were repeated on the same participants after 10 years.

To control the precision of DXA, the equipment was checked at every examination in 1993 and 2003 using the same phantom, and values for BMD of the phantom under DXA were regulated to 1.030 ± 0.016 g/cm^2 (1.5%) during all examinations. All BMD measurements were performed by the same medical doctor (N.Y.). To clarify the coefficient of variation (CV) for BMD measurements from DXA scans by the investigator, the same phantom was measured seven times in 1 day, then once a day at the same time every day for 5 days, and once a week at the same time and same day of the week for 4 weeks. CVs of intraday, interday, and interweek variability for this investigator were 0.13%, 0.39%, and 0.42%, respectively [17].

Measurements of BTMs

Blood examinations both at baseline and at the 10-year follow-up were performed in June. All blood samples were

Table 1 Summary characteristics for participants at baseline classified by age and gender

Birth cohort	Age group (years)	*n*	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	L2–L4 BMD (g/cm^2)	Femoral neck BMD (g/cm^2)	Total hip BMD (g/cm^2)
Men									
1943–52	40–49	50	44.2 (2.6)	168.8 (5.2)	69.0 (10.4)	24.2 (3.2)	1.05 (0.15)	0.86 (0.09)	1.00 (0.12)
1933–42	50–59	50	54.8 (2.7)	165.6 (5.0)[a]	63.5 (9.4)[a]	23.1 (2.9)	0.98 (0.17)	0.80 (0.13)[a]	0.94 (0.14)
1923–32	60–69	50	64.6 (2.5)	163.0 (4.8)[a]	62.9 (9.6)[a]	23.6 (3.2)	1.04 (0.21)	0.77 (0.11)[a]	0.92 (0.12)[a]
1913–22	70–79	50	74.0 (2.7)	160.7 (5.4)[a,b]	57.5 (8.3)[a,b,c]	22.2 (2.8)	0.97 (0.19)	0.71 (0.08)[a,b,c]	0.83 (0.09)[a,b,c]
1913–52	40–79	200	59.4 (11.4)	164.5 (5.9)	63.2 (10.2)	23.3 (3.1)	1.01 (0.18)	0.79 (0.12)	0.92 (0.13)
Women									
1943–52	40–49	50	44.0 (2.8)	154.4 (5.0)	54.1 (8.3)	22.7 (3.1)	1.07 (0.14)	0.79 (0.10)	0.90 (0.11)
1933–42	50–59	50	55.8 (2.8)	154.9 (5.3)	59.4 (10.0)[a]	24.8 (4.0)[a]	0.92 (0.16)[a]	0.70 (0.11)[a]	0.81 (0.12)[a]
1923–32	60–69	50	64.8 (2.6)	151.1 (4.6)[a,b]	52.1 (9.1)[b]	22.8 (3.5)[b]	0.78 (0.17)[a,b]	0.62 (0.09)[a,b]	0.71 (0.10)[a,b]
1913–22	70–79	50	74.4 (2.8)	147.7 (5.4)[a,b,c]	48.4 (8.2)[a,b]	22.2 (3.4)[b]	0.77 (0.12)[a,b]	0.59 (0.10)[a,b]	0.66 (0.12)[a,b]
1913–52	40–79	200	59.7 (11.6)	152.0 (5.8)	53.5 (9.7)	23.1 (3.6)	0.89 (0.19)	0.68 (0.13)	0.77 (0.14)

Values are given as mean with standard deviation in parentheses

BMI body mass index, *BMD* bone mineral density, *n* number of participants

[a] Significantly different ($P < 0.05$) from values of participants in their forties

[b] Significantly different ($P < 0.05$) from values of participants in their fifties

[c] Significantly different ($P < 0.05$) from values of participants in their sixties

obtained between 0900 and 1500 in both surveys. Subjects who provided consent to participate in the blood examination were randomly allocated a specific time to undergo sampling, with times set at 15-min intervals between 0900 and 1500. Participant samplings could not be adjusted according to time after eating.

After centrifugation of blood samples, serum samples were immediately placed in dry ice and transferred to a deep freezer within 24 h. These samples were kept at −80°C until assay. BTMs collected in 1993 were measured after 7 years, when the methods for measurement of novel BTMs were introduced. Samples collected in 2003 were used for measurement within 1 year. Samples in 1993 and 2003 were measured using the same assay.

From the serum samples of participants in the baseline study, total osteocalcin (OC) was measured as a marker of bone formation. OC level was measured using an electrochemiluminescent immunoassay (ECLIA) (Elecsys N-MID Osteocalcin; Roche Diagnostics, Mannheim, Germany) [18]. Intraassay CV was 0.5% and sensitivity was 0.5 ng/ml. To monitor bone resorption, a beta-isomerized C-terminal cross-linking telopeptide of type I collagen (beta-CTX) and an N-terminal cross-linking telopeptide of type I collagen (NTX) were used. Serum beta-CTX was measured using an ECLIA (Elecsys beta-CrossLaps; Roche Diagnostics). Intraassay CV was 2.0% and sensitivity was 0.01 ng/ml [18]. Serum NTX was measured using an enzyme-linked immunosorbent assay (Osteomark NTX serum; Ostex International, Seattle, WA, USA) [19, 20]. Intraassay CV was 4.6% and sensitivity was 3.2 nM bone collagen equivalents (BCE/l).

Statistical analysis

All statistical analyses were performed using STATA statistical software (College Station, TX, USA). Differences in values of BMDs, BTMs, and change rates of BMDs and BTMs were tested for significance using analysis of variance (ANOVA) for comparisons among multiple groups and Scheffe's least significant difference test for pairs of groups. Correlation coefficients were estimated to identify associations between changes in levels of BTMs and BMD over 10 years. After controlling for the potential confounders listed in the Results section, multivariate regression analysis was performed using rates of change for BMDs at each site such as L2–L4, femoral neck, and total hip as an objective factor, and rates of change for each BTM such as total OC, beta-CTX, and NTX as explanatory factors and standardized partial regression coefficients were estimated. To address cohort effects on the values of BTMs, BTM levels of subjects in their fifties, sixties, and seventies in 1993 were compared to those of subjects in their fifties, sixties, and seventies in 2003 using a nonpaired *t* test.

Table 2 Annual change rate (%/year) in bone mineral density (BMD) over 10 years, classified by age and gender

Birth cohort	Age group (years)	*n*	L2–L4 BMD	Femoral neck BMD	Total hip BMD
Men					
1943–1952	40–49	43	−0.02 (0.59)	−0.15 (1.09)	−0.11 (0.71)
1933–1942	50–59	46	0.16 (0.8)	−0.30 (0.70)*	−0.30 (0.50)*
1923–1932	60–69	41	0.23 (0.94)	0.03 (1.25)	−0.36 (0.81)*
1913–1922	70–79	23	−0.15 (0.90)	0.66 (1.62)[b]	−0.24 (1.30)
1913–1952	40–79	153	0.08 (0.81)	−0.03 (1.17)	−0.26 (0.80)*
Women					
1943–1952	40–49	47	−1.14 (1.01)*	−0.86 (0.96)*	−0.68 (0.84)*
1933–1942	50–59	47	−0.79 (1.18)*	−0.64 (0.94)*	−0.70 (0.84)*
1923–1932	60–69	44	−0.32 (0.78)*,[a]	−0.57 (0.89)*	−0.73 (0.80)*
1913–1922	70–79	31	−0.60 (0.92)*	−0.61 (1.08)*	−0.90 (0.68)*
1913–1952	40–79	169	−0.73 (1.03)*	−0.68 (0.96)*	−0.74 (0.80)*

Values are given as mean with standard deviation in parentheses

BMD bone mineral density; *n* number of subjects

* Significantly different ($P < 0.01$) for changes over 10 years

[a] Significantly different ($P < 0.05$) from values of subjects in their forties

[b] Significantly different ($P < 0.05$) from values of subjects in their fifties

Results

Eligible participants and changes in BMD over 10 years

Over the 10 years, 322 of the 400 participants at baseline (80.4%; 153 men, 169 women) completed baseline and follow-up measurements. Among these, one man in his sixties declined to undergo baseline blood examination for BTMs. Evaluations of changes in BTMs were thus performed using the remaining 321 subjects (80.3%; 152 men, 169 women).

Rates of change for BMD during the 10-year period, classified by age and gender, are shown in Table 2. For men, BMD at L2–L4 in their fifties and sixties had increased slightly by the 10-year follow-up but had decreased slightly in their forties and seventies. BMD at the femoral neck had decreased in their forties and fifties and had increased in their seventies. BMD at the total hip had decreased in all age strata. These changes were significant at the femoral neck for men in their fifties ($P < 0.01$) and at the total hip for men in their fifties and sixties ($P < 0.01$). No significant differences were apparent between age strata except at the femoral neck between men in their fifties and those in their seventies ($P < 0.05$).

For women, BMD at the lumbar spine L2–L4, femoral neck, and total hip had decreased in all age strata over the 10 years, similar to findings in men at the total hip. These changes were significant ($P < 0.01$). However, no significant differences in rates of change were seen across age strata, with the exception of women in their forties and sixties at L2–L4.

Mean levels at baseline and comparative changes over 10 years in BTMs

Age–gender distributions of mean BTM levels at the initial survey are shown in Table 3. No significant difference was seen among the age groups for BTM levels in men, whereas significant differences were seen for each marker between women in their forties and women in their fifties to seventies ($P < 0.05$ each). Table 3 also shows the changes in serum total OC, beta-CTX, and NTX over 10 years in men and women. In men, in general, levels of serum total OC significantly decreased ($P < 0.05$) and those of beta-CTX significantly increased ($P < 0.05$), but no significant difference was identified in the rate of change for BTMs among any age strata. Serum levels of total OC, beta-CTX, and NTX for women in their forties were significantly lower than those of women in their fifties to seventies ($P < 0.05$) and change rates over 10 years for women in their forties were significantly higher ($P < 0.05$).

Rates of change of BTMs and BMDs over 10 years were compared by menstrual status over 10 years (Table 4). Among 94 female subjects in their forties and fifties, 52 women (55.3%) were premenopausal at baseline. During

Table 3 Mean values at baseline and annual change rate (%/year) of biochemical markers of bone turnover (BTMs) over 10 years, classified by age and gender

Birth cohort	Age group (years)	Total OC (ng/ml)		Beta-CTX (ng/ml)		NTX (nmol BCE/l)	
		Baseline	Change rate (%/year)	Baseline	Change rate (%/year)	Baseline	Change rate (%/year)
Men							
1943–1952	40–49	18.8 (7.5)	−1.54 (4.80)*	0.190 (0.107)	1.66 (8.00)	13.3 (2.8)	−0.04 (3.44)
1933–1942	50–59	19.7 (18.3)	−1.21 (2.41)*	0.197 (0.162)	4.48 (17.33)	14.0 (6.0)	−0.04 (3.19)
1923–1932	60–69	16.4 (6.1)	−0.20 (3.93)	0.174 (0.107)	4.82 (10.72)*	13.6 (4.1)	0.53 (3.32)
1913–1922	70–79	18.9 (8.1)	−0.95 (3.45)	0.187 (0.099)	13.35 (49.33)	13.5 (3.4)	1.88 (3.76)*
1913–1952	40–79	18.5 (11.1)	−1.00 (3.74)*	0.187 (0.121)	5.10 (22.48)*	13.6 (4.2)	0.40 (3.41)
Women							
1943–1952	40–49	14.9 (5.7)	4.24 (6.94)*	0.103 (0.066)	16.84 (20.55)*	11.6 (2.3)	2.63 (3.29)*
1933–1942	50–59	28.1 (8.8)[a]	−1.08 (3.83)[a]	0.255 (0.121)[a]	1.35 (8.77)[a]	15.4 (3.3)[a]	−0.23 (3.59)[a]
1923–1032	60–69	32.6 (12.4)[a]	−2.06 (2.99)*,[a]	0.301 (0.136)[a]	1.28 (8.71)[a]	17.8 (4.4)[a,b]	−0.25 (2.23)[a]
1913–1022	70–79	28.3 (10.3)[a]	−1.73 (3.21)*,[a]	0.275 (0.153)[a]	1.13 (6.77)[a]	16.0 (3.2)[a]	0.11 (2.66)[a]
1913–1052	40–79	26.0 (11.6)	0.02 (5.32)	0.234 (0.145)	5.53 (14.54)*	15.2 (4.0)	0.62 (3.26)*

Values are given as mean with standard deviation in parentheses

BTMs, biochemical markers of bone turnover; OC, osteocalcin; beta-CTX, beta-isomerized C-terminal cross-linking telopeptide of type I collagen; NTX, N-terminal cross-linking telopeptide of type I collagen; BCE, bone collagen equivalents

* Significantly different ($P < 0.05$) for changes over 10 years

[a] Significantly different ($P < 0.05$) from values of subjects in their forties

[b] Significantly different ($P < 0.05$) from values of subjects in their fifties

Table 4 Mean values at baseline and annual change rate of BTMs over 10 years, classified by menstrual status in women

Menstrual status over 10 years	*n*	Age (years)	Total OC (ng/ml)		Beta-CTX (ng/ml)		NTX (nmol BCE/l)	
			Baseline	Change rate (%/year)	Baseline	Change rate (%/year)	Baseline	Change rate (%/year)
Premenopause	12	41.3 (1.3)	13.7 (5.3)	0.96 (7.53)	0.101 (0.059)	9.63 (24.49)	11.8 (2.5)	0.83 (3.13)
Transition to menopause	40	46.3 (3.6)	16.7 (7.3)[b]	4.40 (6.49)*,[b]	0.120 (0.090)[b]	15.16 (18.21)*,[b]	11.7 (2.3)[b]	2.76 (3.30)*,[b]
Postmenopause	117	63.9 (7.9)	29.5 (9.6)[a]	−1.57 (3.50)*	0.281 (0.136)[a]	1.86 (9.69)*	16.6 (3.7)[a]	−0.13 (2.94)
Total	169	58.1 (11.1)	25.4 (10.9)	0.02 (5.32)	0.231 (0.144)	5.53 (14.54)*	15.1 (4.1)	0.62 (3.26)*

Values are given as mean with standard deviation in parentheses

BMD, bone mineral density; BTMs, biochemical markers of bone turnover; *n*, number of subjects; OC, osteocalcin; beta-CTX, beta-isomerized C-terminal cross-linking telopeptide of type I collagen; NTX, N-terminal cross-linking telopeptide of type I collagen; BCE, bone collagen equivalents

* Significantly different ($P < 0.05$) for changes over 10 years

[a] Significantly different ($P < 0.001$) from values of participants in the premenopausal group

[b] Significantly different ($P < 0.001$) from values of participants in the postmenopausal group

the 10-year observation, 12 (12.8%) remained premenopausal, but 40 (42.6%) progressed into menopause. Table 4 shows that rates of change for all BTMs over the 10 years were significantly increased in the group with transition into menopause ($P < 0.05$). Change rates were significantly higher in women with transition into menopause compared to postmenopausal women ($P < 0.001$).

Association between changes in BTMs and changes in BMD over 10 years

Associations between changes in BTMs and changes in BMD were analyzed. Correlation coefficients of changes to L2–L4 BMD and changes to OC, beta-CTX, and NTX were –0.12 ($P = 0.16$), 0.04 ($P = 0.66$), and –0.08 ($P = 0.35$),

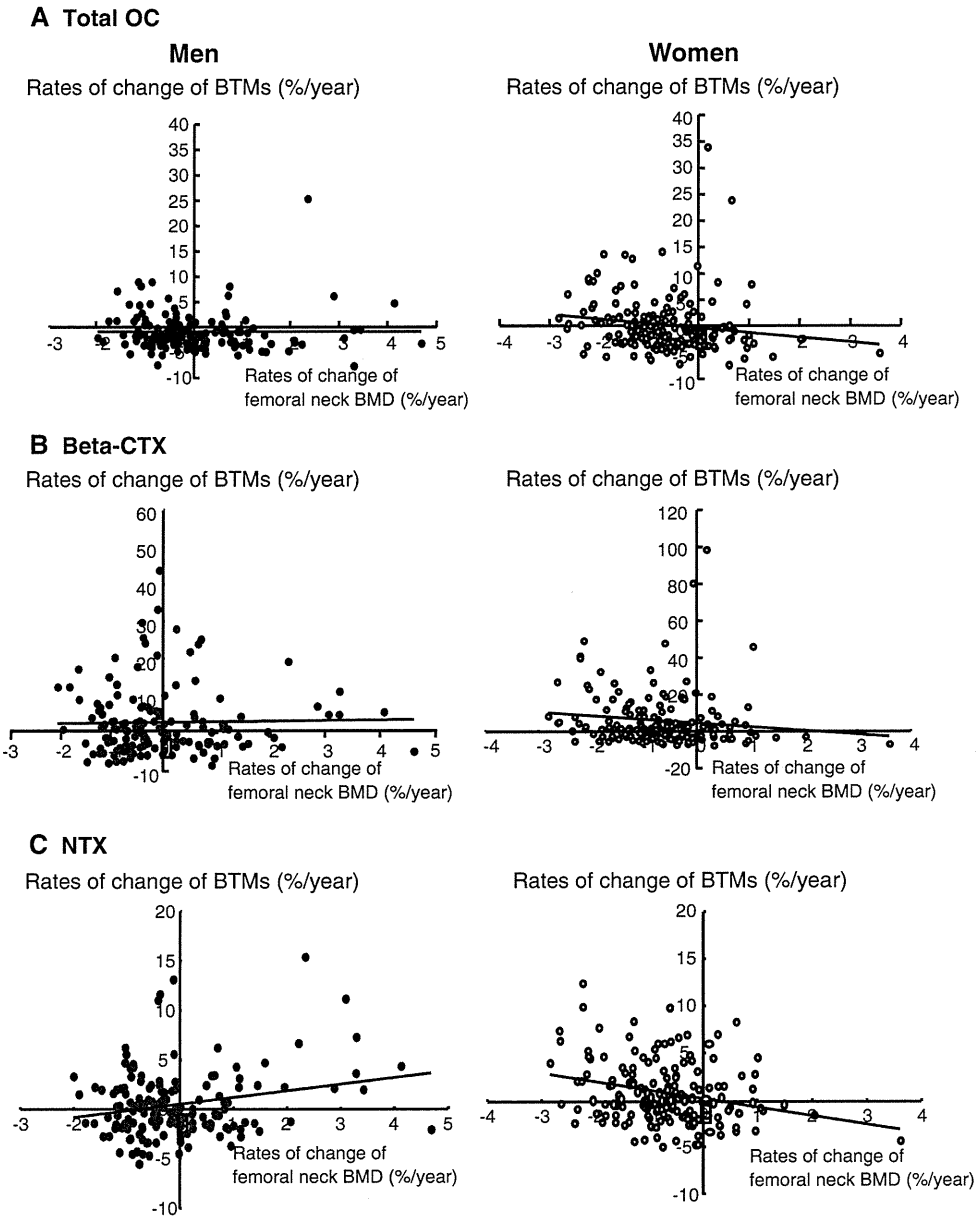

Fig. 1 Association between rates of change of biochemical markers of bone turnover and rates of change of bone mineral densities at the femoral neck. *OC*, total osteocalcin (**a**); *BTM*, biochemical markers of bone turnover; *beta-CTX*, beta-isomerized C-terminal cross-linking telopeptide of type I collagen (**b**); *NTX*, N-terminal cross-linking telopeptide of type I collagen (**c**)

respectively, in men, and –0.20 ($P = 0.01$), –0.16 ($P = 0.04$), and –0.29 ($P = 0.0002$), respectively, in women. Correlation coefficients of changes to femoral neck BMD and changes to OC, beta-CTX, and NTX were –0.003 ($P = 0.98$), 0.19 ($P = 0.02$), and 0.23 ($P = 0.004$), respectively, in men, and –0.15 ($P = 0.04$), –0.13 ($P = 0.09$), and –0.27 ($P = 0.0005$), respectively, in women. Correlation coefficients of changes to total hip BMD and changes to OC, beta-CTX, and NTX were –0.16 ($P = 0.05$), –0.07 ($P = 0.39$), and –0.02 ($P = 0.86$), respectively, in men and –0.19 ($P = 0.01$), –0.12 ($P = 0.12$), and –0.28 ($P = 0.0002$), respectively, in women. These findings indicate that increased BMD at the femoral neck in men correlated significantly with increased serum levels of beta-CTX and NTX. By contrast, decreased BMD at all sites (that is, L2–L4, femoral neck, and total hip) in women was significantly related to increased serum levels of BTMs. Figure 1 shows scatter plots for changes in total OC, beta-CTX, and NTX and changes to BMD at the femoral neck in both men and women. At the femoral neck, the direction of association between changes of bone resorption markers and BMDs differed between men and women, although the direction of association of changes to BTMs and BMD in both men and women were similar at L2–L4 and total hip.

To clarify associations between changes in BTM and BMD after adjusting for confounders, multivariate regression analysis was performed. Regarding the change of values of BMD at L2–L4, multivariate regression analysis

Table 5 Standardized partial regression coefficient (β) of changes of BTMs for annual change rate for BMD

BTMs	L2–L4 BMD		Femoral neck BMD		Total hip BMD	
	β	P	β	P	β	P
Men						
Total OC	−0.12	0.139	0.06	0.455	−0.16	0.056
Beta-CTX	0.03	0.747	−0.04	0.632	0.11	0.166
NTX	−0.08	0.323	0.01	0.875	−0.01	0.938
Women						
Total OC	−0.18	0.024	−0.16	0.068	−0.31	<0.001
Beta-CTX	−0.09	0.269	−0.06	0.457	−0.18	0.027
NTX	−0.21	0.006	−0.06	0.495	−0.34	<0.001

Standardized partial regression coefficients were obtained after adjustment for age and body mass index

BMD, bone mineral density; BTMs, biochemical markers of bone turnover; *n*, number of subjects; OC, osteocalcin; beta-CTX, beta-isomerized C-terminal cross-linking telopeptide of type I collagen; NTX, N-terminal cross-linking telopeptide of type I collagen

was performed using change rates of L2–L4 BMD as an objective factor and change rates of each BTM as an explanatory factor after controlling for age, body mass index (BMI), occurrence of clinical vertebral fractures over 10 years in both men and women, and menstrual status over 10 years (0, premenopausal; 1, transition to menopause; 2, menopausal) in women. Furthermore, with regard to the proximal hip, including the femoral neck and total hip, multivariate regression analysis was performed after controlling for age and BMI in both men and women and menstrual status over 10 years in women. Table 5 shows the standardized partial regression coefficient of change rates of BTMs for annual change rates for BMD. For men, there was no significant association of changes of BTMs and changes of BMDs at any of the sites. By contrast, for women, although no significant association was seen between changes of BMD at the femoral neck and changes in BTM, change rates of total OC and NTX were significantly associated with change rates of L2–L4 BMD, and change rates of total OC, beta-CTX, and NTX were significantly associated with change rates of BMD at the total hip (Table 5).

Comparison of mean BTM levels in given age strata classified by birth cohort

The BTM levels of subjects in their fifties, sixties, and seventies in 1993 were compared to those in their fifties, sixties, and seventies in 2003 (Fig. 2). No significant differences in mean values of BTMs were identified in the same age strata or in different birth cohorts in men. By contrast, the BTM levels of female subjects in 1993 tended

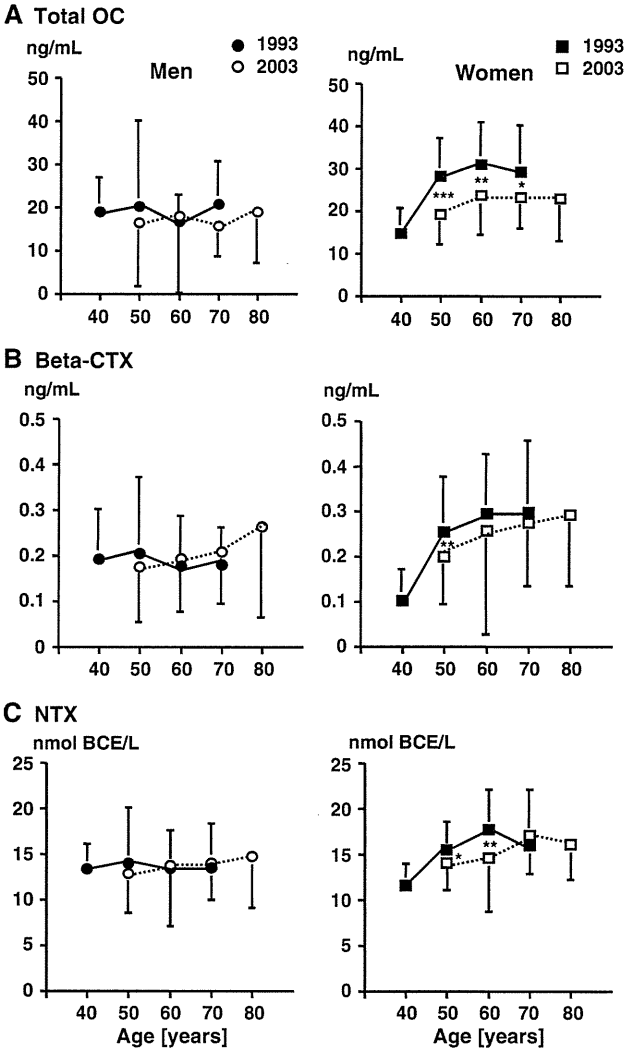

Fig. 2 Changes in serum biochemical markers of bone turnover over 10 years, classified by age strata. **a** Total osteocalcin (*OC*). **b** Beta-isomerized C-terminal cross-linking telopeptide of type I collagen (*beta-CTX*). **c** N-terminal cross-linking telopeptide of type I collagen (*NTX*). *BCE*, bone collagen equivalents. Significantly different from values of participants in the same age strata between different birth-cohorts in 1993 and 2003 (*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$)

to be higher than those in 2003 for the same age strata (Fig. 2). This result suggests an effect of birth cohort for serum levels of BTMs in women, particularly those in their fifties, but not in men. That is, BTM levels were significantly lower for women in their fifties in 2003 compared to those in their fifties in 1993.

Discussion

In this 10-year follow-up study, we clarified changes to levels of BTMs in men and women from a rural community

in Japan. Change rates of BTMs over 10 years were influenced by menstrual transition, age, and sex. Increases in both bone formation and bone resorption markers are associated with decreases in BMD at L2–L4 and the total hip in women after controlling for confounding factors. In terms of birth-cohort effect, values of BTMs for participants in 2003 were significantly lower than those in 1993 when compared between the same age strata in women.

We have already reported the age–sex distribution of values of BTMs, such as intact OC, alkaline phosphatase, C-terminal propeptide of type I procollagen, C-terminal cross-linking telopeptide of type I collagen generated by matrix metalloproteinase, urinary pyridinoline cross-links of collagen, and deoxypyridinoline cross-links of collagen using the same population as the present study [11]. That report showed that levels of all the aforementioned BTMs were significantly lower in the 40–49 age group than in each of the 50–59, 60–69, and 70–79 age groups in women, whereas no significant differences were apparent among age groups in men [11]. Following the previous study, we clarified changes of BTMs in each age group in the present study, with values of BTMs starting to increase in women in their forties, then stabilizing (beta-CTX, NTX) or mildly decreasing (total OC) among older age groups. The rate of decrease of BTMs was greatest in the menopausal transient group compared to the groups remaining premenopausal or postmenopausal. Although the number of subjects in each category of menstrual status was limited, these results suggest that the onset of menopause in their forties causes dramatic changes in bone metabolism in women. With regard to estrogen and changes of BTMs, Ebeling et al. [21] and Sowers et al. [22] reported that levels of BTMs increased before menopause as a consequence of declining concentrations of serum estradiol (E_2) and increasing concentrations of follicle-stimulating hormone. We have already reported that serum levels of total E_2 were associated with decreased BMD over 3 years among premenopausal women [23].

In terms of the effects of BTM changes on changes in BMD over 10 years, the present study revealed that increases in BTMs over 10 years in women, even for bone formation markers or bone resorption markers, are associated with decreased BMD at L2–L4 and total hip. This association remains after controlling for confounding factors. No previous reports appear to have clarified associations between changes in levels of BTMs and bone loss for one decade. The present study revealed that a higher rise in values of BTMs, particularly total OC and NTX, was associated with faster BMD loss in women. These associations were observed over a reasonably long time period. However, these findings were identified at L2–L4 and total hip, but not at the femoral neck. Although reasons for site-specific differences in the association between BTMs and BMD remain uncertain, we have already reported that bone loss rate differs depending on the site involved in another cohort study [13]. We have also reported that characteristics differ between fast bone loss at the lumbar spine and femoral neck [24]. One reason for these site-specific differences might be that fixing the position for BMD examination using DXA was more difficult for the femoral neck than for L2–L4 or total hip, and as a result, the CV tended to be higher there than at other sites [17]. Changes that increase BMD, such as osteophytosis or sclerotic changes, are also observed most frequently at the lumbar spine, which might be another reason for the site-specific differences. We were unable to perform X-ray examinations of participants in the present study. We thus could not control the influence of degenerative changes and fractures on lumbar L2–L4 BMD. Regarding fractures, we analyzed past clinical vertebral fractures as a confounder, but this was not sufficient. However, these changes seem to increase the BMD, so our results in terms of changes to BMD in the present study may be overestimated. Considering the CV and effect of degenerative changes, measurement for the total hip might be the proper site for observation of BMD change over the long term.

The present study also found evidence of differences in BTM values for a given age stratum between different birth cohorts in women. Data on levels of BTMs in 1993 and 2003 showed that accelerated bone remodeling seemed to improve for women in their fifties to seventies in younger cohorts. However, those results were affected by potential confounders such as differences in age, anthropometric measurements, and menstrual status. We then compared the aforementioned factors between women in their fifties to seventies in 1993 and in 2003. Mean age (SD) for groups in 1993 and 2003 was 65.0 (8.1) years and 64.6 (8.9) years, and mean BMI (SD) in 1993 and 2003 was 23.2 (3.8) kg/m^2 and 23.5 (3.9) kg/m^2. No significant differences were identified between birth cohorts. The proportion of women in menopause in their fifties to seventies was 94.7% in 1993 and 91.3% in 2003. No significant difference was seen between birth cohorts ($P = 0.26$). Even if analysis was focused on women in their fifties, no significant differences were apparent ($P = 0.25$). Although other confounders resulting from differences in generation might have influenced the cohort effect, we conclude that a birth-cohort effect was seen on bone metabolism in middle-aged and elderly women in the present cohort. Our results are consistent with findings we have reported elsewhere that community-dwelling inhabitants in later birth cohorts show higher BMD in middle age, using another cohort established in a mountainous area [13]. The results are also consistent with the findings of Fujiwara et al. [25], who assessed the effects of birth cohort on the incidence of vertebral fracture in Hiroshima and found that incidence

decreased with successive birth decades. Thus, given all these findings, levels of BTMs appear significantly lower, levels of BMD appear significantly higher, and the incidence of vertebral fractures is lower in women from younger birth cohorts in Japan compared to those from older birth cohorts. These results suggest that the problem of osteoporosis might be less severe than has previously been predicted for the future in Japan.

The present study shows several limitations. The primary weakness involved the methods of sample collection. First, not all samples of participants were extracted at a fixed time (e.g., morning) under fixed conditions (e.g., fasting). Samples in this study were extracted between 0900 and 1500, rather than at a fixed time. Circadian variability is known to affect BTM levels [4]. Hannon and Eastell [26] reviewed the circadian variability of BTMs, noting that serum levels of OC peaked between 0200 and 0400 and reached a nadir between 1200 and 1600, whereas serum CTX levels peaked between 0130 and 0430, reaching a nadir between 1100 and 1400. We could not find any reports on circadian rhythms for serum NTX, but Delmas et al. [4] stated that most BTM levels increased at night, peaked between 0200 and 0800, then decreased rapidly to a nadir between 1300 and 2300. Based on these reports, the timing of sample collection was based on when BTM levels were supposed to be reaching a nadir. The present results might thus have underestimated levels of BTMs compared to collection at a fixed time in the morning. Although adjustment for the time after eating is important, particularly for measurements of serum CTX, we could not collect samples under absolutely controlled conditions. Delmas et al. [4] reported that fasting diminishes the rhythm of serum CTX-I, particularly with regard to the rapid decrease in the morning. Because we could not control the timing for collecting blood samples and fasting, we might not have accurately evaluated interindividual changes in BTMs. However, all participants in examinations in both 1993 and 2003 were allocated randomly to a specific sampling time and the allocated time was associated with eating behaviors. Random noise resulting from variability in sampling time and eating status might thus have occurred with relatively equal probability in both 1993 and 2003. Comparison of BTM levels between cohorts, rather than individuals, in 1993 and 2003 thus appears valid.

Second, long-term storage might have influenced BTM levels. In this study, serum samples were immediately placed in dry ice and transferred within 24 h to a deep freezer kept at −80°C. BTMs in the present study were measured utilizing baseline samples after 7 years, given that methods to identify these BTMs were unavailable in 1993. Storage for 7 years might therefore have influenced BTM levels, even at −80°C. No data are available regarding the influence of such long-term storage, although Seibel [27] stated that BTMs in sera would be stable with a storage temperature of −70°C. Hannon and Eastell [26] reported that long-term CVs for OC, serum NTX-I, and serum CTX-I were 27.3% at 9 months, 24.0% at 3 years, and 13.1% at 1 year. The CV for 7-year storage might well be higher than these results. If so, levels of BTMs collected in 1993 and measured in 2000 would have been systematically greater than those obtained in the present study, underestimating differences between 1993 and 2003. Changes over 10 years would thus have been greater and the effects of birth cohort even more pronounced.

Another limitation involves withdrawal bias. Although we completed the 10-year follow-up with a high participation rate, 80.4%, the dropout rate among men in their seventies was rather high (54.0%). This high dropout rate might have resulted in a withdrawal bias, meaning that healthier survivors would have skewed the results of long-term observation. Increases in femoral neck BMD might have been skewed by any such withdrawal bias. However, the main reasons for dropout among men in their seventies were death (52%) and illness (31%), which seem unavoidable. We think that this represents an inherent limitation of all longitudinal follow-up studies. The possibility of withdrawal bias should be considered when interpreting the data.

In conclusion, the present study found that change rates of BTMs were higher for women in their forties than for women in their fifties to seventies ($P < 0.05$) and were higher in the menstrual transition group than in the pre- and postmenopausal groups ($P < 0.001$). Changes in BTMs during the 10 years showed significant associations between bone loss at L2–L4 and total hip in women, after adjusting for confounders. Levels of all BTMs in women in their fifties were significantly lower than in younger birth cohorts.

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