

Fig. 1. Input and output of the web application of the FRISC.

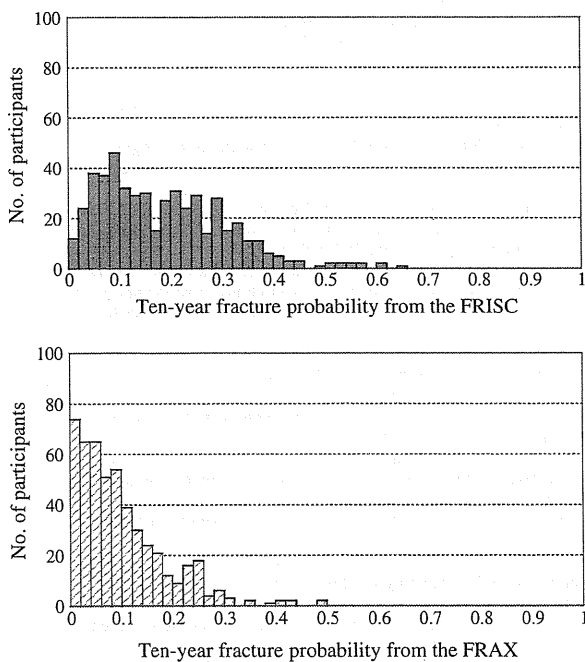


Fig. 2. Histogram of 10-year probabilities of major osteoporotic fracture from the FRISC (upper) and the FRAX (lower) in the Miyama and Taiji Cohorts.

($p < 0.01$) and therefore seemed to be attributable to confounders. This may be one of the causes of discrepancy in 10-year probability between the FRAX and the actual fracture rate in the three cohorts. Recent report indicated that morbid obesity had a higher susceptibility of fractures comparing to the postmenopausal women with normal weight although the BMD of the obesity was higher than the controls [35]. As it is well known that obesity will connect to have diabetes mellitus or at least to have glucose intolerance and diabetes may deteriorate bone quality due to an increase in non-enzymatic glycation induced cross-links of collagen, which increased collagen

Table 4
Predictive accuracy of major osteoporotic fracture probability from the FRISC compared the FRAX evaluated in the validation dataset from general population.

| | Calibration | | | Discrimination | | |
|-----------|------------------------|--------------------------|-------|---------------------------|-------------|--------------|
| | Predicted no. of cases | Observed/predicted ratio | p^* | C statistics [†] | 95% CI | p^\ddagger |
| BMD alone | – | – | – | 0.651 | 0.575–0.728 | – |
| The FRAX | 37.8 | 1.59 | <0.01 | 0.699 | 0.629–0.768 | 0.23 |
| The FRISC | 81.2 | 0.74 | 0.17 | 0.727 | 0.660–0.794 | 0.03 |

CI: confidence interval.
^{*} Hosmer–Lemeshow test, p value less than 0.05 indicates a significant deviation between the observed and predicted event frequencies. Number of strata and degree of freedom are 10 and 8, respectively.
[†] The proportion of all patient pairs in which prediction and observed occurrence of event are concordant.
[‡] Contrast test comparing C statistics of the FRAX and FRISC from that of BMD alone, p value less than 0.05 indicates a significant improvement from BMD alone.

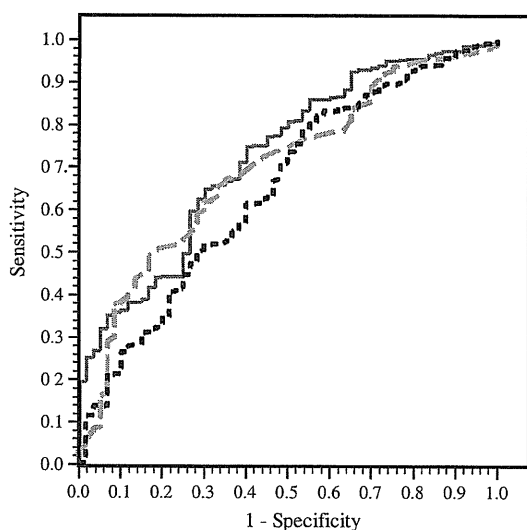


Fig. 3. Receiver operating characteristic curve for major osteoporotic fracture probability from the FRISC (solid curve), the FRAX (dashed curve) and BMD alone (dotted curve) in the Miyama and Taiji Cohorts.

brittleness [36,37]. Lifestyle factors such as diet and exercise may also be other explanations for this observation.

Although the intrinsic properties of the bone are important components of fracture risk, assessment of these factors alone does not adequately reflect the full range of factors associated with the occurrence of fracture [38]. Loss of bone mass and impaired bone quality are commonly held to be the two major causes of increased bone fragility in osteoporosis [2]; however, existing prediction models do not directly take bone quality into consideration. Despite recent progress in understanding the composition and structure of the bone, there are currently no standard assessments of bone quality. Novel bone quality-related markers such as homocysteine [39,40] and pentosidine [41] appear to improve predictive accuracy, but further research is required to determine whether they will be useful in the context of predicting osteoporotic fracture.

The incidence of clinical vertebral fracture in the Japanese population is substantially high (Table 2). As a result, the 10-year fracture probabilities generated using the FRISC is much higher than the FRAX (Fig. 2). The major underlying cause of the discrepancy in the 10-year probabilities is likely to be the difference in population. The FRISC was developed in a cohort study conducted at one medical institute and included subjects who were receiving treatment for osteoporosis, whereas the FRAX was developed using data from a community-based population. Although the effectiveness of bisphosphonate and selective estrogen receptor modulators in reducing fracture risk has been demonstrated, in the current analysis, drug treatment for osteoporosis was not a significant factor at the site of major osteoporotic fracture after adjustment for other risk factors, suggesting that its influence on risk is smaller than that of the risk factors. People who visit a hospital or clinic possibly have a higher prevalence of co-morbid conditions than people in the general population, yielding an increased incidence of fracture because of deterioration in both bone quality and quantity.

Given the large difference in incidence rates of fracture between the Nagano Cohort and the Miyama and Taiji Cohorts (Table 2), it may not seem to be sensible to choose the Miyama and Taiji Cohorts as validation cohorts since a good fit is unexpected. However, as shown in Table 1, the Nagano cohort included older participants and the mean lumbar BMD in this cohort was lower than the other cohorts. Therefore the difference in participants' characteristics may be attributable to the higher incidence rate in the Nagano cohort relative to the other cohorts. Further, the Miyama and Taiji Cohorts followed participants over a 10-year period

and are more suitable for the validation analysis. A limitation of our validation analysis was that parental history or morphometrical vertebral fracture was missing data in either of the validation cohorts systematically. We assumed that participants with these missing data did not have parental history or prior fracture, yielding a somewhat lower 10-year probability of major osteoporotic fracture. Given that we did not find any evidence of deviation between the observed fracture frequency and prediction from the FRISC even in independent community-based cohort studies, the FRISC appears to allow accurate prediction of major osteoporotic fracture both in community-based and hospital-based settings.

Supplementary materials related to this article can be found online at doi:10.1016/j.bone.2010.08.019.

Conclusion

We developed a novel prediction model for fracture and immobilization, FRISC, and the clinical risk factors in the FRISC allows better identification of populations at high risk of fracture than BMD alone.

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Reference values for hand grip strength, muscle mass, walking time, and one-leg standing time as indices for locomotive syndrome and associated disability: the second survey of the ROAD study

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Abstract

Background We established reference values for hand grip strength, muscle mass, walking time, and one-leg standing time as indices reflecting components of locomotive syndrome and associated disability using a large-scale population-based sample from the second survey of the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) cohort.

Methods We measured the above-mentioned indices in 2,468 individuals ≥ 40 years old (826 men, 1,642 women; mean age 71.8 years) during the second visit of the ROAD study. Disability was defined as certified disability according to the long-term care insurance system through public health centres of each municipality.

Results Mean values for hand grip strength (weaker side), muscle mass of the thighs, walking time for 6 m at the

usual pace, and the fastest pace for men were 32.7 kg, 7.0 kg, 5.6 s, and 3.7 s, respectively, and those for women were 20.8 kg, 5.2 kg, 5.9 s, and 4.1 s, respectively. The median values for one-leg standing time (weaker side) were 14 s for men and 12 s for women. The prevalence of disability in men aged 65–69, 70–74, 75–79, and ≥ 80 was 0.0, 1.0, 6.3, and 8.8%, respectively, and in women was 3.4, 3.5, 9.2, and 14.7%, respectively. There were significant associations between the presence of disability and walking time for 6 m at the usual pace and at the fastest pace, and between the presence of disability and walking speed.

Conclusions We established reference values for indices reflecting components of locomotive syndrome, and identified significant associations between walking ability and disability.

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Introduction

Musculoskeletal diseases, including osteoarthritis (OA) and osteoporosis (OP), are major public health problems among the elderly that affect activities of daily living (ADL) and quality of life (QOL), leading to increased morbidity and mortality. According to the recent National Livelihood Survey by the Ministry of Health, Labour, and Welfare in Japan, OA is ranked fourth, while falls and osteoporotic fractures are ranked fifth among diseases that cause disabilities and subsequently require support for ADL [1]. Previous studies have reported increased mortality following osteoporotic fractures at the hip and other sites [2], and have estimated that a total of 47,000,000 people (21,000,000 men and 26,000,000 women) aged ≥ 40 years will eventually be affected by either OA or OP. Considering that the population of Japan is aging very rapidly—more than 22% of the population is aged ≥ 65 years [3]—a comprehensive and evidence-based prevention strategy for musculoskeletal diseases is urgently needed.

The Japanese Orthopaedic Association has proposed the term 'locomotive syndrome' to designate a condition in high-risk groups with musculoskeletal diseases who are highly likely to require nursing care [4]. Locomotive syndrome is caused by weakening of musculoskeletal organs such as bone, joint, and muscle, which in turn interferes with physical performance, especially self-transportation. Loss of locomotor abilities such as walking causes disabilities requiring support. Therefore, to prevent decline into disability, it is important to maintain a healthy range of bone, joint, muscle, and physical performance.

These four components, bone, joint, muscle, and physical performance, each have objective measurements that can be used as indices to evaluate their present condition. For example, bone mineral density (BMD) is a representative index of the condition of the bone. Joint space width (JSW), joint space area (JSA), and osteophyte area (OPA) are indices reflecting the condition of the joint. Regarding muscle, although the best index remains controversial, hand grip strength can be used to reflect muscle strength [5], and muscle mass is one index of muscle volume [6]. In addition, as objective indices of physical performance, walking speed and/or one-leg standing times are candidates [7, 8]. However, at present, it is difficult to use such indices for evaluating, diagnosing, or predicting the future occurrence and progression of locomotive syndrome in Japan, because there is little information on reference values for such indices to distinguish patients at risk from normal individuals in a large population-based cohort.

In 2005–2007, we began a large-scale population-based cohort study entitled Research on Osteoarthritis/

Osteoporosis Against Disability (ROAD), consisting of 3,040 participants in three communities located in urban, mountainous, and coastal areas (baseline study). Following the baseline study, a second survey was performed in the same communities in 2008–2010, in which 2,674 inhabitants participated (second visit).

Through analysis of the baseline data of the ROAD, the age-gender distribution of BMD has been reported as an index for bone mass [3], and the medial and lateral JSW, medial and lateral JSA, OPA, and femorotibial angle of the knee have been reported as indices of the health of joints [9] in these populations. However, there is still scant information regarding the condition of the muscles and physical performance. Therefore, in the present study, we aimed to establish reference values for hand grip strength as an index of muscle power, muscle mass as an index of muscle volume, and walking time and one-leg standing time as indices of physical performance, classified by age and gender, using the data from the second visit of the ROAD study. This information is expected to be valuable for early diagnosis and prevention of locomotive syndrome. In addition, we evaluated the prevalence of disabilities in participants in the ROAD study second visit, and identified associations between hand grip strength, muscle mass, walking time, and one-leg standing time and the presence of disability.

Participants and methods

Participants

Reference values were obtained from the results of cross-sectional measurements of participants enrolled in the second visit of the ROAD study. The ROAD study, which began in 2005, is a nationwide prospective study comprising population-based cohorts established in three communities, such as urban, mountainous, and coastal regions in Japan. Recruitment methods for this study have been described in detail elsewhere [3]. To date, participants in the urban region, aged ≥ 60 years, were recruited from among those enrolled in a randomly selected cohort study from the previously established Itabashi Ward resident's registration database. The response rate was 75.6%. Participants in the mountainous and coastal regions, aged ≥ 40 years, were recruited from listings of resident registration. Residents aged ≤ 60 years in the urban area and ≤ 40 years in the mountainous and coastal areas who were interested in participating in the study were invited. We have completed development of a baseline database including clinical and genetic information for 3,040 inhabitants aged 23–95 years (1,061 men, 1,979 women).

The second visit of the ROAD study began in 2008 and was completed in 2010. All the participants in the baseline study were invited to participate in the second visit. In addition to the former participants, inhabitants aged ≥ 60 years in the urban area and those aged ≥ 40 years in the mountainous and coastal areas who were willing to participate in the ROAD survey performed in 2008–2010 were also included in the second visit. In addition, residents aged ≤ 60 years in the urban area and ≤ 40 years in the mountainous and coastal areas who were interested in participating in the study were invited to be examined as well as the baseline.

The inclusion criteria of participants were as follows: (1) ability to walk to the clinic where the survey was performed, (2) ability to provide self-reported data, and (3) ability to understand and sign an informed consent form. No other exclusion criteria were used.

Thus, a total of 2,674 residents (892 men, 1,782 women) aged 21–97 years participated in the second visit. In the present study, we analysed the data for 2,468 individuals (826 men, 1,642 women; mean age 71.8 years); this population comprised 956 individuals (318 men, 638 women) in the urban region, 726 individuals (258 men, 468 women) in the mountainous region, and 786 individuals (250 men, 536 women) in the coastal region who participated in the second visit and were ≥ 40 years old.

All the participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the participating institutions.

Hand grip strength, muscle mass, walking time, and one-leg standing time

Hand grip strength was measured bilaterally using a Toei Light handgrip dynamometer (Toei Light Co., Ltd., Saitama, Japan). Both hands were tested, and the better value was used to characterise the maximum muscle strength of the subject.

Among the 2,468 participants who participated in the second visit of the ROAD study, 778 residents (248 men, 530 women) in the coastal town of Taiji were examined to determine their segmental muscle mass using the bioelectrical impedance method (BIP; Physion MD; Physion Inc., Kyoto, Japan). We obtained values for the muscle masses of the right and left forearms, upper arms, upper limbs, quadriceps, thighs, lower legs, and lower limbs. This method had previously been validated as having a close correlation to muscle volume as measured by magnetic resonance imaging [10].

Among the 2,468 participants who participated in the second visit of the ROAD study, 1,637 residents (559 men, 1,078 women) of the mountainous town of Hidakagawa and the coastal town of Taiji were examined to determine

their walking time. Walking time was measured as the time required to complete a 6-m course. All participants walked the 6-m course twice; they first walked at their usual walking speed and then repeated the course at their fastest pace.

Among the 2,468 participants who participated in the second visit of the ROAD study, one-leg standing time with eyes open was measured on both sides for 2,433 individuals (816 men, 1,617 women). The time until the raised leg was set down on the floor was measured, with a maximum time of 60 s recorded for those who could stand on one leg for at least that length of time. The shorter value of the two measurements was used as the worse side and the longer measurement as the better side for the one-leg standing time of the subject.

Mean values and standard deviations (SDs) of hand grip strength, muscle mass, and walking time were classified by gender and age group (40, 50, 60, 70, and ≥ 80 s) to establish age-gender reference values for the general population. However, reference values classified by gender and age group for one-leg standing time were established using median (50th percentile) values and 25th–75th percentile ranges. These values were recorded using a maximum time of 60 s for anyone who could exceed that time; thus, the data do not fit a normal distribution, and use of means and SDs is unsuitable for one-leg standing time reference values.

Presence of disability

Disability in the present study was defined as ‘cases requiring long-term care’ as determined by the long-term care insurance system based on the Long-Term Care Insurance Act of 1997 in Japan. The procedure for identifying cases requiring long-term care is as follows: (1) each municipality establishes a long-term care approval board consisting of clinical experts, physicians, and specialists at the Division of Health and Welfare in each municipal office; (2) the long-term care approval board investigates the insured person using an interviewer-administered questionnaire consisting of 82 items regarding mental and physical condition and makes a screening judgement based on the opinion of a regular doctor; and (3) ‘cases requiring long-term care’ are determined according to standards for long-term care certification uniformly and objectively applied nationwide [11].

During the 3 years between the baseline and the second visit of the ROAD study, we annually obtained information on the participating residents regarding deaths, changes of residence, and presence or absence of certified disability according to the long-term care insurance system from the public health centres of the participating municipalities.

Statistical analysis

All statistical analyses were performed using Stata statistical software (Stata, College Station, TX, USA). Differences in the values of the indices were tested for significance using analysis of variance for comparisons among multiple groups. Scheffé's least significant difference test was then used for pairs of age groups.

To ascertain associations between the presence of disability and hand grip strength, muscle mass, walking time, and one-leg standing time, logistic regression analyses were performed using the presence of disability (yes, 1; no, 0) as an objective factor, and values for hand grip strength, muscle mass, walking time, and one-leg standing time as the explanatory factor after adjusting for age, gender, and body mass index (BMI, kg/m²).

Results

Characteristics of participants

Summary characteristics including age, height, weight, and BMI of the participants in the present study are shown in Table 1. Two-thirds of the 2,468 subjects were women, and the mean age of the female participants was 1 year younger than that of the male participants. Height and weight were

significantly lower for women than for men, but no significant difference in BMI was noted between the genders. All anthropometric measurements other than BMI of females tended to decrease with age. BMI of women in their 80s and older was significantly lower than that in younger age groups, while there were no significant differences among age groups 40–70 years old.

Reference values for hand grip strength, muscle mass, walking time, and one-leg standing time

Table 1 also shows the age-gender distribution of hand grip strength for both the better and worse sides. Mean hand grip strength in men was significantly higher than that in women ($p < 0.001$) and decreased with age in both men and women ($p < 0.001$).

Mean muscle mass for both forearms, both upper arms, both upper limbs, both quadriceps, both thighs, both lower legs, and both lower limbs are shown in Table 2. Muscle masses for all parts of the body were significantly higher in men than in women ($p < 0.001$). Mean muscle mass in men decreased with age for all areas except the lower leg. Particularly in the quadriceps and thighs, muscle masses in men aged ≥ 70 were significantly lower than those in their 40s–50s ($p < 0.05$). By contrast, although muscle mass for women aged ≥ 80 and older tended to be lower than those of younger age groups (other than the lower legs), there

Table 1 Mean values (standard deviation) of anthropometric measurements and hand grip strength of the participants classified by sex and gender

| Age strata (years) | Number of subjects | Weight (kg) | Height (cm) | Body mass index (g/cm ²) | Grip strength (better side) (kg) | Grip strength (worse side) (kg) |
|--------------------|--------------------|-------------------------------|--------------------------------|--------------------------------------|----------------------------------|---------------------------------|
| Men | | | | | | |
| 40–49 | 32 | 73.5 (10.2) | 170.3 (7.3) | 25.4 (3.6) | 49.5 (8.2) | 49.3 (8.4) |
| 50–59 | 100 | 68.8 (10.6) | 168.0 (5.2) | 24.3 (3.3) | 47.3 (7.0) | 42.6 (6.9) |
| 60–69 | 137 | 65.4 (11.1) ^a | 165.2 (6.2) ^{a,b} | 23.9 (3.5) | 41.4 (6.6) ^{a,b} | 36.9 (7.9) ^{a,b} |
| 70–79 | 308 | 60.0 (8.1) ^{a,b,c} | 161.1 (5.7) ^{a,b,c} | 23.1 (2.7) ^{a,b} | 35.4 (6.8) ^{a,b,c} | 31.5 (7.1) ^{a,b,c} |
| 80 and older | 249 | 57.2 (8.9) ^{a,b,c,d} | 159.7 (6.0) ^{a,b,c} | 22.4 (2.9) ^{a,b,c} | 29.7 (6.2) ^{a,b,c,d} | 26.3 (6.3) ^{a,b,c,d} |
| Total | 826 | 61.6 (10.3) | 162.5 (6.7) | 23.3 (3.1) | 36.6 (9.1) | 32.7 (9.1) |
| Women | | | | | | |
| 40–49 | 93 | 55.9 (9.5) | 157.0 (4.4) | 22.6 (3.5) | 31.2 (4.3) | 28.2 (4.4) |
| 50–59 | 191 | 55.3 (8.9) | 154.4 (5.8) ^a | 23.2 (3.7) | 28.7 (4.9) ^a | 25.4 (4.9) ^a |
| 60–69 | 316 | 54.2 (8.0) | 152.0 (5.5) ^{a,b} | 23.4 (3.2) | 26.6 (4.3) ^{a,b} | 23.77 (4.5) ^{a,b} |
| 70–79 | 599 | 51.3 (8.5) ^{a,b,c} | 148.4 (5.9) ^{a,b,c} | 23.3 (3.5) | 22.6 (4.6) ^{a,b,c} | 19.7 (4.7) ^{a,b,c} |
| 80 and older | 443 | 47.4 (8.3) ^{a,b,c,d} | 145.5 (5.9) ^{a,b,c,d} | 22.4 (3.6) ^{c,d} | 19.4 (4.4) ^{a,b,c,d} | 16.6 (4.6) ^{a,b,c,d} |
| Total | 1,642 | 51.6 (8.9) | 149.5 (6.7) | 23.0 (3.5) | 23.7 (5.8) | 20.8 (5.8) |

^a Significantly different ($p < 0.05$) from values of the age group in their 40s

^b Significantly different ($p < 0.05$) from values of the age group in their 50s

^c Significantly different ($p < 0.05$) from values of the age group in their 60s

^d Significantly different ($p < 0.05$) from values of the age group in their 70s

Table 2 Mean values (standard deviation) of segmental muscle mass (kg) in total right and left sides classified by age and gender

| Age strata (years) | Number of subjects | Forearm | Upper arm | Upper limb | Quadriceps | Thigh | Lower leg | Lower limb |
|--------------------|--------------------|--------------------------|-------------|-------------|----------------------------|----------------------------|----------------------------|--------------|
| Men | | | | | | | | |
| 40–49 | 25 | 1.20 (0.19) | 1.59 (0.36) | 2.79 (0.54) | 3.91 (0.64) | 7.76 (1.19) | 3.41 (0.66) | 11.16 (1.69) |
| 50–59 | 60 | 1.18 (0.16) | 1.53 (0.28) | 2.71 (0.41) | 3.73 (0.64) | 7.45 (1.22) | 3.41 (0.66) | 10.86 (1.60) |
| 60–69 | 67 | 1.15 (0.17) | 1.50 (0.28) | 2.65 (0.42) | 3.50 (0.68) | 7.02 (1.28) | 3.52 (0.86) | 10.54 (1.89) |
| 70–79 | 66 | 1.17 (0.20) | 1.43 (0.28) | 2.60 (0.46) | 3.37 (0.66) ^a | 6.78 (1.26) ^a | 3.51 (0.68) | 10.29 (1.70) |
| 80 and older | 30 | 1.11 (0.17) | 1.37 (0.26) | 2.48 (0.38) | 3.10 (0.62) ^{a,b} | 6.27 (1.18) ^{a,b} | 3.92 (1.11) | 10.18 (2.05) |
| Total | 248 | 1.16 (0.18) | 1.48 (0.29) | 2.65 (0.44) | 3.52 (0.69) | 7.04 (1.30) | 3.53 (0.80) | 10.57 (1.79) |
| Women | | | | | | | | |
| 40–49 | 67 | 0.77 (0.12) | 0.86 (0.19) | 1.63 (0.30) | 2.65 (0.60) | 5.37 (1.12) | 2.65 (0.47) | 8.02 (1.45) |
| 50–59 | 124 | 0.76 (0.10) | 0.82 (0.16) | 1.58 (0.24) | 2.56 (0.44) | 5.20 (0.82) | 2.58 (0.51) | 7.78 (1.20) |
| 60–69 | 161 | 0.78 (0.11) | 0.84 (0.16) | 1.62 (0.25) | 2.55 (0.45) | 5.18 (0.84) | 2.57 (0.42) | 7.74 (1.10) |
| 70–79 | 130 | 0.80 (0.12) ^b | 0.85 (0.16) | 1.66 (0.27) | 2.54 (0.46) | 5.17 (0.85) | 2.66 (0.53) | 7.83 (1.24) |
| 80 and older | 48 | 0.79 (0.43) | 0.82 (0.16) | 1.61 (0.28) | 2.39 (0.45) | 4.90 (0.84) | 2.91 (0.69) ^{b,c} | 7.81 (1.38) |
| Total | 530 | 0.78 (0.11) | 0.84 (0.16) | 1.62 (0.26) | 2.55 (0.47) | 5.18 (0.88) | 2.63 (0.51) | 7.81 (1.23) |

^a Significantly different ($p < 0.05$) from values of the age group in their 40s

^b Significantly different ($p < 0.05$) from values of the age group in their 50s

^c Significantly different ($p < 0.05$) from values of the age group in their 60s

were no specific trends in muscle mass among age groups ≤ 79 years old. However, as for men, the muscle mass of the quadriceps in women tended to decline with age, although the difference was not statistically significant.

Mean 6-m walking time and the calculated walking speed (m/s) using the walking time, classified by age and gender, are shown in Table 3. Six-meter walking time was significantly lower in men than in women ($p < 0.05$), indicating that men tended to walk faster than women in this study population. Mean 6-m walking time for both men and women increased with age. In particular, 6-m walking times for men and women ≥ 70 years old were significantly higher than those in younger age groups ($p < 0.05$).

Table 4 shows median one-leg standing time classified by age and gender with 25th–75th percentile ranges. For both men and women in their 40s–50s, all median, 25th percentile, and 75th percentile values were 60 s, with no gender difference. One-leg standing times for men ≥ 60 years old tended to be higher than those for women, and median values declined with age in both men and women.

Prevalence of disability among subjects ≥ 65 years old

Among the 2,468 participants in the second visit of the ROAD study, we surveyed 1,845 subjects (625 men, 1,220 women) ≥ 65 years old and obtained information on the presence or absence of disability certified for long-term care insurance. We found a total of 149 individuals (8.1%;

36 men, 5.8%; 113 women, 9.3%) that were certified as requiring support. Figure 1 shows the prevalence of disability classified by gender and age. The prevalence of disability in men 65–69, 70–74, 75–79, and ≥ 80 years old was 0.0, 1.0, 6.3, and 8.8%, respectively, and that in women in the same age groups was 3.4, 3.5, 9.2, and 14.7%, respectively (Fig. 1). The prevalence of disability in women was significantly higher than that in men ($p < 0.05$) and increased with age in both genders ($p < 0.01$).

Associations between disability and hand grip strength, muscle mass, walking speed, and one-leg standing time

Logistic regression analysis was performed using the presence of disability (1, yes; 0, no) as an objective factor, and hand grip strength on the better side and the worse side; muscle mass of the forearms, upper arms, upper limbs, quadriceps, thighs, lower legs, and lower limbs; walking time for 6 m at the usual pace and at the fastest pace; and quartile of one-leg standing time [0: 0–25% (highest quartile), 1: 25–50% (higher quartile), 2: 50–75% (lower quartile), 3: 75–100% (the lowest quartile)] on the better and worse sides as explanatory factors, after adjusting for age, gender, and BMI. No significant associations were found between the presence of disability and hand grip strength, muscle mass, or one-leg standing time. However, there were significant associations between the presence of disability and 6-m walking time at the usual

Table 3 Mean values (standard deviation) of 6-m walking time (s) and walking speed (m/s) with usual pace and the fastest pace classified by age and gender

| Age strata (years) | Number of subjects | Usual pace | | Fastest pace | |
|--------------------|--------------------|------------------------------|--------------------------------|------------------------------|--------------------------------|
| | | Time for 6 m (s) | Walking speed (m/s) | Time for 6 m (s) | Walking speed (m/s) |
| Men | | | | | |
| 40–49 | 32 | 4.4 (0.6) | 1.38 (0.19) | 3.0 (0.5) | 2.09 (0.43) |
| 50–59 | 100 | 4.8 (0.9) | 1.29 (0.20) | 3.2 (0.6) | 1.97 (0.36) |
| 60–69 | 134 | 5.1 (0.9) | 1.21 (0.20) ^a | 3.4 (0.7) | 1.82 (0.33) ^a |
| 70–79 | 196 | 5.9 (1.8) ^{a,b,c} | 1.09 (0.25) ^{a,b,c} | 4.0 (1.4) ^{a,b,c} | 1.62 (0.39) ^{a,b,c} |
| 80 and older | 97 | 6.8 (3.0) ^{a,b,c,d} | 0.99 (0.33) ^{a,b,c,d} | 4.5 (1.8) ^{a,b,c,d} | 1.48 (0.44) ^{a,b,c} |
| Total | 559 | 5.6 (1.9) | 1.15 (0.27) | 3.7 (1.3) | 1.73 (0.42) |
| Women | | | | | |
| 40–49 | 92 | 4.7 (1.0) | 1.32 (0.24) | 3.2 (0.6) | 1.95 (0.31) |
| 50–59 | 190 | 4.9 (0.9) | 1.27 (0.23) | 3.3 (0.7) | 1.87 (0.33) |
| 60–69 | 299 | 5.1 (1.1) | 1.22 (0.23) | 3.7 (0.8) | 1.71 (0.32) ^{a,b} |
| 70–79 | 345 | 6.3 (2.4) ^{a,b,c} | 1.03 (0.25) ^{a,b,c} | 4.4 (1.5) ^{a,b,c} | 1.46 (0.36) ^{a,b,c} |
| 80 and older | 152 | 8.4 (3.9) ^{a,b,c,d} | 0.82 (0.27) ^{a,b,c,d} | 5.8 (2.7) ^{a,b,c,d} | 1.17 (0.36) ^{a,b,c,d} |
| Total | 1,078 | 5.9 (2.4) | 1.12 (0.29) | 4.1 (1.6) | 1.60 (0.42) |

^a Significantly different ($p < 0.05$) from values of the age group in their 40s

^b Significantly different ($p < 0.05$) from values of the age group in their 50s

^c Significantly different ($p < 0.05$) from values of the age group in their 60s

^d Significantly different ($p < 0.05$) from values of the age group in their 70s

Table 4 Values of median (25–75 percentile) of one-leg standing time (s, maximum = 60 s) in a better side and a worse side classified by age and gender

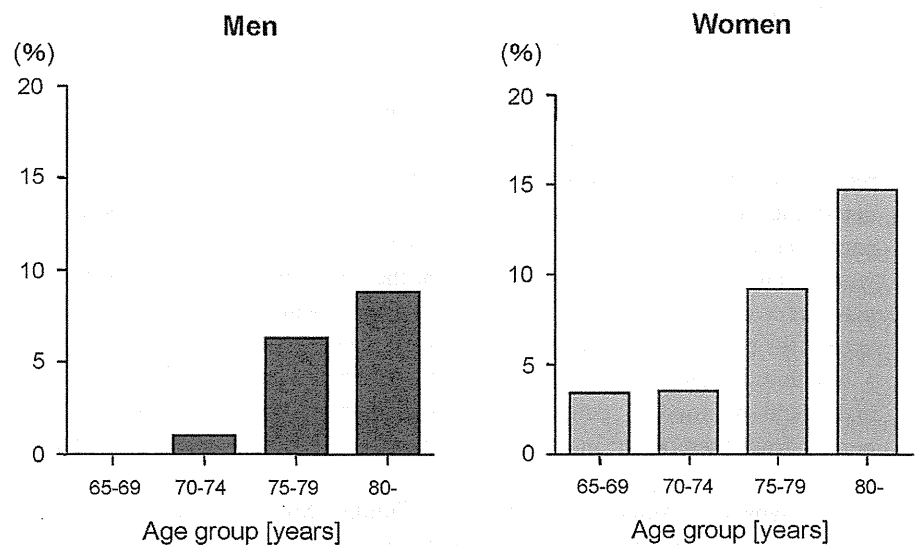
| Age strata (years) | Number of subjects | One-leg standing time (better side) (s) | One-leg standing time (worse side) (s) |
|--------------------|--------------------|---|--|
| Men | | | |
| 40–49 | 32 | 60 (60–60) | 60 (60–60) |
| 50–59 | 99 | 60 (60–60) | 60 (60–60) |
| 60–69 | 136 | 60 (34.5–60) | 45 (14.25–60) |
| 70–79 | 303 | 27 (9–60) | 9 (4–35) |
| 80 and older | 246 | 8 (4–32) | 4 (2–12) |
| Total | 816 | 39.5 (8–30) | 14 (4–60) |
| Women | | | |
| 40–49 | 92 | 60 (60–60) | 60 (60–60) |
| 50–59 | 191 | 60 (60–60) | 60 (43–60) |
| 60–69 | 317 | 60 (41.5–60) | 43 (13–60) |
| 70–79 | 593 | 21 (8–57.5) | 8 (3–25) |
| 80 and older | 424 | 7 (3–18.8) | 3 (2–7) |
| Total | 1,617 | 31 (8–60) | 12 (4–60) |

pace [+1 s, odds ratio (OR) 1.15, 95% confidential interval (CI) 1.07–1.24, $p < 0.001$] and at the fastest pace (+1 s, OR 1.22, 95% CI 1.08–1.38, $p < 0.01$). In addition, there were significant associations between the presence of disability and walking speed at the usual pace (+1 m/s, OR 0.07, 95% CI 0.02–0.27, $p < 0.001$) and at the fastest pace (+1 m/s, OR 0.16, 95% CI 0.06–0.41, $p < 0.001$).

Discussion

In this study, we established age-gender-classified mean values for hand grip strength as an index of muscle strength, muscle mass as an index of muscle volume, and walking time and median one-leg standing time as indices of physical performance, using data for a large-scale

Fig. 1 Prevalence of disability among subjects ≥ 65 years old classified by gender and age



population-based cohort. We found that mean hand grip strength, muscle mass, walking time, and median one-leg standing time were higher in men than in women, and decreased with age (with the exception of the muscle mass of the lower legs).

The Japanese Ministry of Education, Culture, Sports, Science, and Technology has reported ranges for physical strength and sporting ability in 69,745 Japanese men and women 6–79 years old. Mean hand grip strength in both men and women reaches peak values between the ages of 20–40, and decreases with age after 40 [12]. In the present study of a population aged ≥ 40 years, hand grip strength declined significantly with age, consistent with the previous report of the Japanese government.

Although computed tomography or MRI scans are the most reliable methods of measuring segmental muscle mass, these methods are not suitable for a large-scale population-based study. The BIA method is rapid, inexpensive, portable, and importantly, a noninvasive measuring method. Previous studies have shown that there is a strong correlation between BIA resistance and measurements of skeletal muscle mass in the arms [13], legs [13], and whole body [14]. For the BIA method used in the present study, Miyatani et al. [10] had previously compared values for muscle mass using a series of cross-sectional images of the forearm, upper arm, lower leg, and thigh on the right side of 22 male subjects as determined by the BIA and MRI methods. The BIA impedance index (L^2/Z) for every segment, calculated as the ratio of the segment length squared to the impedance, was significantly correlated with the muscle volume measured by MRI, with $r = 0.902$ – 0.976 ($p < 0.05$). These previous results demonstrate that the BIA method used in the present study is sufficiently reliable as an index of muscle volume.

In the present study, age-related differences were observed in the thighs and quadriceps. In addition, the age-related decreases in muscle mass were greater in the lower limbs than in the upper limbs, and in proximal sites than in distal sites. Yamada et al. [15] estimated the bioelectrical impedance (BI) index, calculated as the ratio of the square of segmental length to impedance in a Japanese population consisting of 1,006 individuals (374 men, 632 women) and reported that the BI index decreased most with age in the thighs, whereas there were no significant age-related changes in the forearms or lower limbs. Miyatani et al. [16] studied muscle thickness at nine sites, the forearm, anterior and posterior upper arm, abdomen, subscapular, anterior and posterior thigh, and anterior and posterior lower leg, using brightness-mode ultrasonography in 348 Japanese men aged 20–79 years. They found a greater decrease in muscle thickness in the trunk and anterior thigh than at other sites, consistent with our results. They speculated that site-related differences in muscle loss with aging may be attributed to age-related changes in the patterns of loading to and/or activation of individual muscles in daily life. However, because these results were obtained from a cross-sectional study, longitudinal data would be required to determine the mechanism of these differences. We have begun the third visit of the ROAD study, 6 years after the baseline and 3 years after the second visit, to measure losses of skeletal muscle mass at various sites. Losses of muscle mass in the quadriceps and/or thighs may result in a decrease in walking ability, including walking speed. Therefore, establishment of reference values for muscle mass is useful for prediction of future disability.

Walking ability is regarded as the most important activity for the elderly to maintain an independent life in the community, and walking speed is an important index of

walking ability. Reference values have been published for populations in western countries [17, 18]; however, there has been little information available for the Japanese population. Takahashi et al. [19] surveyed walking speed at 130 crosswalks and reported that at least 1.0 m/s was required to safely cross the street. In the present study, we determined that the mean 6-m walking time at the usual pace at an age of ≥ 40 years was 5.6 s for men and 5.9 s for women, and the mean 6-m walking time at the fastest pace was 3.7 s in men and 4.1 s in women. These walking speeds for both the usual pace and the fastest pace provide a baseline for clinical judgments of patient performance and could be used to determine which subjects would benefit from therapeutic intervention to improve locomotive function.

The Japanese Ministry of Education, Culture, Sports, Science and Technology published mean values for one-leg standing time with a maximum time of 120 s using 5,500 individuals (2,741 men, 2,759 women) with an age range of 65–79 years in each prefecture who participated in an examination of sporting ability, including walking ability [12]. They reported that mean one-leg standing times for men 65–69, 70–74, and 75–79 years old were 79.9, 66.5, and 50.5 s, respectively, and those for women were 80.8, 62.1, and 45.0 s, respectively. These values were measured up to 120 s, and ours were measured up to 60 s. Because the measuring method was different and their outcomes are means while our results are medians, the results cannot be compared directly. However, one-leg standing time was significantly lower with age in both studies. Again, establishment of reference values for physical performance, including walking and standing ability, would be useful for prediction of future disability.

We then evaluated associations between hand grip strength, muscle mass, walking time, and one-leg standing time, as indices reflecting components of locomotive syndrome and the presence of disability. We found that the 6-m walking time may be a useful index for detection of disability. To evaluate the independence of elderly persons in daily life, physical performance has been measured using various outcomes. Walking speed has been reported to be one important index that can predict future disability, hospitalisation, and mortality in the general geriatric population [20, 21]. In a Japanese population, Shinkai et al. [22] demonstrated that lower scores on baseline performance measures, particularly maximum walking speed, predicted an increased risk of onset of functional dependence, based on their 6-year follow-up of a cohort in a rural community consisting of 736 participants. In the present study, a 1-s slower normal walking time for 6 m was associated with a 15% increase in the presence of disability, and a 1-s slower fastest walking time for 6-m was associated with a 22% increase in the presence of disability. Our study evaluated

only walking ability and the presence of disability, not the occurrence of disability; however, we expect to follow these populations and clarify the predictive ability of walking speed for the occurrence of disability over the next few years.

On the other hand, no associations were found between indices such as hand grip strength, muscle mass, and one-leg standing time and the presence of disability. There is growing evidence that reduced hand grip strength is associated with adverse outcomes in older years, including morbidity, lower quality of life, higher fracture rates, increased length of hospital stay, and mortality [23–25]. Progressive decline in muscle mass has been defined as sarcopenia, which represents an impaired state of health associated with morbidity disorders, increased risk of falls and fractures, impaired ADL, loss of independence, and increased risk of death [6, 26–29]. Lang et al. [29] stated that loss of muscle mass and power increases the difficulties associated with procuring adequate nutrition and the effort required to undertake exercise; the combination of nutritional loss and reduced physical activity levels results in further loss of muscle mass and power. The resulting decrements in power, endurance, and physical performance lead to a loss of independence. In addition to muscle strength and mass, balance appears to be an important index of disability. Shinkai et al. [22] measured the one-leg standing time of 736 participants in a cohort established in a rural community, and the individuals in the lowest performance quartile had a significantly higher occurrence of disability.

Self-selection bias is suggested as a possible reason for the lack of associations between hand grip strength, muscle mass, and one-leg standing time and disability observed here, compared with previous reports. Self-selection bias is one type of sampling bias exhibited by subjects who voluntarily enrol in an epidemiological study. In this second visit of the ROAD study, volunteers who could walk to the clinic where the survey was performed, and could understand and sign an informed consent form, and who wanted to learn about their bone and joint conditions were welcomed. Therefore, the participants in the second survey may have been healthier than the general Japanese population. In fact, the estimated number of persons with disability in Japan using the age-gender prevalence of the second visit and the age-gender distribution of the Japanese population based on the national census in 2007 would be estimated at 1,510,000 (350,000 men, 1,160,000 women), considerably lower than the 4,940,000 reported by the government in 2010. Thus, self-selection bias likely affected the reference values; the reference values for hand grip strength, muscle mass, and one-leg standing time obtained from the present study may be higher, and walking speed faster, than the actual values. However, self-selection bias is somewhat unavoidable in such an

examination, because it is impossible to obtain measurements for individuals who cannot grasp a handgrip dynamometer or walk 6 m. This bias should be taken into consideration when reference values are used, including not only those obtained from the present study, but also from the national survey of physical strength and sporting ability published by the government.

In addition to self-selection bias, this study has several limitations. First, our results were obtained from a cross-sectional study of the second visit of the ROAD study; thus, we can not conclude causal relationships between such indices and disability, since some of the indices, such as muscle mass and one-leg standing time, were first introduced and performed during the second visit. We have begun the third visit of the ROAD study to clarify the relationships between physical performance and the occurrence of disability. Once the significance of indices reflecting components of locomotive syndrome can be determined as predictors for the occurrence of disability, appropriate thresholds can be developed as predictors of future disability. In addition, because of the lack of sufficient information, we could not determine the disorders that caused the disability. Thus, the disabled status of the participants in the present study might have been affected by various diseases such as cardiovascular diseases, dementia, or other diseases. However, regardless of the cause of disability, we found that walking ability was significantly associated with the presence of disability.

Conclusions

We have established reference values for hand grip strength, muscle mass, walking time, and one-leg standing time using data for a large-scale population-based cohort, and identified gender and age differences in the reference values. In addition, we determined that walking ability, including walking time and walking speed at the usual and maximum pace, was significantly associated with the presence of disability.

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Conflict of interest No conflict of interest has been declared by the authors.

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Association of Knee Osteoarthritis with the Accumulation of Metabolic Risk Factors Such as Overweight, Hypertension, Dyslipidemia, and Impaired Glucose Tolerance in Japanese Men and Women: The ROAD Study

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ABSTRACT. *Objective.* To clarify the association of knee osteoarthritis (KOA) with overweight (OW), hypertension (HTN), dyslipidemia (DL), and impaired glucose tolerance (IGT), which are components of metabolic syndrome (MS), in a Japanese population.

Methods. We enrolled 1690 participants (596 men, 1094 women) from the large-scale cohort study Research on Osteoarthritis Against Disability (ROAD), begun in 2005 to clarify epidemiologic features of OA in Japan. KOA was evaluated by the Kellgren-Lawrence grade, minimum joint space width (MJSW), minimum joint space area (JSA), and osteophyte area (OPA). OW, HTN, DL, and IGT were assessed using standard criteria.

Results. The prevalence of KOA in the total population in the age groups ≤ 39 , 40–49, 50–59, 60–69, 70–79, and ≥ 80 years was 2.2%, 10.7%, 28.2%, 50.8%, 69.0%, and 80.5%, respectively. Logistic regression analyses after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercise, and history of knee injuries revealed that the OR of KOA significantly increased according to the number of MS components present (1 component: OR 1.21, 95% CI 0.88–1.68, $p = 0.237$; 2 components: OR 1.89, 95% CI 1.33–2.70, $p < 0.001$; 3 or more components: OR 2.72, 95% CI 1.77–4.18; $p < 0.001$). The number of MS components was inversely related to medial MSJW ($\beta = -0.148$, $R^2 = 0.21$, $p < 0.001$), medial JSA (women only; $\beta = -0.096$, $R^2 = 0.18$, $p = 0.001$), and positively related to OPA ($\beta = 0.12$, $R^2 = 0.11$, $p < 0.001$).

Conclusion. The accumulation of MS components is significantly related to presence of KOA. MS prevention may be useful to reduce cardiovascular disease and KOA risk. (First Release Feb 15 2011; J Rheumatol 2011;38:921–30; doi:10.3899/jrheum.100569)

Key Indexing Terms:

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Osteoarthritis (OA), which causes cartilage and disc degeneration and osteophyte formation at joints in the limbs and spine, is a major public health problem in the elderly that affects activities of daily living (ADL) and quality of life, leading to increased morbidity and mortality^{1,2,3}. According

to the recent National Livelihood Survey by the Ministry of Health, Labour and Welfare in Japan, OA is ranked fourth among diseases that cause disabilities requiring support and longterm care⁴.

In the same report, cardiovascular disease (CVD) is

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ranked first in causing disabilities in the elderly⁴. Most individuals who develop CVD have multiple risk factors⁵. The presence of these risk factors in specific combinations, called metabolic syndrome (MS), is a complex risk factor that predisposes affected individuals to CVD morbidity and mortality. Although various terms have been used to define MS, it is generally thought to consist of a combination of overweight (OW), hypertension (HTN), dyslipidemia (DL), and impaired glucose tolerance (IGT)⁶.

Knee OA (KOA) and MS share age and obesity as risk factors^{1,7,8,9,10,11}. Many investigators have considered the association of OA with other components of MS. In an early population study, Lawrence first reported that diastolic blood pressure was associated with KOA in women¹². Regarding DL, Kellgren reported a significant association between women with hand OA and above-average serum cholesterol levels in the 1960s¹³. Cimmino and Cutolo examined the role of glucose and OA, and observed significantly higher levels of plasma glucose in women with OA than in those without OA¹⁴. Although contradictory findings regarding the association of such metabolic factors with OA have been reported^{15,16,17,18,19}, Hart, *et al* found that metabolic factors such as blood glucose, hypercholesterolemia, and even treated HTN were associated with the development of KOA. Based on that evidence, they proposed that the etiology of OA had an important systemic and metabolic component²⁰. This hypothesis has been supported by data from several population-based studies performed in the United States^{21,22}. However, to our knowledge, few population-based studies have demonstrated a dose-response relationship between the severity of KOA and an increasing number of the components of MS. Our first purpose was to clarify the association between the presence of KOA, defined using the Kellgren-Lawrence (KL) scale, and the number of MS components in a Japanese population.

Moreover, in most of these studies that confirmed the association between the presence of KOA and the components of MS, KOA was defined according to KL grade²³. KL grade is the most conventional system for measuring the radiographic severity of KOA, but does not separately assess joint space narrowing and osteophyte formation. Accumulating evidence has shown that osteophytosis and joint space narrowing have distinct etiologic mechanisms, and their progression is neither constant nor proportional^{24,25,26}. Thus, to examine the factors associated with KOA, these 2 OA features should be assessed separately. However, no reports to date have clarified the association of indices of KOA, such as minimum joint space width (MJSW), joint space area (JSA), and osteophyte area (OPA), with the accumulation of the number of components of MS. Our second purpose was to determine whether the accumulation of MS components influenced the values of MJSW, JSA, and OPA.

Further, MS is an emerging epidemic in both men and women worldwide, and with the increase in the global pop-

ulation of Asians, an understanding of the epidemiology of diseases as they relate to Asian populations is required. We have reported that the prevalence of KOA was much higher in a Japanese population than in elderly whites in the United States and Europe, although not largely different from that of African American and Chinese populations²⁷. In contrast, the prevalence of MS in East Asian countries including China, Korea, and Japan was reported to be lower than in white populations²⁸. In light of the rapid increase in the population of Asian countries, prevention strategies for obesity-related chronic diseases such as MS and KOA should be implemented immediately. Our final aim was to clarify the association between MA components and KOA in people of Asian ethnicity.

MATERIALS AND METHODS

Study population. We used the cohorts established in 2005 for a program called Research on Osteoarthritis Against Disability (ROAD). The ROAD study is a nationwide, prospective study of OA composed of population-based cohorts in several communities in Japan. Details of the cohort profile have been reported^{29,30}, thus the study population is described here only in brief. We created a baseline database including clinical and genetic information from 3040 residents of Japan (1061 men and 1979 women) with a mean age (SD) of 70.3 (11.0) years [71.0 (10.7) years in men and 69.9 (11.2) years in women]. These subjects were recruited from resident registration listings in 3 communities with different characteristics: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.

We enrolled 1690 Japanese subjects (596 men; 1094 women) residing in the mountainous and coastal areas. Table 1 lists the background characteristics of all the participants. All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo. Participants completed an interviewer administered questionnaire of 400 items that included lifestyle information such as occupation, smoking habit, alcohol consumption, family history, medical history, physical activity, reproductive variables, and health-related quality of life. Anthropometric measurements included height, weight, waist length (seaside region only), wrist circumference, bilateral grip strength, and body mass index [BMI; weight (kg)/height (m)²]. Systolic and diastolic blood pressure (BP) were measured by an experienced public health nurse using a mercury sphygmomanometer. Medical information on systemic, local, and mental health status, including information concerning knee, hip, and lower back pain; swelling and range of motion of the joints; and patellar and Achilles tendon reflex was collected by experienced orthopedic surgeons.

Radiographic assessment. All participants underwent radiographic examination of both knees using an anterior-posterior view with weight-bearing and foot-map positioning. Fluoroscopic guidance with a horizontal anterior-posterior radiograph beam was used to visualize the joint space. Knee radiographs were read by a single experienced orthopedist without knowledge of participants' clinical status, and categorized using the KL grading scale²³. Regarding the differences in knee OA grades between the 2 sides, among 1681 participants who underwent X-ray examinations of both knees, 1226 (72.9%) individuals had the same KL grades for both knees. For 396 (23.6%) participants, the difference in knee KL grades between the 2 knees was 1, and for the remaining 59 (3.5%) subjects, the KL grades differed by more than 2 grades. In such cases, the higher KL grade was assigned to the participant. The same observer scored 100 randomly selected knee radiographs more than 1 month after the first reading to determine intraobserver variability. The intraobserver variability (0.86) evaluated for KL grade (0–4) was confirmed by kappa analysis to be sufficient for the assessment.

Table 1. Background characteristics of the participants.

| | Total | Men | Women |
|--|--------------|--------------|--------------|
| Age, yrs | | | |
| ≤ 39 | 45 | 14 | 31 |
| 40–49 | 149 | 44 | 105 |
| 50–59 | 316 | 107 | 209 |
| 60–69 | 482 | 157 | 325 |
| 70–79 | 539 | 220 | 319 |
| ≥ 80 | 159 | 54 | 105 |
| Total, n | 1690 | 596 | 1094 |
| Mean (SD) selected characteristics | | | |
| Age, yrs | 65.2 (12.0) | 66.3 (11.7) | 64.7 (12.1) |
| Height, cm | 155.2 (9.3) | 163.4 (7.2) | 150.7 (6.9) |
| Weight, kg | 55.6 (10.8) | 62.2 (10.9) | 52.0 (8.8) |
| BMI, kg/m ² | 23.0 (3.4) | 23.2 (3.2) | 22.9 (3.5) |
| Systolic BP, mm Hg | 135.1 (20.7) | 137.9 (19.6) | 133.5 (21.1) |
| Diastolic BP, mm Hg | 74.2 (11.5) | 77.0 (11.6) | 72.7 (11.2) |
| Serum levels of HDL cholesterol, mg/dl | 60.8 (15.7) | 56.1 (15.8) | 63.4 (15.0) |
| Serum levels of HbA1c, % | 5.20 (0.74) | 5.23 (0.83) | 5.19 (0.68) |
| Prevalence of selected characteristics, % | | | |
| Current smoking habit | 13.1 | 29.9 | 3.8 |
| Current alcohol consumption | 39.8 | 66.7 | 25.1 |
| Medication for hypertension | 32.3 | 29.5 | 33.9 |
| Medication for dyslipidemia | 6.5 | 3.0 | 8.5 |
| Medication for diabetes mellitus (including insulin injection) | 5.9 | 7.7 | 4.9 |
| Prevalence of each component of metabolic syndrome, % | | | |
| Obesity | 25.3 | 26.7 | 24.6 |
| Hypertension | 69.7 | 74.8 | 66.9 |
| Dyslipidemia | 12.3 | 13.9 | 11.4 |
| Impaired glucose tolerance | 21.5 | 24.3 | 20.0 |

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; HbA1c: hemoglobin A1c.

Further, to evaluate the KOA severity using quantitative measurements, the medial and lateral MJSW, medial and lateral JSA, and OPA were measured separately, using a KOA computer-assisted diagnostic system (KOA-CAD). The KOACAD was programmed to measure MJSW and JSA in the medial and lateral compartments, OPA at the medial tibia, and femorotibial angle (FTA) using digitized knee radiographs. Initially, correction for radiographic magnification was performed on the basis of the image size of a rectangular metal plate.

Next, to determine the region of interest (ROI) including the tibiofemoral joint space, a vertical neighborhood difference filter was applied to identify points with high absolute values for difference of scales. The centers of all points were then calculated, and the ROI was selected. Within the ROI, the outline of the femoral condyle was designated as the upper rim of the joint space. The 2 ends were determined, and vertical lines from the ends were designated as the outside rims of the joint space. Outlines of the anterior and posterior margins of the tibial plateau were drawn similarly to that of the femoral condyle, and the middle line between the 2 outlines was designated as the lower rim of the joint space. A straight regression line for the lower rim outline was then drawn, and the intersection of the lower rim outline and the regression line were designated as the inside rims. Medial and lateral JSA were determined as areas surrounded by the upper, lower, inside, and outside rims. Medial and lateral MJSW were further determined as the minimum vertical distances in the respective JSA. To measure osteophyte area and FTA, medial and lateral outlines of the femur and tibia were drawn. Inflection points for these outlines were then calculated. The medial outline of the tibia from the inflection point was drawn upward to the joint level, and the area that was medially prominent

over the smoothly extended outline was designated as the osteophyte area. For FTA, a middle line between the medial and lateral outlines of the femur from the top of the image to the inflection points was drawn, and the straight regression line was determined as the axis of the femur. Similarly, the straight regression line of the middle line of the tibia from the bottom to the inflection points was designated as the axis of the tibia. The lateral angle between the 2 axes lines was calculated as FTA. In general clinical practice, this system can quantify the major features of knee OA on standard radiographs and allows objective, accurate, simple, and easy assessment of the structural severity of knee OA without any manual operation.

Regarding the relationship between the measurements of KOA, we have confirmed the correlation values were more than 0.5 between medial JSA and medial MJSW, and between lateral JSA and lateral MJSW, indicating that these are confounding factors for each other. Osteophyte area was not significantly associated with either medial JSA or medial MJSW. Further, JSA and MJSW on the lateral side were positively correlated with those on the medial side. These measurements showed good correlation between KL grades ($p < 0.0001$)³¹.

Blood examination. All blood and urine samples were extracted between 9:00 AM and 3:00 PM. Some samples were extracted under fasting conditions. After centrifugation of blood samples, sera were immediately placed in dry ice and transferred to a deep freezer within 24 hours. These samples were stored at -80°C until assayed.

For the samples of participants in the baseline study, the following items were measured: blood counts, hemoglobin, hemoglobin A1c (HbA1c), blood sugar, total protein, aspartate aminotransferase, alanine aminotransferase, γ -glutamyltranspeptidase, high-density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides (TG), blood urea nitrogen, uric acid, and creatinine. These analyses were performed at the same laboratory within 24 hours after the extraction (Osaka Kessei Research Laboratories Inc., Osaka, Japan).

Definition of MS components. This definition was based mainly on the criteria of the Examination Committee of Criteria for Metabolic Syndrome in Japan³². According to these criteria, an abdominal circumference ≥ 85 cm in men and ≥ 90 cm in women is a necessary condition for MS. HTN was diagnosed as systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg, DL as serum TG level ≥ 150 mg/dl and/or serum HDL cholesterol level < 40 mg/dl, and IGT as fasting serum glucose ≥ 110 mg/dl. Because there has been considerable debate regarding the measurement of abdominal circumference^{33,34}, we decided to use BMI ≥ 25 instead as an indicator of overweight, based on the criteria of the Japan Society for the Study of Obesity³³. Also, because not all blood samples were obtained under fasting conditions, we did not use participants' data concerning serum levels of glucose and TG, because of their large variation depending on hours after eating. Instead, we used a serum HDL cholesterol level < 40 mg/dl to indicate DL, and serum HbA1c level $\geq 5.5\%$ to indicate IGT. These are indices used in the National Health and Nutrition Survey in Japan, and they were adopted as criteria for MS in this national screening based on the difficulty of collecting the samples under fasting conditions³⁵. Further, subjects being treated with medication for HTN, DL, or diabetes mellitus were regarded as having the respective disorder.

Statistical analysis. All statistical analyses were performed using Stata statistical software (Stata Corp., College Station, TX, USA). Differences in proportion were compared by the chi-squared test. Differences in continuous values were tested for significance using ANOVA for comparisons among multiple groups, and Scheffe's least significant difference test for pairs of groups. Significant items were selected, and multiple regression and logistic regression analyses were performed by adjusting selected variables. Various confounding factors were used for the adjustment for each multivariate analysis.

RESULTS

Study population. Table 1 shows selected characteristics of the participants including age, height, weight, BMI, systolic

and diastolic BP, and serum levels of HDL cholesterol and HbA1c, classified by sex. Two-thirds of the 1690 participants were women, and their mean age was 1.5 years younger than that of the men ($p = 0.0098$).

Height, weight, and BMI were significantly lower in women than in men (height, $p < 0.0001$; weight, $p < 0.0001$; BMI, $p = 0.049$). Both measurements of systolic BP and diastolic BP were significantly higher in men than in women (systolic BP and diastolic BP, $p < 0.0001$). However, there was no significant difference in serum levels of HbA1c between men and women ($p = 0.2472$). The serum level of HDL cholesterol was significantly lower in men than in women ($p < 0.0001$).

Table 1 also shows the proportion of subjects who smoked (regularly or more than once a month) and consumed alcohol (drinking regularly or more than once a month); medication use; and the prevalence of OW, HTN, DL, and IGT. Smoking and drinking were significantly more common in men than in women ($p < 0.001$). In the total population, the component of MS with the highest prevalence was HTN, followed by OW, IGT, and DL. The prevalence of HTN and IGT was significantly higher in men than in women (HTN, $p = 0.001$; IGT, $p = 0.039$).

Prevalence of KOA and its association with components for MS. The prevalence of KOA in the total population in the age groups ≤ 39 , 40–49, 50–59, 60–69, 70–79, and ≥ 80 years was 2.2%, 10.7%, 28.2%, 50.8%, 69.0%, and 80.5%, respectively. KOA prevalence tended to be higher with increasing age in both the sexes. The prevalence of KOA was significantly higher in women than in men ($p < 0.001$). Table 2 shows the mean values of each component of MS compared between the absence and presence of KOA. In the overall population, mean values of age, BMI, systolic BP, and HbA1c were significantly higher, and HDL cholesterol significantly lower, in subjects with KOA than in those without KOA. This tendency was much more pronounced in women than in men.

Logistic regression analysis was performed using the presence of KOA as an objective variable and OW, HTN, DL, and IGT each as explanatory variables, after adjusting for age and sex. In the overall population, the analysis

revealed that only OW was significantly positively associated with KOA (OR 2.33, 95% CI 1.79–3.04, $p < 0.001$). Logistic regression analysis using the same objective and explanatory factors and stratified according to sex indicated that only HTN was positively associated with KOA in men (OR 1.61, 95% CI 1.03–2.53, $p = 0.038$), and only OW in women (OR 3.48, 95% CI 2.42–5.01, $p < 0.001$).

Table 3 shows the prevalence of potential associated lifestyle factors for KOA classified by the absence or presence of KOA. In the overall population, significantly associated factors for KOA included residential area, smoking habit, alcohol consumption, bicycling regularly as a factor of physical activity, and regular exercises. These factors should be taken into consideration as confounders for the following multivariate analysis.

Then, logistic regression analysis was repeated using the presence of KOA as an objective variable and OW, HTN, DL, and IGT each as explanatory variables, after adjusting for age, sex, regional difference, smoking habit, alcohol consumption, physical activities including regular bicycling in the past 12 months, regular exercises such as football, tennis, baseball, and golf; and history of knee injuries. The analysis revealed that OW and HTN were significantly positively associated with KOA (OW: OR 2.74, 95% CI 1.07–3.62, $p < 0.001$; HTN: OR 1.43, 95% CI 1.09–1.86, $p < 0.001$). Logistic regression analysis using the same objective and explanatory factors and stratified according to sex indicated that OW and HTN were positively associated with KOA in men (OW: OR 1.76, 95% CI 1.13–2.74, $p < 0.05$; HTN: OR 1.77, 95% CI 1.11–2.84, $p < 0.05$), and only OW in women (OR 3.63, 95% CI 2.51–5.25, $p < 0.001$). These results suggest that all components of MS were not equally associated with the presence of KOA.

Then, to clarify the association between all the components of MS and KOA, logistic regression analysis was repeated using the presence of KOA as an objective variable and all components for MS, such as OW, HTN, DL, and IGT, as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. In the overall population, the analysis revealed that

Table 2. Mean (SD) of each component of metabolic syndrome in the absence or presence of knee osteoarthritis (KOA).

| | KOA– | Total KOA+ | p | KOA– | Men KOA+ | p | KOA– | Women KOA+ | p |
|---|--------------|---------------|--------|--------------|--------------|--------|--------------|---------------|--------|
| Age, yrs | 59.8 (12.1) | 70.5 (9.1) | 0.0001 | 62.5 (12.1) | 71.5 (8.8) | 0.0001 | 57.8 (11.8) | 70.3 (9.1) | 0.0001 |
| BMI, kg/m ² | 22.4 (3.2) | 23.5 (3.4) | 0.0001 | 23.0 (3.2) | 23.5 (3.2) | 0.0931 | 22.0 (3.1) | 23.6 (3.6) | 0.0001 |
| Systolic BP, mm Hg | 130.7 (19.9) | 139.3 (20.7) | 0.0001 | 134.5 (18.9) | 142.5 (19.6) | 0.0001 | 127.9 (20.0) | 138.0 (21.0) | 0.0001 |
| Diastolic BP, mm Hg | 74.2 (11.2) | 74.2 (11.8) | 0.9890 | 77.1 (11.6) | 76.8 (11.5) | 0.6970 | 72.1 (10.4) | 73.1 (11.8) | 0.1380 |
| Serum levels of HDL cholesterol, mg/dl | 62.8 (16.6) | 58.9 (14.5) | 0.0001 | 57.5 (16.2) | 54.1 (15.0) | 0.0095 | 6.6 (15.8) | 60.8 (13.9) | 0.0001 |
| Serum levels of HbA1c, % | 5.13 (0.68) | 5.26 (0.78) | 0.0003 | 5.22 (0.83) | 5.23 (0.80) | 0.9409 | 5.07 (0.53) | 5.28 (0.77) | 0.0001 |

BMI: body mass index; BP: blood pressure; HDL: high-density lipoprotein; HbA1c: hemoglobin A1c.

Table 3. Prevalence (%) of potential associated factors for knee osteoarthritis (KOA) classified by the absence or presence of KOA.

| | Total | | | Men | | | Women | | |
|---|-------|------|-------|------|------|-------|-------|------|-------|
| | KOA- | KOA+ | p | KOA- | KOA+ | p | KOA- | KOA+ | p |
| Residing in coastal area | 65.6 | 32.1 | 0.000 | 60.8 | 26.7 | 0.000 | 69.0 | 34.3 | 0.000 |
| Current smoking | 16.7 | 9.5 | 0.000 | 34.7 | 23.5 | 0.012 | 3.92 | 3.53 | 0.060 |
| Current alcohol drinking | 46.2 | 33.4 | 0.000 | 68.1 | 65.3 | 0.475 | 30.8 | 20.2 | 0.000 |
| Bicycling every day in the past 12 mo | 52.6 | 59.3 | 0.006 | 55.1 | 55.1 | 0.998 | 50.8 | 61.0 | 0.001 |
| Regular exercise such as football, tennis, baseball, and golf | 18.3 | 10.6 | 0.000 | 34.9 | 30.0 | 0.209 | 6.53 | 2.51 | 0.001 |
| Past injury of either knee | 2.4 | 2.8 | 0.560 | 1.4 | 4.1 | 0.046 | 3.1 | 2.4 | 0.466 |

OW was significantly positively associated with KOA (OR 2.65, 95% CI 1.98–3.54, $p < 0.001$). Logistic regression analysis using the same objective and explanatory factors and stratified according to sex indicated that, in both sexes, OW was the only factor that was significantly associated with KOA (men: OR 1.64, 95% CI 1.04–2.59, $p < 0.05$; women: OR 3.64, 95% CI 2.48–5.34, $p < 0.001$), while in men, there was weak but not significant association between HTN and KOA (OR 1.61, 95% CI 0.99–2.60, $p = 0.053$). These results suggest that obesity, among the various components for MS, was most significantly correlated to KOA.

Prevalence of KOA and its association with the number of components for MS. Table 4 shows the prevalence of KOA classified by the number of components for MS: the prevalence of KOA tended to increase with the increase in the number of MS components (p for trend < 0.001) in the total population. However, the prevalence of KOA in men and women did not tend to increase monotonically. Thus, in men, the prevalence of KOA in the groups with 2 MS components was lower than that in the groups with 1 component. Similarly, in women, the prevalence of KOA in the group with 2 MS components was higher than that in the group with 3 or more components.

To clarify the effect of the accumulation of MS components on the presence of KOA, logistic regression analysis was performed using the presence of KOA as the objective variable and the MS components (OW, HTN, DL, and IGT) present as explanatory variables after adjustment for age and sex. Compared to the reference condition (no MS components), increasing the number of components of MS significantly

increased the OR for the presence of KOA (vs no component; 1 component: OR 1.18, 95% CI 0.87–1.61, $p = 0.273$; 2 components: OR 1.74, 95% CI 1.25–2.44, $p = 0.001$; more than 3 components: OR 2.15, 95% CI 1.44–3.23; $p < 0.001$). Again, the same analysis was also performed stratified by sex. In men, although no dose-response effects of the accumulation of MS components on KOA were observed when the number of the components was 1 or 2, the accumulation of 3 or more components of MS tended to be significantly associated with a higher OR of KOA (vs no component; 1 component: OR 1.94, 95% CI 1.11–3.39, $p = 0.021$; 2 components: OR 1.61, 95% CI 0.89–2.91, $p = 0.117$; more than 3 components: OR 2.96, 95% CI 1.5–5.85, $p = 0.002$). In contrast, in women, no significant difference was observed between the presence of no components and 1 component; however, 2 or more components of MS increased the risk of KOA significantly (vs no component; 1 component: OR 0.89, 95% CI 0.61–1.29, $p = 0.527$; 2 components: OR 1.94, 95% CI 1.27–2.96, $p = 0.002$; more than 3 components: OR 1.71, 95% CI 1.01–2.87, $p = 0.044$).

Logistic regression analysis was performed using the presence of KOA as the objective variable and the number of MS components present (OW, HTN, DL, and IGT) as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. Figure 1 shows the OR of the association between accumulation of components of MS and presence of KOA. Compared to the reference condition (no components of MS), increasing the number of components of MS significantly increased the OR for the presence of KOA (vs no component; 1 component: OR 1.21, 95% CI 0.88–1.68, $p = 0.237$; 2 components: OR 1.89, 95% CI 1.33–2.70, $p < 0.001$; > 3 components: OR 2.72, 95% CI 1.77–4.18, $p < 0.001$). Again, the same analysis was also performed stratified by sex. In men, although no dose-response effects of the accumulation of MS components on KOA were observed when the number of the components was 1 or 2, the accumulation of 3 or more components of MS tended to be significantly associated with a higher OR of KOA (vs no com-

Table 4. Prevalence (%) of knee osteoarthritis, classified by the number of components of metabolic syndrome (MS). MS components consisted of obesity, hypertension, dyslipidemia, and impaired glucose tolerance.

| No. MS Components | Total | Men | Women |
|-------------------|-------|------|-------|
| 0 | 32.5 | 24.8 | 35.4 |
| 1 | 49.9 | 44.8 | 52.9 |
| 2 | 60.5 | 42.7 | 71.8 |
| ≥ 3 | 62.2 | 51.3 | 69.4 |

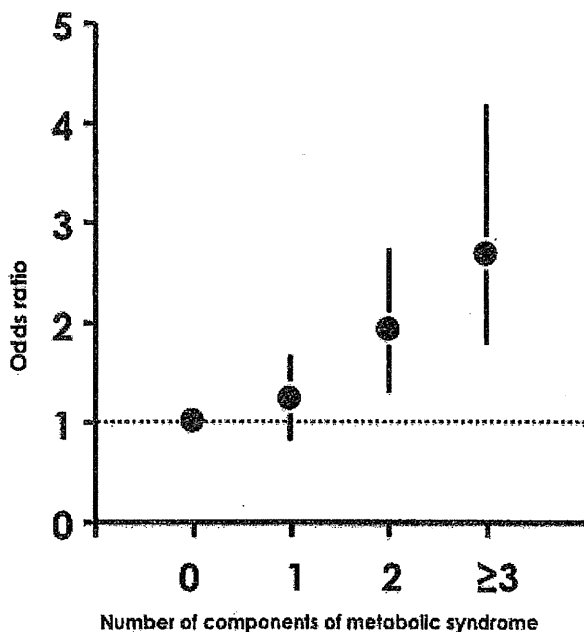


Figure 1. Odds ratios of the association between the number of components of metabolic syndrome and the presence of knee osteoarthritis, compared to no components present.

ponent; 1 component: OR 2.07, 95% CI 1.15–3.74, $p = 0.016$; 2 components: OR 1.68, 95% CI 0.89–3.17, $p = 0.110$; more than 3 components: OR 3.88, 95% CI 1.87–80.6, $p < 0.001$). In contrast, in women, no significant difference was observed between the presence of no component and 1 component; however, 2 or more components of MS increased the OR of KOA significantly (vs no component; 1 component: OR 0.88, 95% CI 0.59–1.32, $p = 0.541$; 2 components: OR 2.13, 95% CI 1.36–3.34, $p = 0.001$; > 3 components: OR 2.17, 95% CI 1.25–3.77, $p = 0.006$).

Joint space narrowing and areas of osteophytes in the knee, and their association with components of MS. Tables 5A and 5B show the mean measurements of indices for KOA, medial MJSW (mm), lateral MJSW (mm), medial JSA (mm²), lateral JSA (mm²), and OPA (mm²), classified by the number of components of MS. The values of medial MJSW tended to be significantly lower, and those of OPA significantly higher, with the increasing number of components of MS. The values of medial JSA in women belonging to the group with no component of MS were significantly higher than in those belonging to the groups with 1, 2, 3, or more components of MS, but no such tendency was observed in men. There was no relationship between the values of lateral MJSW, lateral JSA, and the number of components of MS.

Multiple regression analysis was performed using values of medial MJSW as the objective variable and the number of components of MS present as explanatory variables, after adjustment for age, sex, regional difference, smoking habit,

alcohol consumption, physical activities, regular exercises, and history of knee injuries. In the overall population, we found that the number of components of MS was inversely related to the values of medial MSJW ($\beta = -0.148$, $R^2 = 0.21$, $p < 0.001$). An analysis performed using the same objective and explanatory factors and stratified by sex showed the same tendency in both men and women (men: $\beta = -0.152$, $R^2 = 0.14$, $p < 0.001$; women: $\beta = -0.149$, $R^2 = 0.18$, $p < 0.001$).

Multiple regression analysis was then performed using OPA values as the objective variable and the number of components of MS present as explanatory variables, after adjustment for age, sex, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. The analysis revealed that the number of components of MS was positively related to OPA values ($\beta = 0.12$, $R^2 = 0.11$, $p < 0.001$). An analysis performed using the same objective and explanatory factors and stratified by sex showed the same tendency in both men and women (men: $\beta = 0.15$, $R^2 = 0.08$, $p < 0.001$; women: $\beta = 0.11$, $R^2 = 0.11$, $p < 0.001$).

In women, multiple regression analysis was performed using values of medial JSA as the objective variable and the number of components of MS present as explanatory variables, after adjustment for age, regional difference, smoking habit, alcohol consumption, physical activities, regular exercises, and history of knee injuries. The analysis revealed that the number of components of MS was inversely related to the values of medial JSA in women ($\beta = -0.096$, $R^2 = 0.18$, $p = 0.001$).

DISCUSSION

We found that an increase in the number of components of MS was significantly associated with the presence of KOA diagnosed by using the KL scale in Japanese men and women. We also clarified that the values of medial MJSW and OPA in men and women, and medial JSA in women as features of KOA, were significantly associated with the increase in the number of MS components.

KOA and MS share age and OW as risk factors^{1,7,8,9,10,11}. We have already reported that higher BMI was associated with radiographic KOA based on an analysis using the same population evaluated in our study³⁶, and it was also clarified that OW was the strongest factor that influenced the prevalence of KOA.

Regarding the association between clustering of metabolic factors and KOA, Hart, *et al* found that metabolic factors including blood glucose, hypercholesterolemia, and HTN were associated with both unilateral and bilateral KOA and were independent of OW²⁰. Sowers, *et al*²¹ defined the presence of ≥ 2 of the following criteria as cardiometabolic clustering: low levels of HDL cholesterol, elevated levels of low-density lipoprotein cholesterol, TG, BP, C-reactive protein, waist/hip ratio, glucose levels, and dia-

Table 5A. Mean (SD) of medial and lateral minimum joint space width (MJSW) classified by the number of components of metabolic syndrome (MS). MS components consisted of obesity, hypertension, dyslipidemia, and impaired glucose tolerance.

| No. MS Components | Medial MJSW, mm | | | Lateral MJSW, mm | | |
|-------------------|---------------------------|--------------------------|---------------------------|------------------|-------------|-------------|
| | Total | Men | Women | Total | Men | Women |
| 0 | 2.98 (0.81) | 3.33 (0.66) | 2.85 (0.82) | 4.00 (1.18) | 4.37 (1.13) | 3.86 (1.17) |
| 1 | 2.69 (1.01) ^a | 3.05 (0.97) | 2.49 (0.98) ^a | 3.96 (1.13) | 4.43 (1.05) | 3.70 (1.08) |
| 2 | 2.43 (1.19) ^{ab} | 2.87 (1.10) ^a | 2.15 (1.17) ^{ab} | 3.85 (1.19) | 4.15 (1.10) | 3.66 (1.22) |
| ≥ 3 | 2.42 (1.22) ^{ab} | 2.73 (1.24) ^a | 2.22 (1.17) ^a | 4.06 (1.27) | 4.26 (1.29) | 3.93 (1.24) |

^a Significantly different from values obtained in the absence of components ($p < 0.05$). ^b Significantly different from values obtained with 1 component ($p < 0.05$).

Table 5B. Mean (SD) of medial and lateral joint space area (JSA) and area of osteophytosis (OPA), classified by number of components of metabolic syndrome (MS). MS components consisted of obesity, hypertension, dyslipidemia, and impaired glucose tolerance.

| No. MS Components | Total | Medial JSA, mm ² | | Total | Lateral JSA, mm ² | | Total | OPA, mm ² | |
|-------------------|--------------------------|-----------------------------|---------------------------|--------------|------------------------------|---------------------------|----------------------------|---------------------------|----------------------------|
| | | Men | Women | | Men | Women | | Men | Women |
| 0 | 96.3 (27.6) | 111.4 (25.6) | 98.8 (26.2) | 111.0 (33.2) | 132.2 (34.2) | 103.3 (29.2) | 1.81 (6.42) | 0.93 (2.97) | 2.13 (7.26) |
| 1 | 90.2 (31.7) ^a | 104.0 (30.7) | 82.3 (29.6) ^a | 111.0 (32.4) | 131.2 (30.5) | 99.5 (27.5) | 3.06 (7.89) | 1.33 (4.26) | 4.05 (9.21) |
| 2 | 85.2 (36.7) ^a | 101.1 (34.3) | 75.0 (34.6) ^{ab} | 111.7 (32.2) | 128.9 (29.6) | 100.6 (28.8) | 5.34 (11.25) ^{ab} | 2.45 (5.36) | 7.18 (13.44) ^{ab} |
| ≥ 3 | 88.2 (39.3) | 102.0 (40.1) | 79.1 (36.0) ^a | 118.2 (35.3) | 132.5 (34.7) | 108.8 (32.5) ^b | 6.26 (9.59) ^{ab} | 3.82 (8.70) ^{ab} | 7.86 (9.85) ^{ab} |

^a Significantly different from values obtained in the absence of components ($p < 0.05$). ^b Significantly different from values obtained with 1 component ($p < 0.05$).

betes mellitus, and assessed the association between cardiometabolic clustering and KOA. They found that KOA was significantly more frequent in obese women with cardiometabolic clustering compared with those without it²¹. Using data from the National Health and Nutrition Examination Survey III (NHANES III), Singh, *et al* suggested that adults with OA in the United States have a high prevalence of CVD risk factors¹⁹, and Puenpatom and Victor demonstrated that each of the 5 cardiovascular risk factors that comprise MS, HTN, abdominal OW, hyperglycemia, elevated TG, and low HDL cholesterol, was more prevalent in the population with OA than in the population without OA²². However, to our knowledge, few population-based studies have shown a dose-response relationship between the presence of KOA and the accumulation of the number of MS components.

In our study, the logistic regression analysis revealed that only OW was significantly associated with KOA, and other components were not significant, using the presence of KOA as an objective variable and all components for MS, such as OW, HTN, DL, and IGT as explanatory variables and after adjustment for potential confounders. However, we found that the higher the number of components of MS, the greater the OR of the presence of KOA. This result indicates that, even if the effect of each component of MS on KOA may be weak, accumulation of the number of components may significantly worsen KOA.

In addition, we found that medial MJSW values in men and women, and medial JSA values in women tended to be significantly lower with the increase in the number of components of MS. In contrast, OPA values became significantly higher with the increase in the number of components of MS. Regarding the association between JSW and KOA, Sowers, *et al* used statistical models that included variables representing obesity, cardiometabolic status, and lateral and medial JSW differences to show that a 1-mm increase in the difference between lateral and medial JSW was associated with 2.1 times greater odds of having KOA, and subjects who were obese with cardiometabolic clustering had 4.5 times greater odds of having KOA²¹. However, no other reports have addressed direct associations between indices of KOA, such as MJSW, JSA, and OPA values, with the accumulation of the number of components of MS. In our study, we confirmed that the accumulation of the number of MS components present influenced the values of both MJSW, JSA (women only), and OPA, which determine the features and severity of KOA.

Regarding the association of clustering of components for MS and KOA, a few hypotheses have been suggested. Hart, *et al* attributed the effect of excess endogenous estrogens to the aromatization of estrone in fat tissue²⁰. Regarding the endogenous secreted products, Sowers, *et al* suggested that leptin and adiponectin levels influenced the development of OA²¹. They stated that leptin concentrations