

COHORT PROFILE

Cohort Profile: Research on Osteoarthritis/ Osteoporosis Against Disability study

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How did the study come about?

Since the proportion of the ageing population in Japan is increasing, a comprehensive and evidence-based strategy is urgently required for the prevention of musculoskeletal diseases, including osteoarthritis (OA) and osteoporosis (OP), both of which affect the activities of daily living (ADL) and quality of life (QOL) and increase morbidity and mortality.^{1–4} However, few prospective, longitudinal studies for the purpose of developing such a strategy have been conducted, and little information is available regarding the prevalence and incidence of musculoskeletal disorders, including OA and OP, as well as pain and disability in the Japanese population.^{5–10} It is difficult to design rational clinical and public health approaches for the diagnosis, evaluation and prevention of OA and OP without such epidemiological data.

The Research on Osteoarthritis/osteoporosis Against Disability (ROAD) study was established in 2005 by N.Y., T.A., H.O., S.M., H.K. and K.N. (principal investigators). The principal investigators are affiliated with the 22nd Century Medical and Research Center, University of Tokyo.

What does the ROAD study cover?

The ROAD study is a multi-centre prospective observational study that aims to elucidate the environmental and genetic background of bone and joint diseases (with OA and OP as the representative bone and joint diseases). It is designed to examine the extent to which risk factors for these diseases are related to

the clinical features of the diseases, laboratory and radiographic findings, bone mass, bone geometry, lifestyle, nutritional factors, anthropometric and neuromuscular measures and fall propensity. It also aims to determine how these diseases affect the ADL and QOL of Japanese men and women.

The study will provide the information required to develop clinical algorithms for the early identification of potential high-risk populations. It will also provide information required to develop policies for the detection and prevention of OA, OP and osteoporotic fractures. The immediate goal of this study is to establish a representative population of elderly people, principally for the study of bone and joint health. The establishment of this cohort will also facilitate the expansion of other studies in related areas of investigation. Moreover, the knowledge gained from the ROAD study will have major implications for understanding and managing several other common problems of ageing.

Who are in the sample?

The subjects were residents of any one of the three communities that have different characteristics: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama (Figure 1). The inclusion criteria, apart from residence in the communities mentioned above, were the ability to (i) walk to the survey site, (ii) report data and (iii) understand and sign an informed consent form. The age of the participants recruited from the urban region was ≥ 60 years, and that of the participants from the other

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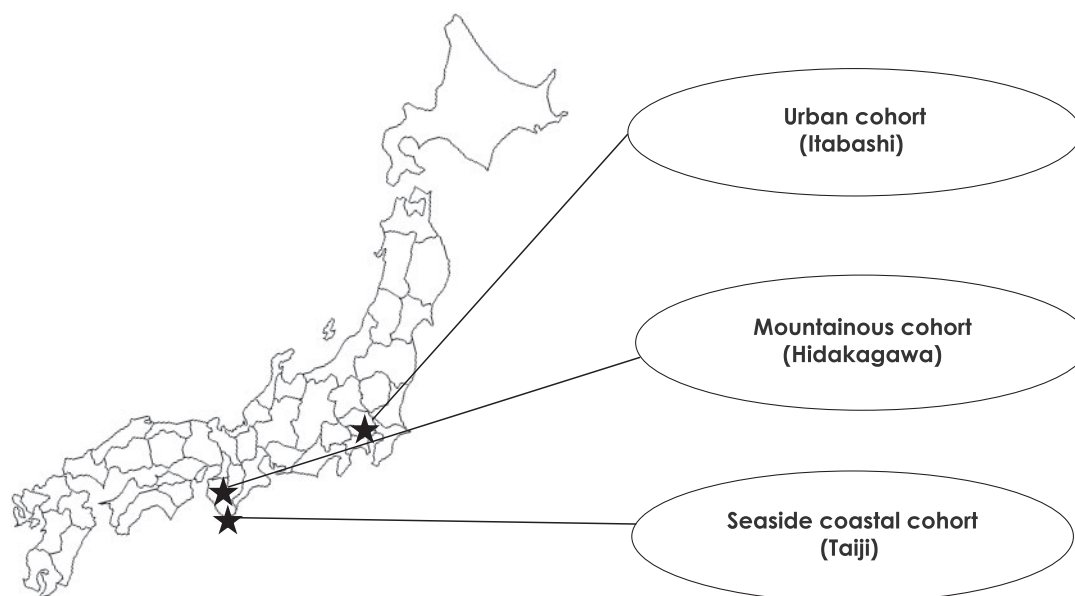


Figure 1 Locations of the three regions from which the study cohort was derived

Table 1 Age–sex distribution and mean values [standard deviation (SD)] of selected characteristics of the participants

| Age strata (years) | Men | | | | Women | | | |
|--------------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| | Total | Urban | Mountainous | Coastal | Total | Urban | Mountainous | Coastal |
| ≤39 | 14 | 0 | 2 | 12 | 31 | 0 | 7 | 24 |
| 40–49 | 44 | 0 | 7 | 37 | 105 | 0 | 17 | 88 |
| 50–59 | 107 | 0 | 36 | 71 | 211 | 2 | 67 | 142 |
| 60–69 | 168 | 11 | 93 | 64 | 385 | 60 | 183 | 142 |
| 70–79 | 535 | 315 | 150 | 70 | 913 | 594 | 196 | 123 |
| ≥80 | 193 | 139 | 31 | 23 | 334 | 229 | 75 | 30 |
| Total | 1061 | 465 | 319 | 277 | 1979 | 885 | 545 | 549 |
| Age (years) | 71.0 (10.7) | 77.2 (4.3) | 69.5 (9.1) | 62.6 (13.2) | 69.9 (11.2) | 76.3 (5.0) | 68.6 (10.4) | 60.8 (12.5) |
| Height (cm) | 162.5 (6.7) | 161.3 (5.9) | 161.4 (6.9) | 165.8 (6.8) | 149.8 (6.5) | 148.5 (5.6) | 148.2 (6.7) | 153.2 (6.2) |
| Weight (kg) | 61.3 (10.0) | 60.0 (8.5) | 60.0 (10.2) | 64.8 (11.0) | 51.5 (8.6) | 50.8 (8.3) | 50.5 (8.6) | 53.5 (8.8) |
| BMI (kg/m ²) | 23.1 (3.0) | 23.0 (2.8) | 23.0 (3.0) | 23.5 (3.4) | 22.9 (3.5) | 23.0 (3.4) | 23.0 (3.4) | 22.8 (3.6) |
| Current smoker (%) | 25.9 | 19.0 | 28.9 | 31.1 | 3.5 | 2.9 | 4.7 | 2.9 |
| Current drinker (%) | 64.4 | 60.5 | 69.8 | 63.2 | 25.9 | 27.4 | 26.1 | 24.2 |

BMI = body mass index.

two regions was ≥40 years. In the urban region, invitation letters were distributed only to the inhabitants whose name was on a list of community-dwelling people that was prepared in 2002.¹¹

Subjects from each area who were willing to attend the study were invited to participate. Despite being younger (58 years) than the age limit defined in the inclusion criteria, 2 inhabitants from the urban area, 9 from the mountainous area and 36 from the coastal area were included in the study because they were very keen to participate. Over the 1.5-year

period from October 2005 to March 2007, 3040 of 5785 candidates were enrolled from the three regions (participation rate, 52.5%).

Selected characteristics of the study population, including age, height, weight, BMI and proportions of participants who smoked and consumed alcohol, are shown in Table 1. In the urban, mountainous and coastal areas, 99.8, 84.3 and 54.7% of the participants, respectively, were >60 years of age. Two-thirds of the participants were women, and their mean age was 1 year less than that of the male

participants. No significant differences were observed in BMI values between the genders, but the proportions of both current smokers and alcohol consumers were significantly higher among men than among women.

All participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo (nos 1264 and 1326) and the Tokyo Metropolitan Institute of Gerontology (no. 5). Careful consideration was given to ensure a safe experience for the participants during the examination and during any other study procedures.

How often have they been followed up?

We intend to follow-up the three population-based cohorts of the ROAD study for at least 10 years. In October 2008, after a follow-up period of 3 years, a second comprehensive clinical examination

was started and is ongoing. We will repeat the baseline measurements during the second examination. A third and fourth examination will be performed at 6 and 10 years, respectively, after the baseline examination.

What has been measured?

The baseline examination of the ROAD study consisted of the following: interviewer-administered questionnaire, dietary assessment, anthropometric measurements, visual and neuromuscular function assessment, biochemical measurements, medical history taking, radiographic assessment and bone mineral density (BMD) measurement (Table 2).

Interviewer-administered questionnaire

A questionnaire was prepared by modifying the questionnaire used in the Osteoporotic Fractures in Men Study (MrOS),¹² and adding some new items to the modified questionnaire. Knee symptoms were

Table 2 Summary of data collected in the ROAD study

Interviewer-administrated questionnaire

Cigarette smoking, alcohol consumption
 Medical history, medications
 Reproductive variables, lactation
 Dietary history, history of falls and fractures
 Physical activity using PASE
 Family history
 Evaluation of knee symptoms using WOMAC
 Health-related QOL (EQ5D, SF-8)

Dietary assessment

Nutrient intake calculated using BDHQ

Anthropometric measurements

Height, weight, arm span, grip strengths
 Circumference of both wrists, circumference of waist
 Heart rate, systolic and diastolic blood pressure

Visual and neuromuscular function

Visual acuity
 Walking speed with tandem walking 6 m x 20 cm
 Rise from a chair

Biochemical measurements

| | |
|-----------------------|--|
| Blood samples | Blood counts, haemoglobin, haemoglobin A1C, blood sugar |
| Sera | Total protein, AST, ALT, GGT, total cholesterol, HDL-cholesterol, triglyceride BUN, uric acid, creatinine |
| DNA samples extracted | |
| Urine samples | Urinary protein, occult blood, sugar, urobilinogen |

Medical information

Pain in back, lumbar, knee and hip
 Swelling and range of motion of the joints
 Tendon reflexes
 Cognitive function used by Mini-Mental Status Examination

Radiographic assessment

Anteroposterior and lateral views of lumbar spine
 Anteroposterior view of both knees
 Anteroposterior view of both hips

BMD measurements

Lumbar spine and proximal femur (mountainous and coastal areas)

AST=aspartate aminotransferase; ALT=alanine aminotransferase; GGT= γ -glutamyltranspeptidase; HDL=high-density lipoprotein; BUN=blood urea nitrogen; BDHQ=Brief Diet History Questionnaire; PASE=Physical Activity Scale for the Elderly; WOMAC=Western Ontario and McMaster University Osteoarthritis Index; EQ5D=European QOL-5 dimensions instrument; SF-8=Medical Outcomes Study 8-item Short Form.

evaluated using the WOMAC.¹³ The health-related QOL was evaluated using the EuroQOL, EQ5D¹⁴ and the SF-8.¹⁵ The study staff recorded all the medications administered and their doses. Physical activity was quantified using the PASE.¹⁶

Dietary assessment

Dietary assessment was made using a BDHQ, and the dietary intakes of nutrients during the previous month were determined. Each participant received a questionnaire that included detailed explanations. Well-trained interviewers clarified any unclear sections in the questionnaire, which was to be completed by the participants at their leisure. The BDHQ is a four-page structured questionnaire that includes questions about the frequency of consumption of 80 principal foods. The serving sizes of the foods are described as normal portions, i.e. the standard weight and volume of servings commonly consumed by the general Japanese population. The BDHQ was modified from a comprehensive, 16-page version of a validated self-administered diet history questionnaire.¹⁷ A total of 141 components, including dietary energy and nutrient intakes, were calculated using an *ad hoc* computer algorithm for the BDHQ.

Anthropometric measurements

Anthropometric factors were measured by well-trained medical nurses. The height and weight of the participants at age 25 years were also noted. BMI [weight in kilograms/(height in metres)²] was calculated on the basis of the current height and weight.

Visual and neuromuscular function

Visual acuity was assessed by the Landolt ring test. Walking speed was determined by recording the time taken by a subject to walk 6 m at the fastest possible speed. The time required for tandem walking across a 6-m long and 20-cm wide path was used to determine balance. The ability to rise from a chair without using the arms (chair stand) and the ability to perform five chair stands was evaluated; the time required to complete the tasks was noted.

Biochemical measurements

Blood and urine samples were obtained from each participant for biochemical and genomic examinations. Urinary protein, occult blood, sugar and urobilinogen were tested using disposable reagent strips (uro-hema-combi sticks; Siemens Medical Solutions Diagnostics, Tokyo, Japan). Residual blood, plasma, serum and urine specimens were processed and stored in a deep freezer (−80°C). DNA was extracted from stored whole-blood specimens, and biochemical markers of bone turnover and cartilage will be measured using these stored serum and urine samples.

Medical history

Medical history was obtained by experienced orthopaedic surgeons (S.M. and H.O.). To quantify cognitive function, the participants were instructed to complete the modified Mini-Mental Status Examination—Japanese version.¹⁸ Physicians explained any unclear sections of this questionnaire to the participants and assessed the participants' cognitive status on the basis of the completed questionnaire.

Radiographic assessment

The severity of OA was radiographically determined according to the Kellgren–Lawrence (KL) grading system as follows¹⁹: KL0—normal joint; KL1—slight osteophytes; KL2—definite osteophytes; KL3—disc-space narrowing and large osteophytes; and KL4—bone sclerosis, disc-space narrowing and large osteophytes. In the ROAD study, joints that exhibited only disc-space narrowing and no large osteophytes were graded as KL3. The radiographs were examined by a single, experienced orthopaedic surgeon (S.M.), who was blinded to the clinical status of the participants. If at least one knee joint was graded as KL2 or higher, the participant was diagnosed with radiographic knee OA. Similarly, if at least one intervertebral joint of the lumbar spine was graded as KL2 or higher, the participant was diagnosed with radiographic lumbar spondylosis.

BMD measurement

In the mountainous and coastal areas, the BMD of the lumbar spine and proximal femur was measured using dual energy X-ray absorptiometry (DXA) (Hologic Discovery; Hologic, Waltham, MA, USA) during the baseline examination. Another BMD measurement was scheduled for the second examination.

To maintain the quality of measurement, the same DXA equipment was used, and the same spine phantom was scanned daily to monitor the machine's performance in study populations from different regions. The BMD of the phantom was adjusted to $1.032 \pm 0.016 \text{ g/cm}^2$ ($\pm 1.5\%$) during all examinations. In addition, to exclude inter-observer variability, the same physician (N.Y.) examined all participants. In another study, N.Y. had measured the intra-observer variability in both *in vitro* and *in vivo* experiments using Lunar DPX.²⁰ In the case of the *in vitro* experiment, the coefficient of variance (CV) for the BMD of the L2–L4 vertebrae was 0.35%. In the case of the *in vivo* experiments, which were performed on five male volunteers, the CVs for the BMDs of the L2–L4 vertebrae, the proximal femur, Ward's triangle and the trochanter were 0.61–0.90, 1.02–2.57, 1.97–5.45 and 1.77–4.17%, respectively.

OP was defined on the basis of the World Health Organization (WHO) criteria; specifically, it was diagnosed when the BMD T-scores were lower than the mean lumbar peak bone mass minus 2.5 SDs.²¹

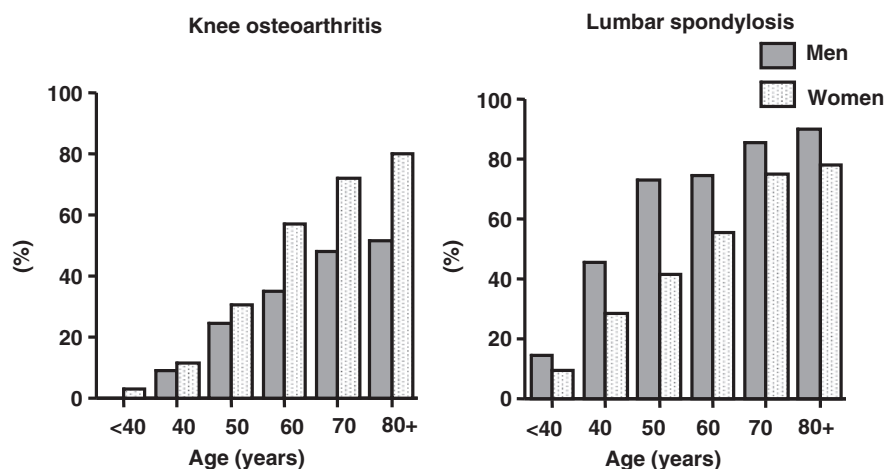


Figure 2 Prevalence of radiographic knee osteoarthritis and lumbar spondylosis, classified by age and gender

In Japan, the mean BMD of the L2–L4 vertebrae among both young male and female adults has been measured using Hologic DXA.²² These indices were used in the present study; lumbar spine BMD $<0.714 \text{ g/cm}^2$ (in case of both men and women), and femoral neck BMD $<0.546 \text{ g/cm}^2$ (men) or 0.515 g/cm^2 (women) were considered to indicate OP.

All assessments performed in the baseline study will be repeated at the first, second and third follow-ups.

What is attrition like?

The first follow-up (second examination) commenced on October 2008, 3 years from baseline assessment. By the end of 2008, follow-up was completed in Hidakagawa, the mountainous region. Of the 864 participants (319 men and 545 women) in the baseline study, 635 subjects (224 men and 411 women) attended the second examination. The response rate for the second examination in the mountainous area was 73.5%. The most common reasons for non-participation were illness and difficulty in visiting the clinic (43% of the dropouts). Further, 26 people (12% of the dropouts) who participated in the baseline study died during the 3-year period following the initial assessment. In other two areas, the follow-ups are on going. The total attrition will be determined at the end of March 2010.

What has the ROAD study found?

By analysing the data from the baseline study, we have determined the prevalence of OA and OP.

OA

The age–sex distribution of radiographic knee OA and lumbar spondylosis was calculated (Figure 2); both conditions were diagnosed at KL grades of ≥ 2 .

In the overall population, the prevalence of radiographic knee OA and lumbar spondylosis was 54.6% (42.0% in men and 61.5% in women) and 70.2% (80.6% in men and 64.6% in women), respectively. Thus, both the overall and sex-specific prevalence of lumbar spondylosis were higher than those of knee OA.²³

OP

The prevalence of OP was calculated for the participants from mountainous and coastal regions in the ROAD study (Figure 3). The prevalence of OP of the lumbar spine and femoral neck in women was 6- and 5-fold, respectively, than in men. The differences were significant ($P < 0.001$).²³

What are the main strengths and weaknesses of the ROAD study?

Strengths

In Japan, little epidemiological information is available of musculoskeletal diseases such as OA and OP. The ROAD study is the first large population-based prospective study conducted on the Japanese population and is designed to supply essential information, chiefly of OA and OP.

We confirmed the high prevalence of OA and OP among the ROAD study participants, and we will conduct follow-up examinations for at least 10 years in order to clarify the relationships of OA, OP and osteoporotic fractures with the following parameters: lifestyle, anthropometric and neuromuscular measurements, bone mass, bone geometry and fall propensity. Further, we will determine how these impairments affect QOL and mortality. We also expect to assess the similarities and differences in the risk factors of OA and OP. In addition, we will clarify the incident morbidity of other lifestyle-related disorders,

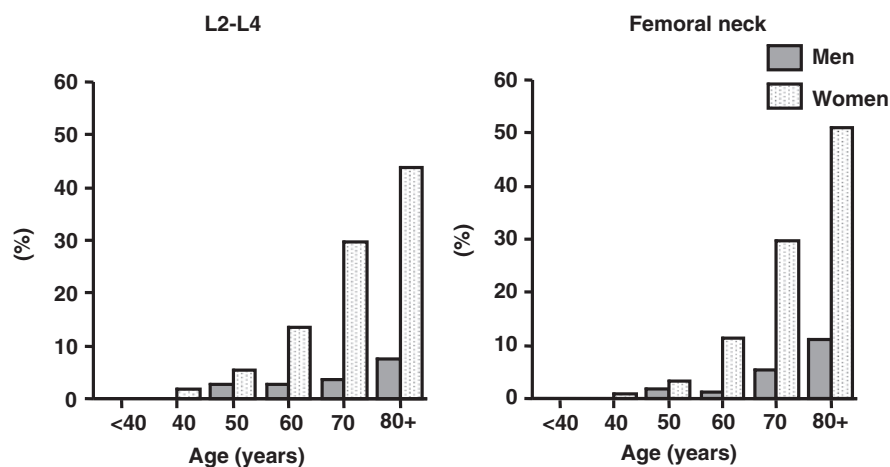


Figure 3 Prevalence of osteoporosis of the lumbar spine and femoral neck

such as obesity, hypertension, diabetes mellitus, cardiovascular and metabolic diseases and dementia.

The ROAD study data will facilitate the development of clinical guidelines for the detection and prevention of osteoporotic fractures in other countries. This study was designed such that it would be similar to the Study of Osteoporotic Fractures, a large observational study on the determinants of fractures in older women,²⁴ and to MrOS, a large observational study on the determinants of fractures in older men²⁵ in the USA.

Finally, the completion of the ROAD study will provide unique opportunities for the study of other conditions that are common among older men and women, such as obesity, diabetes, cardiovascular disease, cognitive disorders and frailty. The blood, plasma, serum and urine specimens stored during the ROAD study will enable the clarification of a variety of new biochemical and genetic factors associated with musculoskeletal disorders and the aforementioned diseases.

Weaknesses

Although the ROAD study includes a large number of subjects (more than 3000), these subjects are voluntary participants and have been recruited from only three areas; hence, they do not truly represent the general population. The 'healthy' and 'regional' selection biases should be confirmed.²⁶ We could not directly compare the baseline characteristics between the responders and non-responders owing to lack of data regarding the non-responders. Hence, to determine whether a selection bias existed in the ROAD study, we compared the anthropometric measurements and frequencies of smoking and alcohol drinking between the participants and the general Japanese population. The values for the general population were obtained from the 2005 National Health and Nutrition Survey conducted by the Ministry of Health, Labour and Welfare, Japan, which is an annual survey to clarify the health status of the Japanese population and is

conducted on approximately 18 000 inhabitants from 6000 randomly selected families.²⁷

The BMIs of ROAD study participants and the Japanese population were compared (Table 3). No significant differences were identified, except that the male participants aged 70–74 years were significantly smaller in build than men of this age group in the overall Japanese population ($P < 0.05$).

The proportion of current smokers and current drinkers (those who regularly smoked or drank more than once a month) in the general Japanese population was compared with that in the study population (Figure 4). Both proportions were significantly higher in the general Japanese population than in the study population (smokers: men, $P < 0.001$ and women, $P < 0.001$; drinkers: men, $P < 0.01$ and women, $P < 0.001$), suggesting that participants of the ROAD study had healthier lifestyles than the general Japanese population. This bias due to the selection of 'healthy' individuals should be taken into consideration while generalizing the results of the ROAD study.

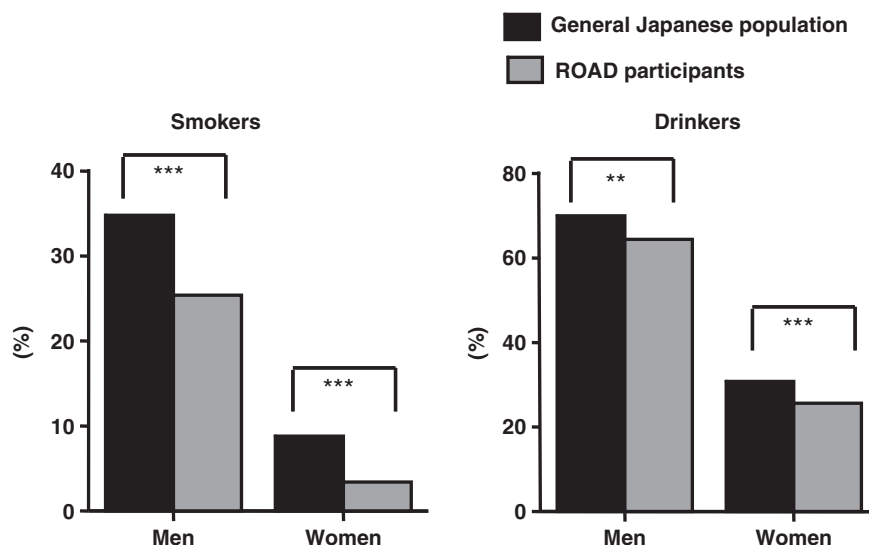
Further, BMD was measured only in the participants from the mountainous and coastal areas. The total number of participants from these two areas (1690) may be large enough to accurately estimate the incidence and evaluate risk factors. Nevertheless, regional bias should be taken into account while generalizing the results.

Can I get hold of the data? Where can I find out more?

The ROAD study group welcomes specific and detailed proposals for new collaborations. Initial enquiries should be addressed to N.Y. Some information about the ROAD study is available on the website of the Department of Joint Disease Research, 22nd Century Medical and Research Centre,

Table 3 Comparison of BMI (SD) (kg/m²) of the participants with general Japanese population

| Age strata (years) | Men | | Women | |
|--------------------|------------|------------|------------|------------|
| | ROAD | Japanese | ROAD | Japanese |
| 40–49 | 24.5 (4.4) | 24.0 (3.3) | 21.9 (4.1) | 22.4 (3.5) |
| 50–59 | 23.6 (2.9) | 23.7 (3.1) | 23.0 (3.3) | 23.1 (3.4) |
| 60–69 | 23.8 (3.2) | 23.8 (2.9) | 23.3 (3.2) | 23.5 (3.7) |
| 70–74 | 23.1 (2.8) | 23.7 (3.2) | 23.4 (3.5) | 23.2 (3.4) |
| 75–79 | 22.8(2.9) | 23.3 (3.0) | 23.0 (3.7) | 23.4 (3.5) |
| ≥80 | 22.6 (2.9) | 22.3 (2.6) | 22.2 (3.2) | 22.5 (4.0) |

**Figure 4** Comparison of the proportion of current smokers and drinkers between the participants of the ROAD study and the general Japanese population. ** $P < 0.01$, *** $P < 0.001$

University of Tokyo Hospital (<http://www.h.u-tokyo.ac.jp/center22/kansetu.html>).

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Conflict of interest: None declared.

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