Prevalence and correlates of regional pain and associated disability in Japanese workers

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ABSTRACT

Objectives To assess the prevalence and correlates of regional pain and associated disability in four groups of Japanese workers.

Methods As part of a large international survey of musculoskeletal symptoms (the CUPID study), nurses, office workers, sales/marketing personnel and transportation operatives in Japan completed a self-administered questionnaire (response rate 83%) covering experience of pain in six anatomical regions, associated disability and sickness absence, and various possible occupational and psychosocial risk factors for these outcomes. Associations with risk factors were assessed by logistic regression.

Results Analysis was based on 2290 subjects. Rates of regional pain were generally less than in the UK, with a particularly low prevalence of wrist/hand pain among office workers (6% in past month). The strongest and most consistent risk factor for regional pain in the past month was tendency to somatise (ORs (95% CIs) for report of ≥2 versus 0 distressing somatic symptoms 3.1 (2.4 to 4.0) for low back pain, 2.8 (2.1 to 3.8) for shoulder pain, and 2.5 (1.6 to 4.1) for wrist/hand pain). Sickness absence for regional pain complaints in the past year was reported by 5% of participants, the major risk factor for this outcome being absence during the same period for other medical reasons (OR 3.7, 95% CI 2.4 to 5.8).

Conclusions Japanese office workers have markedly lower rates of wrist/hand pain than their UK counterparts. In Japan, as in Western Europe, somatising tendency is a major risk factor for regional pain. Sickness absence attributed to regional pain complaints appears to be much less common in Japan than in the UK, and to be driven principally by a general propensity to take sickness absence.

What this paper adds

- Japanese office workers have markedly lower rates of wrist/hand pain than office workers in the UK.
- In Japan, as in Western Europe, somatising tendency is a major risk factor for musculoskeletal complaints.
- Sickness absence attributed to musculoskeletal disorders appears to be much less common in Japan than in the UK.
- Our findings add weight to a growing body of evidence that the prevalence of musculoskeletal symptoms and resultant disability and sickness absence varies markedly between countries.
- Strategies to control work-related musculoskeletal disorders should take into account the factors that underlie these differences, which may include culturally determined health beliefs and expectations.

INTRODUCTION

Musculoskeletal pain, especially in the back, neck and upper limbs, is a common complaint in many developed countries, and an important cause of disability and work incapacity. It is often attributed to strain from forceful or repetitive occupational activities, and epidemiological research has demonstrated fairly consistent associations of low back pain with work involving heavy lifting and/or repeated bending of the trunk,[1] and of painful disorders of the forearm with work that entails repetitive movements of the wrist or hand.[2]

However, regional pain complaints and associated disabilities are not a simple consequence of physical stresses to tissues. There is strong evidence that they are influenced also by psychological factors such as low mood and a general tendency to worry about common somatic symptoms (somatising tendency).[3 4] In addition, culturally determined health beliefs could also have an important role, and may explain large variations in the incidence and prevalence of pain and disability that have been observed between countries,[5 6] and within countries over time.[5] It is important to understand the contribution of these psychosocial influences if preventive measures are to be optimised.

To help advance knowledge in this area, a multicentre international study, CUPID (Cultural and Psychosocial Influences on Disability), has been established. The study, which is being carried out in 19 countries (both developing and developed) from six continents, involves a baseline cross-sectional survey that will allow comparison of rates of regional pain and associated disability in samples of workers who carry out similar physical activities but in widely different cultural environments. This is followed by a longitudinal component, which explores predictors of persistent and newly incident pain.

In this paper, we report findings from the initial cross-sectional survey that was carried out in Japan as part of the CUPID study, and draw comparisons with experience in the UK.

METHOD

The survey focused on four occupational groups—nurses, office workers, sales/marketing personnel and transportation operatives. All participants worked in or near Tokyo. The nurses were employed

at Tokyo University Hospital, the office workers in administrative and clerical jobs at the same hospital and at four pharmaceutical companies and a private trading company, the sales/marketing personnel at six pharmaceutical companies, and the transportation operatives (mainly lorry drivers and loaders) at two companies transporting baggage and mail.

Within each participating organisation, a manager agreed to act as a coordinator for data collection. The coordinator distributed a self-administered questionnaire to all employees in relevant jobs, with a covering letter from the survey team. Completed questionnaires were then returned to the survey team via the coordinator. A total of 3187 questionnaires were distributed to 1074 nurses, 425 office workers, 380 sales/marketing personnel and 1308 transportation operatives. No reminders were sent to non-responders.

The questionnaire was a Japanese translation of the survey instrument that is being used throughout the CUPID study. The accuracy of the translation was checked by independent back-translation to English and comparison with the original. Amendments were then made as necessary. Among other things, the questionnaire asked about demographic characteristics, hours of work and duration of employment in current job, whether the job involved certain specified activities in an average working day, job satisfaction, mental health, indicators of tendency to somatise, experience of pain during the past month and past year at each of six anatomical sites (low back, neck, shoulder, elbow, wrist/hand and knee), disability for specified everyday tasks arising from such pain, and absence from work in the past year because of musculoskeletal pain or for other reasons. Mental health (mood) was assessed from the relevant subscale from the SF-36 questionnaire,[7] and was graded to three levels defined by approximate thirds of the distribution of scores in all subjects combined. Somatising tendency was assessed using a subset of items from the Brief Symptom Inventory,[8] and was graded according to the number of symptoms (out of a total of seven) that were reported as causing at least moderate concern in the past week.

Data from the completed questionnaires were entered onto computer, and after checks for errors, were analysed using SPSS V.15 and STATA V.10 software. Because a major focus of the study was pain and disability during the past year, subjects were excluded from the main analysis if they had worked in their current job for less than a year.

In addition to the compilation of simple descriptive statistics, logistic regression was used to explore associations with regional pain (classified in various ways) and associated disability and sickness absence. Pain at an anatomical site was considered disabling if during the past month it had made at least one of the everyday activities specified in the questionnaire difficult or impossible. These activities were: getting dressed (all sites of pain), doing normal household jobs (all sites of pain), cutting toe nails (low back), combing or brushing hair (shoulder), bathing/showering (shoulder), opening bottles, jars or taps (elbow and wrist/hand), writing (wrist/hand), locking and unlocking doors (wrist/hand), walking up and down stairs (knee) and walking on level ground (knee). When looking at associations with occupational activities, we defined for each site of pain an activity in an average working day that could cause physical stress to local tissues. These activities were: lifting weights of ≥25 kg by hand (low back); work with the hands above shoulder height for ≥1 h in total (neck and shoulders); repeated bending and straightening of the elbow for ≥1 h in total (elbow); use of a keyboard or other repetitive movements of the wrist/fingers for ≥4 h in total (wrist/hand); and kneeling or squatting for ≥1 h in total (knees). Associations in the logistic regression analyses were summarised by ORs with associated 95% CIs.

RESULTS

Questionnaires were returned by 2651 (83%) of the workers to whom they were issued, but 285 were excluded from analysis because the individual had been in his/her current job for less than a year, and a further 76 because of missing information on age (52), sex (1) or both (23). Of the remaining 2290 subjects, 599 were nurses, 316 were office workers, 355 were sales/marketing personnel and 1020 were transportation operatives, representing 56%, 74%, 93% and 78% of those mailed in the respective occupational groups.

Table 1 summarises various characteristics of the participants. Most of the nurses were women, whereas almost all of the sales/marketing personnel and transportation operatives were men. The majority of subjects were employed full-time, including 30% of the sample (mostly sales/marketing personnel and transportation operatives) who indicated that they worked for more than 60 h per week. Reported occupational activities were much as would be expected, with a high frequency of keyboard use by office workers (89%). Transportation operatives and nurses had the highest prevalence of heavy lifting (83% and 66%, respectively) and of repeated bending and straightening of the elbow (78% and 72%). Rates of job satisfaction were relatively low in office workers (28%) and sales/marketing personnel (31%). Poor mental health and tendency to somatise were most common among nurses. In the study sample overall, the somatic symptoms most frequently reported as distressing were nausea or upset stomach (14%), weakness (12%) and faintness or dizziness (8%).

Table 2 shows the prevalence of pain at different anatomical sites in the study sample as a whole. The lower back was the site most commonly affected by pain, with a prevalence of 28% in the past month. Next most common were pain in the neck (21% in the past month) and shoulder (17%). In comparison, pain in the elbow and wrist/hand was much less frequent. The sites most commonly affected by disabling pain in the past month were the lower back (11%) and knee (8%). Only 4% of subjects had been absent from work during the past year because of low back pain, and absence because of pain in the elbow or wrist/hand was extremely rare.

The prevalence of regional pain by occupational group is summarised in table 3 (data for men and women separately are given in online supplementary tables 1 and 2). At almost all anatomical sites, pain in the past month was most common in nurses or transportation operatives, and least frequent in sales/marketing personnel. However, office workers had the highest prevalence of sickness absence in the past year attributed to regional pain (11%). A total of 251 subjects (11%) reported pain in the past month at three or more anatomical sites, 744 (32%) reported disabling pain at one or more sites during the past month, and 125 (5%) indicated that they had taken sickness absence during the past year because of regional pain.

Table 4 gives results from logistic regression analyses exploring risk factors for pain at different anatomical sites. For each site, two outcomes were examined—any pain in the past month and disabling pain in the past month—the comparator in both cases being no pain at the site in the past month. All analyses were adjusted for sex, age, mental health and occupational group. Significant associations with locally stressful physical activities were observed for pain in the low back (lifting ≥25 kg), wrist/hand (use of keyboard or repeated movements of hands/fingers for ≥4 h) and knee (kneeling or squatting for ≥1 h). However,

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Table 1 Characteristics of participants by occupational group

Characteristic	Nurses (n=599)		Office workers (n=316)		Sales/ marketing personnel (n=355)		Transportation operatives (n=1020)		Total (n=2290)	
	n	%	n	%	n	%	n	%	n	%
Sex										
Male	20	3.3	181	57.3	331	93.2	1016	99.6	1548	67.6
Female	579	96.7	135	42.7	24	6.8	4	0.4	742	32.4
Age (years)										
19–29	253	42	14	4	103	29	214	21	584	26
30–39	193	32	112	35	178	50	415	41	898	39
40–49	81	14	101	32	63	18	278	27	523	23
50–64	72	12	89	28	11	3	113	11	285	12
Hours worked per week										
Up to 20	30	5	35	11	30	8	142	14	237	10
21–40	248	41	114	36	33	9	97	10	492	21
41–60	286	48	148	47	188	53	214	30	836	37
≥61	20	3	15	5	103	29	552	54	690	30
Missing	15	3	4	1	1	0.2	15	1	35	2
Occupational activities in an average working day										
Use of keyboard ≥4 h	142	24	281	89	99	28	25	2	547	24
Other repeated movements of wrist/fingers ≥4 h	144	24	44	14	36	10	336	33	560	24
Repeated bending and straightening of elbow for ≥1 h in total	434	72	74	23	107	30	795	78	1410	62
Work with hands above shoulder height ≥1 h in total	73	12	5	2	15	4	343	34	436	19
Lifting weights of ≥25 kg by hand	398	66	10	3	33	9	849	83	1290	56
Kneeling or squatting ≥1 h in total	289	48	7	2	43	12	534	52	873	38
Satisfied with current job										
Yes	329	55	91	28	108	31	589	58	1117	49
Mental health										
Good	164	27	142	45	119	34	297	29	722	32
Intermediate	190	32	85	27	121	34	331	32	727	32
Poor	234	39	84	27	110	31	371	36	799	35
Somatising tendency (number of symptoms in past week causing at least moderate concern)										
0	170	28	141	45	146	41	516	51	973	42
1	237	40	107	34	121	34	278	28	743	32
≥2	183	31	66	21	86	24	213	21	548	24

the strongest and most consistent associations were with somatising tendency. For disabling pain in the low back, neck and shoulder, the ORs for report of ≥2 versus 0 distressing somatic symptoms were all 4.5 or higher. Associations with poor mental health (not shown) were much weaker than with somatising tendency, and not statistically significant.

Table 5 presents findings from two regression analyses, one for the risk of pain in the past month at three or more anatomical sites, and the other for disabling pain at one or more anatomical sites in the past month. In each case, the comparator was no pain at any site in the past month. Both variables were strongly associated with somatising tendency and showed a clear, progressive increase in risk in relation to the number of stressful physical activities reported. In addition, both were more frequent at older ages. Associations with poor mental health and job dissatisfaction were much weaker.

In contrast, sickness absence because of regional pain in the past year was unrelated to occupational physical activities and showed no clear association with somatising tendency (table 6). It was, however, strongly associated with sickness absence during the past year for other reasons (OR 3.7, 95% CI 2.4 to 5.8), which was reported by 16% of participants.

DISCUSSION

In this cross-sectional survey of Japanese workers, rates of regional pain were generally lower than have been reported in

Table 2 Prevalence of regional pain by anatomical site

Anatomical site	Any pain in past month		Disabling pain in past month*		Any pain in past year		Pain for ≥1 month in past year†		Pain causing absence from work in past year	
	n	%	n	%	n	%	n	%	n	%
Low back	636	28	255	11	1075	47	293	13	101	4
Neck	484	21	91	4	735	32	209	9	40	2
Shoulder	382	17	107	5	549	24	193	8	25	1
Elbow	123	5	39	2	170	7	36	2	7	0.3
Wrist/hand	161	7	72	3	236	10	69	3	9	0.4
Knee	285	12	181	8	429	19	116	5	27	1

*For definition of disabling pain, please see text.
†Pain for at least 1 month in total.

Table 3 Prevalence of regional pain by occupational group

Category of pain	Nurses		Office workers		Sales/marketing personnel		Transportation operatives	
	n	%	n	%	n	%	n	%
Low back pain in past month	182	30	68	22	68	19	318	31
Neck pain in past month	184	31	85	27	63	18	152	15
Shoulder pain in past month	132	22	61	19	47	13	142	14
Elbow pain in past month	16	3	13	4	11	3	83	8
Wrist/hand pain in past month	39	7	19	6	15	4	88	9
Knee pain in past month	74	12	36	11	34	10	141	14
Pain at ≥3 sites in past month	80	13	34	11	16	5	121	12
Disabling pain at any site in past month*	220	37	79	25	65	18	380	37
Pain at any site causing absence from work in past year	15	3	34	11	13	4	63	6

*For definition of disabling pain, please see text.

the UK, with a particularly low frequency of pain in the wrist and hand. The prevalence of sickness absence attributed to regional pain was also substantially lower than in the UK. Pain at most sites was more common in workers who indicated that they were exposed to stressful physical activities in their job, but the strongest and most consistent risk factor for regional pain and associated disability was somatising tendency. In contrast, risk of sickness absence because of regional pain was related not to physical activities or somatising tendency, but to absence from work because of other health problems.

The occupational groups that were studied cannot necessarily be regarded as representative of the general population of working age in Japan. Nevertheless, they encompass a range of occupational tasks, both manual and non-manual, and provide useful insights into patterns of musculoskeletal symptoms and disability in a cultural environment that is notably different from that in, say, Western Europe. Furthermore, the high response rate that was achieved makes it likely that the samples of workers who participated were fairly typical of the occupational groups from which they were drawn.

A concern always in international studies of this type is that the meaning of questions may be distorted in translation between languages. Thus, care was taken to check the accuracy of the Japanese questionnaire by back-translation to English. It remains possible that a term such as "pain" is understood somewhat differently in Japan. However, this should not affect the relative frequency of the symptom at different anatomical sites, and is less likely to have been a problem in relation to more objective outcomes such as sickness absence.

Another possible source of error was incomplete recall of symptoms, particularly if they last occurred many months before the questionnaire was completed. For this reason, we based most of our analysis on pain and disability that was reported in the past month. An exception was sickness absence, for which a longer time period was required to give meaningful numbers of cases. However, we would expect spells of sickness absence to be more memorable than more minor episodes of pain.

The prevalence of pain at most of the anatomical sites considered was somewhat lower than has been recorded in UK workers who were surveyed using similar questions.[6] For example, low back pain in the past month was reported by 28% of the Japanese workers as compared with 28% in a sample of white UK office workers and 37% in a group of white UK manual workers, while the corresponding figures were 21% versus 26% and 23% for neck pain, 17% versus 20% and 24% for shoulder pain, and 5% versus 10% and 9% for elbow pain. More remarkable, however, is the much lower prevalence of wrist/hand pain in Japanese workers (7% vs 30% and 23%). This lower prevalence extended to Japanese office workers (6% with wrist/hand pain), most of whom were regular users of computer keyboards. The difference in the prevalence of wrist/hand pain

Table 4 Risk factors for regional pain in past month

Risk factor	Low back		Neck		Shoulder		Elbow		Wrist/hand		Knee	
	n	OR* (95% CI)	n	OR* (95% CI)	n	OR* (95% CI)	n	OR* (95% CI)	n	OR* (95% CI)	n	OR* (95% CI)
Any pain in past month†												
Physical activity‡	421	1.9 (1.4 to 2.5)	87	1.2 (0.9 to 1.6)	76	1.2 (0.9 to 1.7)	81	1.2 (0.8 to 2.0)	86	1.9 (1.3 to 2.6)	144	2.0 (1.5 to 2.7)
Somatising tendency§												
0	348	1	240	1	98	1	71	1	90	1	160	1
1	113	1.7 (1.3 to 2.3)	106	2.3 (1.8 to 3.1)	77	1.9 (1.4 to 2.6)	16	1.2 (0.7 to 2.1)	29	1.6 (1.0 to 2.5)	52	1.7 (1.2 to 2.4)
≥2	158	3.1 (2.4 to 4.0)	125	3.2 (2.4 to 4.2)	97	2.8 (2.1 to 3.8)	31	2.5 (1.6 to 4.1)	38	2.2 (1.4 to 3.3)	71	2.6 (1.9 to 3.6)
Job dissatisfaction	260	1.3 (1.0 to 1.6)	225	1.1 (0.8 to 1.4)	201	1.1 (0.9 to 1.5)	68	1.1 (0.7 to 1.7)	64	1.5 (1.0 to 2.1)	133	1.1 (0.8 to 1.4)
Disabling pain in past month†												
Physical activity‡	180	2.2 (1.5 to 3.4)	24	1.6 (0.9 to 2.7)	24	1.1 (0.6 to 1.8)	24	0.7 (0.3 to 1.4)	39	1.8 (1.1 to 3.0)	95	2.0 (1.4 to 2.9)
Somatising tendency§												
0	128	1	37	1	39	1	20	1	32	1	90	1
1	38	1.6 (1.0 to 2.4)	17	2.3 (1.2 to 4.2)	19	2.5 (1.4 to 4.5)	4	1.0 (0.3 to 2.9)	18	2.7 (1.4 to 4.9)	38	2.1 (1.4 to 3.2)
≥2	82	4.5 (3.2 to 6.4)	33	5.0 (2.9 to 8.4)	45	7.2 (4.4 to 11.8)	14	3.9 (1.8 to 8.2)	21	3.4 (1.8 to 6.3)	51	3.3 (2.2 to 4.9)
Job dissatisfaction	157	1.5 (1.1 to 2.0)	36	1.1 (0.7 to 1.8)	38	1.2 (0.8 to 2.0)	18	0.7 (0.3 to 1.3)	27	1.5 (0.9 to 2.7)	79	1.1 (0.8 to 1.6)

*For each anatomical site and pain outcome, ORs were derived from a logistic regression model that included all of the risk factors presented together with sex, age (in four strata), mental health (in three strata) and occupational group.
†Risks are relative to no pain at site in past month.
‡Stressful occupational activity in an average working day defined as lifting weights of ≥25 kg by hand (low back), work with the hands above shoulder height for ≥1 h (neck and shoulder), repeated bending and straightening of elbow for ≥1 h (elbow), use of a keyboard or repeated movements of hands/fingers for ≥4 h (wrist/hand), kneeling or squatting for ≥1 h (knee).
§Number of somatic symptoms causing at least moderate concern in past week.

Table 5 Risk factors for multi-site and disabling pain in the past month

Risk factor	Pain at ≥3 sites		Disabling pain at any site	
	n	OR* (95% CI)	n	OR* (95% CI)
Sex				
Male	144	1	327	1
Female	97	1.8 (0.9 to 3.7)	161	0.8 (0.4 to 1.3)
Age (years)				
19–29	44	1	107	1
30–39	84	1.7 (1.1 to 2.6)	179	1.4 (1.0 to 1.9)
40–49	72	4.4 (2.7 to 7.1)	136	2.7 (1.9 to 3.9)
50–64	41	4.4 (2.5 to 7.8)	66	2.6 (1.7 to 4.0)
Number of stressful occupational physical activities†				
0	11	1	36	1
1	49	2.8 (1.3 to 5.9)	104	1.9 (1.2 to 3.0)
2	46	3.1 (1.5 to 6.6)	97	2.2 (1.3 to 3.5)
3	50	4.3 (2.0 to 9.3)	106	2.8 (1.7 to 4.5)
4	50	6.0 (2.7 to 13.2)	89	3.5 (2.1 to 5.9)
5	35	9.3§ (4.0 to 21.5)	56	5.0¶ (2.8 to 9.0)
Somatising tendency‡				
0	108	1	259	1
1	55	3.4 (2.3 to 5.1)	90	2.2 (1.6 to 3.0)
≥2	78	6.2 (4.1 to 9.3)	139	4.5 (3.3 to 6.2)
Mental health				
Good	57	1	119	1
Intermediate	73	1.3 (0.8 to 1.9)	146	1.2 (0.9 to 1.6)
Poor	111	1.4 (0.9 to 2.1)	223	1.5 (1.1 to 2.1)
Job satisfaction				
Satisfied	148	1	281	1
Dissatisfied	93	1.3 (0.9 to 1.9)	207	1.2 (0.9 to 1.6)
Occupational group				
Nurses	77	1	140	1
Office workers	33	1.1 (0.6 to 2.2)	61	0.8 (0.5 to 1.3)
Sales/marketing personnel	14	0.9 (0.3 to 2.2)	46	0.6 (0.3 to 1.1)
Transportation operatives	117	1.1 (0.5 to 2.5)	241	0.6 (0.3 to 1.1)

*OR relative to no pain at any site. ORs for each pain outcome were derived from a single regression model incorporating all of the variables.
†Occupational activities in an average working day (lifting weights of ≥25 kg by hand, work with the hands above shoulder height for ≥1 h, repeated bending and straightening of the elbow for ≥1 h, use of a keyboard or repeated movements of hands/fingers for ≥4 h, kneeling or squatting for ≥1 h).
‡Number of somatic symptoms causing at least moderate concern in past week.
§p for trend <0.001.
¶p for trend <0.001.

Table 6 Risk factors for sickness absence because of regional pain in past year

Risk factor	n	OR* (95% CI)
Sex		
Male	86	1
Female	26	0.7 (0.4 to 1.5)
Age (years)		
19–29	17	1
30–39	49	1.4 (0.8 to 2.5)
40–49	31	1.3 (0.7 to 2.6)
50–64	15	1.2 (0.5 to 2.5)
Number of stressful occupational physical activities†		
0	13	1
1	42	1.2 (0.6 to 2.5)
2	22	1.0 (0.5 to 2.1)
3	14	0.7 (0.3 to 1.6)
4	13	0.8 (0.3 to 2.0)
5	8	0.9 (0.3 to 2.4)
Somatising tendency‡		
0	71	1
1	16	1.0 (0.5 to 1.8)
≥2	25	1.4 (0.9 to 2.4)
Mental health		
Good	35	1
Intermediate	23	0.7 (0.4 to 1.2)
Poor	54	1.6 (1.0 to 2.7)
Job satisfaction		
Satisfied	52	1
Dissatisfied	60	0.9 (0.6 to 1.5)
Sickness absence in past year for reasons other than regional pain		
No	67	1
Yes	45	3.7 (2.4 to 5.8)
Occupational group		
Nurses	13	1
Office workers	33	2.9 (1.2 to 6.7)
Sales/marketing personnel	13	1.1 (0.4 to 3.3)
Transportation operatives	53	2.5 (1.0 to 6.3)

*OR relative to no sickness absence for regional pain in past year. ORs were derived from a single regression model incorporating all of the variables.
†Occupational activities in an average working day (lifting weights of ≥25 kg by hand, work with the hands above shoulder height for ≥1 h, repeated bending and straightening of the elbow for ≥1 h, use of a keyboard or repeated movements of hands/fingers for ≥4 h, kneeling or squatting for ≥1 h).
‡Number of somatic symptoms causing at least moderate concern in past week.

between Japanese and UK office workers was much larger than that between manual and non-manual workers in the UK, or between white workers in the UK and those of South Asian origin.[6]

Also notable is the low rate of sickness absence that was attributed to regional pain complaints. Overall, only 4% of study participants had been absent from work in the past year because of low back pain, 2% for neck pain, 1% for shoulder pain, 0.3% for elbow pain and 0.4% for wrist/hand pain. In comparison, reported rates in UK workers were more than three times higher.[6] Workers from Japan tend to claim compensation and take time off work for illness attributed to occupation less often than their counterparts in the USA.[9] However, the differences we found are not explained simply by low overall rates of sickness absence in Japan—16% of participants reported absence in the past year because of non-musculoskeletal illness. Rather the proportion of absence attributed to musculoskeletal disorders was much lower than in the UK.

Earlier studies of musculoskeletal symptoms in Japan have focused mainly on low back pain,[10–22] with prevalence rates varying from 13% (in female nursing students [18]) to 83% (in nurses[19]), according to the population studied and case definition. Where assessed, rates of neck pain have been lower than those for low back pain in the same study,[16–19] and the prevalence of pain in the wrist or hand has been even lower.[19 21]

Although there are many published surveys of regional pain in other countries, few studies to date have compared rates of musculoskeletal illness between countries, using standardised methods for data collection. In an analysis of data from surveys of the general adult population in 10 developed and seven developing countries, the age-standardised prevalence of chronic back pain was somewhat higher in developing countries (24.3%) than in developed countries (18.5%).[23] A comparative survey of nursing personnel found a higher 12-month prevalence of back complaints among Greek hospital nurses (75%) than in Dutch nurses and caregivers employed in nursing homes (62%).[24] And in another study, rates of pain among manual workers were substantially lower in Mumbai, India, than in the UK, at each of five anatomical sites (low back, neck, shoulder, elbow and wrist/hand).[6] For office workers, the differences were much smaller.

Within our Japanese sample of workers, analysis of risk factors for regional pain revealed expected associations with stressful physical activities. However, associations with somatising tendency were stronger, especially when pain was disabling.

Given that the data analysed were cross-sectional, it is possible that the observed associations between physical activities and regional pain arose in part because of greater awareness, and therefore more frequent reporting, of such activities among workers who found them painful. It seems less likely, however, that the presence of back, neck or arm pain would cause a person to over-report worry about somatic symptoms such as nausea, weakness, or faintness and dizziness. Furthermore, in other countries, longitudinal studies have found that somatising tendency predicted the future incidence and persistence of musculoskeletal pain,[3 4 25 26] and was associated with subsequent poor outcome in patients presenting to primary care or treated by physiotherapy for musculoskeletal disorders.[27–30] Tendency to somatise has also been associated with other complaints, including irritable bowel syndrome[31] and report of symptoms following exposure to pesticides.[32] In comparison with somatising tendency, low mood was a much weaker risk factor for regional pain in the Japanese workers.

In contrast, neither physical activity nor somatising tendency were clearly related to sickness absence because of regional pain, which was associated much more strongly with absence attributed to non-musculoskeletal disorders. It may be that in Japan, the major determinant of variation in rates of absence ascribed to musculoskeletal symptoms is not differences in the occurrence of such symptoms but differences in workers' general inclination to take sickness absence when they perceive a health problem.

In summary, this study provides further evidence that the prevalence of musculoskeletal symptoms varies importantly between countries, and suggests that, as in the UK, a major risk factor for musculoskeletal complaint in Japan is tendency to somatise.

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Osteoarthritis and Cartilage

Accumulation of metabolic risk factors such as overweight, hypertension, dyslipidaemia, and impaired glucose tolerance raises the risk of occurrence and progression of knee osteoarthritis: a 3-year follow-up of the ROAD study

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SUMMARY

Objective: To clarify the association between the occurrence and progression of knee osteoarthritis (KOA) with components of metabolic syndrome (MS), including overweight (OW), hypertension (HT), dyslipidaemia (DL), and impaired glucose tolerance (IGT), in a general population.
Design: From the large-scale population-based cohort study entitled Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) initiated in 2005, 1,690 participants (596 men, 1,094 women) residing in mountainous and coastal areas were enrolled. Of these, 1,384 individuals (81.9%; 466 men, 918 women) completed the second survey, including knee radiography, 3 years later. KOA was defined as Kellgren–Lawrence (KL) grade ≥ 2 using paired X-ray films. Based on changes in KL grades between the baseline and second surveys, cumulative incidence and progression of KOA were determined. OW, HT, DL, and IGT at baseline were assessed using standard criteria.
Results: The cumulative incidence of KOA among 1,384 completers over 3 years was 3.3%/year, and progression in KL grades for either knee, 8.0%/year. Logistic regression analyses after adjusting for potential risk factors revealed that the odds ratio (OR) for the occurrence of KOA significantly increased according to the number of MS components present (OR vs no component: one component, 2.33; two components, 2.82; ≥three components, 9.83). Similarly, progression of KOA significantly increased according to the number of MS components present (OR vs no component: one component, 1.38; two components, 2.29; ≥three components: 2.80).
Conclusion: Accumulation of MS components is significantly related to both occurrence and progression of KOA. MS prevention may be useful in reducing future KOA risk.

Introduction

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 and affects activities of daily living and quality of life, leading to increased morbidity and mortality[1–3]. 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 long-term care[4]. The National Livelihood Survey also shows that cardiovascular disease (CVD) is ranked first in causing disabilities in the elderly[4]. Most CVD patients have multiple risk factors[5]. The presence of these risk factors in a specific combination, entitled metabolic syndrome (MS), is a multiplex risk factor that predisposes affected individuals to CVD morbidity and mortality. MS is generally considered a combination of being overweight (OW) and having hypertension (HT), dyslipidaemia (DL), and impaired glucose tolerance (IGT)[6].

Knee OA (KOA) and MS share age and obesity as risk factors[1,7–12]. Numerous investigators have associated OA with

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various MS components. Lawrence first reported that diastolic blood pressure (BP) was associated with KOA in women[13]. Kellgren reported that hand OA was significantly associated with above-average serum cholesterol levels in women[14]. Cimmino *et al.* observed significantly higher plasma glucose levels in women with OA than in those without[15]. Contradictory findings regarding the association of such metabolic factors with OA have been reported[16–19]. Hart *et al.* found that metabolic factors such as blood glucose, hypercholesterolaemia, and even treated HT were associated with KOA development[20]. A few population-based studies have demonstrated a dose–response relationship between risk factor accumulation for MS and KOA; we have previously reported that KOA presence was significantly associated with increase in the number of MS components[21]. However, to our knowledge, no study has clarified the associations between KOA occurrence or progression and MS component accumulation, using a prospective cohort of general inhabitants.

This study evaluated the incidence and progression of radiographic KOA and its associations with individual and cumulative MS components (OW, HT, DL, and IGT) among men and women using the large-scale, population-based cohort from the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study.

Method

Participants

This study involved the cohorts established in 2005 for the ROAD study. Details of the cohort profile have been reported elsewhere[22,23] and are only briefly described here. In 2005–2007, we created a baseline database including clinical information for 3,040 residents of Japan (men, 1,061; women, 1,979). The subjects were recruited from resident registration listings in three communities with different characteristics: 1,350 individuals (men, 465; women, 885) from an urban region in Itabashi, Tokyo; 864 individuals (men, 319; women, 545) from a mountainous region in Hidakagawa, Wakayama; and 826 individuals (men, 277; women, 549) from a coastal region in Taiji, Wakayama. In 2008–2010, we attempted to locate and follow-up all 3,040 subjects. They were invited for the second survey of the ROAD study, a 3-year follow-up examination identical to the baseline examinations.

For the current study, we enrolled all 1,690 subjects (men, 596; women, 1,094) resided in the mountainous and coastal areas, where blood examination had been performed on all participants at baseline. All participants provided written informed consent, and the study was conducted with approval from the ethics committees of the University of Tokyo.

Baseline examination procedures

At the baseline examination, participants completed an interviewer-administered questionnaire of 400 items, including lifestyle information such as primary occupation; smoking habits (0: ex- or non-smoker, 1: current smoker); alcohol consumption (0: ex- or non-drinker, 1: current drinker); physical activity, including bicycling every day over the past 12 months (0: no, 1: yes); regular exercise (0: no, 1: yes); and medical history, including history of knee injuries (0: no, 1: yes). The participants were asked whether they took prescription medication daily or nearly every day (0: no, 1: yes). If they did not know what their medications were prescribed for, they were asked to bring their medications to the medical doctor (NY).

Anthropometric measurements included height, weight, and body mass index [BMI: weight (kg)/height^2 (m^2)]. Systolic and diastolic BP was measured by an experienced public health nurse using a mercury sphygmomanometer. Medical information, including information on knee joints, was collected by experienced orthopaedic surgeons (SM and HO). All participants underwent radiographic examination of both knees using an anterior–posterior view with weight-bearing and foot-map positioning.

All blood samples were obtained between 09:00 and 15:00. Haemoglobin A1c (HbA1c), blood sugar, high-density lipoprotein cholesterol (HDL-cho), total cholesterol, and triglyceride (TG) levels were measured. All analyses were performed at the same laboratory within 24 h of extraction (Osaka Kessei Research Laboratories, Inc., Osaka, Japan).

In this study, definitions of MS components were based on criteria defined by the Examination Committee of Criteria for Metabolic Syndrome in Japan[24] and the Japan Society for the Study of Obesity[25]. However, because not all blood samples were obtained under fasting conditions, we used indices from the National Health and Nutrition Survey in Japan adopted as MS criteria in this national screening study due to the difficulty of collecting samples under fasting conditions[26]. The following definitions were used for MS components: OW, BMI $\geq$ 25 kg/m^2; HT, systolic BP $\geq$ 130 mm Hg and/or diastolic BP $\geq$ 85 mm Hg; DL, serum HDL-cho level $<$ 40 mg/dL; and IGT, serum HbA1c level $\geq$ 5.5%. Furthermore, subjects being treated with medication for HT, DL, or diabetes mellitus were regarded as having HT, DL, or IGT, respectively.

Three-year follow-up and definition of KOA occurrence and progression

In 2008–2010, the 1,690 subjects were invited to attend the second survey of the ROAD study, a 3-year follow-up consisting of examinations identical to those at baseline. Knee radiographs were read by a single experienced orthopaedist (SM) without knowledge of participants' clinical status and were categorized using the Kellgren–Lawrence (KL) grading scale[27]. When there were differences in the KL grades between the two knees, the higher KL grade was assigned to the participant. A subject with KL $\geq$ 2 was defined as having radiographic KOA. A new KOA case was identified if both knees had a KL grade $<$ 2 at baseline and if at least one knee developed a KL of $\geq$2 during follow-up. KOA progression was defined as the KL grade for either knee being higher during follow-up than at baseline.

Statistical analysis

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

To clarify associations between KOA occurrence or progression and MS risk factors, we performed three types of multivariate logistic regression analysis. Model 1 was performed using KOA occurrence or progression (over 3 years, 1: yes, 0: no) as the objective variable. Each risk factor for MS, that is, continuous variables such as BMI, systolic BP, diastolic BP, and serum HDL-cho and HbA1c levels, and categorical variables such as OW (1: presence, 0: absence), HT (1: presence, 0: absence), DL (1: presence, 0: absence), and IGT (1: presence, 0: absence) were considered as an individual explanatory variable after adjusting for age and gender. Model 2 was performed using the same objective variable and individual explanatory factor for MS as in Model 1, after adjustment for age, gender, regional differences, smoking, alcohol

consumption, bicycling, regular exercise, and history of knee injuries, all of which had been found to be significantly associated with KOA presence in a previous study using the same population[17]. Model 3 was obtained by multivariate logistic regression analysis using the same objective variable and the same adjustment factors as in Model 2; furthermore, other MS components were included in the mutual adjustment model. For example, when BMI was selected as an objective factor, Model 3 was obtained by multivariate logistic regression after adjustment for age, gender, regional differences, smoking, alcohol consumption, bicycling, regular exercise, history of knee injuries, systolic BP, and serum HDL-cho and HBA1c levels. Similarly, when OW was selected as an objective factor, Model 3 was obtained by multivariate logistic regression after adjustment for age, gender, regional differences, smoking, alcohol consumption, bicycling, regular exercise, history of knee injuries, HT, DL, and IGT. Because systolic and diastolic BP was moderately correlated ($r = 0.5643$, $P < 0.001$), only values of systolic BP were used as representative of BP in Model 3.

To further evaluate associations between the number of MS components and KOA occurrence and progression, we used two multivariate logistic regression models. In Model 4, we used KOA occurrence or KL grade progression as the objective variable and the number of MS components present (OW, HT, DL, and IGT) as the explanatory variable, after adjusting for age and gender. In Model 5, we used KOA occurrence or progression as the objective variable and the number of MS components present as the explanatory variable, after adjusting for age, gender, regional differences, smoking, alcohol consumption, bicycling, regular exercise, and history of knee injuries.

Results

Eligible participants

Of the 1,690 baseline survey participants, 251 (14.9%; men, 104; women, 147) dropped out of the follow-up study. The reasons for the drop-outs are shown in Fig. 1. In this study, we used the data for the remaining 1,384 subjects (81.9%; men, 466; women, 918) who completed all examinations in both baseline and follow-up surveys.

Table I shows baseline characteristics of the 1,384 participants and mean values for BMI, systolic and diastolic BP, and serum HDL-cho and HbA1c levels, classified by gender. Men had significantly higher BMI, higher systolic and diastolic BP, and lower serum HDL-cho levels than women. However, serum HbA1c levels did not show

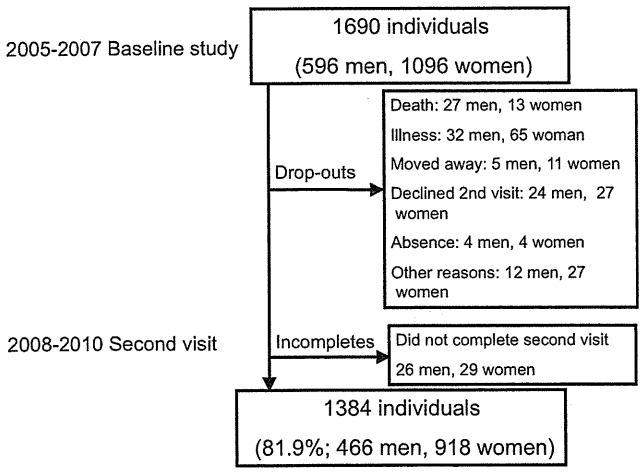


Fig. 1. Flow of participants in the baseline and second surveys.

Table I
Baseline characteristics of subjects who participated in both the first and second surveys

	Total	Men	Women	*P* (men vs women)
Number of subjects classified by age-strata (%)				
≤39 (year)	39 (2.8)	10 (2.1)	29 (3.2)	0.23
40–49	135 (9.8)	40 (8.6)	95 (10.3)	
50–59	298 (21.5)	99 (21.2)	199 (21.7)	
60–69	413 (29.8)	131 (28.1)	282 (30.7)	
70–79	404 (29.2)	155 (33.3)	249 (27.1)	
≥80	95 (6.9)	31 (6.7)	64 (7.0)	
Total	1384 (100.0)	466 (100.0)	918 (100.0)	
Means (standard deviations) of selected characteristics				
Age (year)	63.9 (11.8)	64.9 (11.6)	63.4 (11.9)	0.0246*
Height (cm)	155.6 (9.0)	164.0 (7.0)	151.3 (6.7)	<0.001***
Weight (kg)	56.0 (10.7)	62.1 (10.7)	52.5 (8.7)	<0.001***
Prevalence of selected characteristics, %				
Residing in a coastal area	54.1	51.9	55.2	0.245
Current smoking habit (more than once a month)	12.3	29.4	3.5	<0.001***
Current alcohol consumption (more than once a month)	40.6	68.2	26.6	<0.001***
Bicycling every day in the past 12 months	55.5	55.2	55.7	0.859
Regular exercise, i.e., football, tennis, baseball, or golf, after graduation from school (%)	15.3	36.1	4.7	<0.001***
Past injury of either knee (%)	2.5	1.9	2.8	0.313
Medication for components of MS, %				
Medication for HT	29.8	27.5	31.1	0.169
Medication for DL	7.2	3.4	9.2	<0.001***
Medication for diabetes mellitus, including insulin injection	5.6	7.3	4.8	0.056
Mean values (standard deviations) for components of MS				
BMI (kg/m^2)	23.1 (3.4)	23.4 (3.2)	22.9 (3.4)	0.0089
Systolic BP (mm Hg)	134.1 (20.4)	136.6 (18.3)	132.9 (21.4)	0.0015**
Diastolic BP (mm Hg)	74.2 (11.4)	77.0 (11.5)	72.8 (11.0)	<0.0001***
Serum levels of HDL-cho (mg/dL)	61.2 (15.9)	55.8 (16.1)	64.0 (15.0)	<0.0001***
Serum levels of HbA1c (%)	5.19 (0.73)	5.23 (0.85)	5.17 (0.67)	0.1900
Prevalence of components of MS, %				
OW	25.7	28.1	24.4	0.135
HT	67.2	72.7	64.4	0.002**
DL	13.0	15.2	11.9	0.079
IGT	21.1	24.7	19.3	0.020*

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

significant gender-based differences. In the total population, the MS component with the highest prevalence was HT, followed by OW, IGT, and DL. The prevalences of HT and IGT were significantly higher in men than in women.

KOA occurrence and progression and MS components

Baseline KOA prevalence in the 1,384 individuals was 46.8% (men, 37.3%; women, 51.6%). After exclusion of subjects having KOA (KL grade ≥ 2 in at least one knee) at baseline, the cumulative KOA incidence during the 3-year follow-up was estimated using a population-at-risk of 728 individuals (men, 290; women, 438) without

KOA in either knee at baseline. Among these subjects, 71 new KOA cases (men, 18; women, 53) were detected, with a cumulative incidence of 3.3%/year (men, 2.1%/year; women, 4.0%/year). After excluding subjects with KL grade = 4 for at least one knee at baseline, the progression rate over the 3-year follow-up was estimated using the population-at-risk of 1,296 individuals (men, 445; women, 851). Among these, 311 individuals (men, 86; women, 225) had a higher KL grade for one or both knees at follow-up than at baseline. The progression proportion of the KL grade for either knee over the 3-year period was 24.0% (8.0%/year; men, 6.4%/year; women, 8.8%/year) in the overall population-at-risk.

Table II shows cumulative KOA incidence and progression, classified by age groups of ≤39, 40–49, 50–59, 60–69, 70–79, and ≥80 years, which significantly increased with age. BMI, systolic BP, and HbA1c levels at baseline were significantly higher and HDL-cho levels significantly lower in subjects with KOA than in those without KOA. Similar to KOA, BMI, systolic BP, and HbA1c levels were significantly higher and HDL-cho levels significantly lower in subjects with KL grade progression than in those without. This tendency was much more pronounced in women than in men.

Table III shows multivariate logistic regression analysis results for KOA occurrence vs values for each MS component, including BMI, systolic BP, diastolic BP, and serum HDL-cho and HbA1c levels measured at baseline (Table III). Model 2 showed that BMI, systolic BP, and serum HDL-cho levels were significantly associated with KOA occurrence after adjustment for various risk factors. However, Model 3, incorporating mutual adjustment for each MS component, indicated that only BMI was significantly associated with KOA occurrence. The three types of multivariate logistic regression analyses using KOA progression as the objective factor showed similar results as for KOA occurrence described above.

Table IV shows associations between KOA occurrence and MS risk factors. Both Models 1 and 2 revealed that OW, HT, and IGT were significantly associated with KOA. Analysis using OW, HT, DL, and IGT as explanatory variables with mutual adjustment (Model 3) indicated that HT and IGT were significantly associated with KOA. Table IV also shows associations between KOA progression and MS risk factors, indicating that OW and HT were significantly associated with KOA progression. Although IGT was significantly associated with KOA progression after adjustment for age and gender, the effect diminished after adjustment for various other risk factors.

KOA occurrence and progression and the number of MS components

Figure 2 shows the cumulative KOA incidence (%/year) classified by the number of MS components present. In the total population, the cumulative incidence classified by the number of MS

Table II
Mean values (standard deviations) for components of MS vs occurrence and progression of KOA

	Total			Men			Women		
	KOA (−)	KOA (+)	*P*	KOA (−)	KOA (+)	*P*	KOA (−)	KOA (+)	*P*
	(*n* = 657)	(*n* = 71)		(*n* = 272)	(*n* = 18)		(*n* = 385)	(*n* = 53)	
Occurrence of KOA									
Number of subjects classified by age-strata (cumulative incidence, %/year)									
≤39 (year)	38	0 (0.0)	<0.001	10	0 (0.0)	0.009	28	0 (0.0)	<0.001
40–49	118	1 (0.3)		36	0 (0.0)		82	1 (0.4)	
50–59	201	15 (2.3)		77	0 (0.0)		124	15 (3.6)	
60–69	177	27 (4.4)		76	11 (4.2)		101	16 (4.6)	
70–79	108	23 (5.9)		62	6 (2.9)		46	17 (9.0)	
≥80	15	5 (8.3)		11	1 (2.8)		4	4 (16.7)	
Mean values (standard deviations) for age and components of MS									
Age (year)	58.2 (11.8)	67.3 (8.2)	<0.0001	61.0 (11.8)	70.0 (6.1)	0.0021	56.4 (11.4)	66.4 (8.7)	<0.0001
BMI (kg/m^2)	22.4 (3.2)	23.6 (2.9)	0.0035	23.2 (3.2)	24.2 (3.1)	0.1709	21.9 (3.1)	23.4 (2.8)	0.0012
Systolic BP (mm Hg)	129.6 (19.4)	138.2 (19.1)	0.0005	133.4 (17.9)	143.4 (17.7)	0.0255	127.0 (20.0)	136.5 (19.4)	0.0014
Diastolic BP (mm Hg)	74.3 (11.2)	74 (11.0)	0.8599	77.5 (11.8)	76.7 (10.7)	0.7907	72.0 (10.2)	73.2 (11.0)	0.4544
Serum levels of HDL-cho (mg/dL)	63.4 (16.8)	59.2 (13.3)	0.0414	57.3 (16.3)	54.6 (15.7)	0.5017	67.7 (15.8)	60.8 (12.1)	0.0021
Serum levels of HbA1c (%)	5.11 (0.67)	5.32 (0.79)	0.0142	5.24 (0.87)	5.09 (0.75)	0.4644	5.01 (0.46)	5.39 (0.80)	<0.0001
	Total			Men			Women		
	Progression (−) (*n* = 985)	Progression (+) (*n* = 311)	*P*	Progression (−) (*n* = 359)	Progression (+) (*n* = 86)	*P*	Progression (−) (*n* = 626)	Progression (+) (*n* = 255)	*P*
Progression of KOA									
Number of subjects classified by age-strata (proportion of progression, %/year)									
≤39 (year)	37	2 (1.7)	<0.001***	9	1 (3.3)	<0.001***	28	1 (1.1)	<0.001***
40–49	128	7 (1.7)		38	2 (1.7)		90	5 (1.8)	
50–59	248	44 (5.0)		89	8 (2.8)		159	36 (6.2)	
60–69	292	105 (8.2)		101	26 (6.8)		191	79 (9.8)	
70–79	241	115 (10.8)		105	38 (8.9)		136	77 (12.1)	
≥80	39	38 (16.5)		17	11 (13.1)		22	27 (18.4)	
Mean values (standard deviations) for age and components of MS									
Age (year)	61.6 (11.9)	68.7 (9.3)	<0.0001***	63.3 (11.8)	70.0 (9.4)	<0.0001***	60.7 (11.9)	68.2 (9.3)	<0.0001***
BMI (kg/m^2)	22.7 (3.3)	23.6 (3.1)	<0.0001***	23.2 (3.2)	23.9 (3.1)	0.0643	22.4 (3.3)	23.5 (3.1)	<0.0001***
Systolic BP (mm Hg)	132.2 (20.0)	137.9 (19.3)	<0.0001***	135.4 (17.9)	138.6 (17.0)	0.1390	130.4 (20.9)	137.6 (20.1)	<0.0001***
Diastolic BP (mm Hg)	74.0 (11.2)	74.5 (11.8)	0.5517	77.1 (11.6)	76.3 (10.6)	0.5698	72.3 (10.5)	73.8 (12.2)	0.0792
Serum levels of HDL-cho (mg/dL)	62.3 (16.6)	59.0 (13.8)	0.0018**	56.7 (16.4)	53.5 (15.2)	0.0921	65.4 (15.8)	61.1 (12.6)	0.0003***
Serum levels of HbA1c (%)	5.15 (0.72)	5.27 (0.74)	0.0133*	5.20 (0.84)	5.30 (0.88)	0.3687	5.11 (0.64)	5.25 (0.68)	0.0069**

KOA(−), non-occurrence of KOA; KOA(+), occurrence of KOA; progression(−), no progression of the KL grade; progression(+), progression of the KL grade.
n, number of subjects.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table III
ORs for occurrence and progression of KOA during the 3-year follow-up period vs BMI, systolic and diastolic BP, serum levels of HDL-cho, and HbA1c level

Explanatory variables	Reference	Model 1*			Model 2†			Model 3‡		
		Adjusted OR1	95% CI	P	Adjusted OR2	95% CI	P	Adjusted OR3	95% CI	P
Occurrence of KOA										
BMI (kg/m^2)	+1 kg/m^2	1.22	1.12–1.33	<0.001***	1.22	1.12–1.34	<0.001***	1.18	1.07–1.30	0.001**
Systolic BP (mm Hg)	+1 mm Hg	1.54	0.87–2.72	0.136	1.01	1.00–1.03	0.038*	1.01	1.00–1.03	0.188
Diastolic BP (mm Hg)	+1 mm Hg	1.51	0.71–3.19	0.282	1.01	0.99–1.04	0.373	–	–	–
Serum levels of HDL-cho (mg/dL)	+1 mg/dL	0.980	0.962–0.999	0.039*	0.980	0.960–0.999	0.039*	0.989	0.968–1.009	0.256
Serum levels of HbA1c (%)	+1%	1.29	0.92–1.81	0.136	1.34	0.96–1.88	0.089	1.07	0.73–1.56	0.743
Progression of KOA										
BMI (kg/m^2)	+1 kg/m^2	1.12	1.08–1.17	<0.001***	1.13	1.08–1.18	<0.001***	1.11	1.06–1.17	<0.001***
Systolic BP (mm Hg)	+1 mm Hg	1.47	1.10–1.97	0.010*	1.01	1.00–1.01	0.039*	1.00	1.00–1.01	0.352
Diastolic BP (mm Hg)	+1 mm Hg	1.33	0.92–1.91	0.124	1.01	1.00–1.025	0.057	–	–	–
Serum levels of HDL-cho (mg/dL)	+1 mg/dL	0.988	0.979–0.997	0.011*	0.987	0.978–0.997	0.008**	0.992	0.983–1.002	0.137
Serum levels of HbA1c (%)	+1 %	1.11	0.94–1.33	0.227	1.11	0.93–1.32	0.277	0.99	0.81–1.19	0.881

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

* Model 1 was obtained by a series of multivariate logistic regression analyses using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (BMI, systolic BP, diastolic BP, serum HDL-cho, or HbA1c) after adjusting for age and gender.

† Model 2 was obtained by a series of multivariate logistic regression analyses using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (BMI, systolic BP, diastolic BP, serum HDL-cho, or HbA1c) after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: current drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), and past history of knee injuries (0: no, 1: yes).

‡ Model 3 was obtained by multivariate logistic regression analysis using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (BMI, systolic BP, diastolic BP, serum HDL-cho, or HbA1c) after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: current drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), and past history of knee injuries (0: no, 1: yes), and other potential risk factors such as BMI, systolic BP, serum levels of HDL-cho, and HbA1c levels, mutually.

components (0, 1, 2, or ≥3) was 1.0, 3.5, 3.4, and 8.7, respectively, which increased with the number of MS components (P for trend < 0.001). Figure 2(A) also shows the cumulative KOA incidence according to the number of MS components by gender. The cumulative incidence among individuals with one or more MS components was higher in women than in men.

Figure 2 also shows KL grade progression (%/year) for either knee classified by the number of MS components present. In the total population, KL grade progression classified by 0, 1, 2, or ≥3 MS components was 4.3, 7.6, 10.8, and 11.3, respectively, which significantly increased with the number of MS components (P for trend < 0.001). The progression among individuals with one or more MS components was higher in women than in men [Fig. 2(B)].

To further illustrate the effects of the number of MS components on KOA occurrence and progression, Fig. 3 presents the results of the multivariate logistic regression analysis models for KOA occurrence. Model 4 used KOA occurrence or KL grade progression as the objective variable and the number of MS components present (OW, HT, DL, and IGT) as the explanatory variable, adjusted

Table IV
ORs for occurrence and progression of KOA during the 3-year follow-up period vs risk factors for MS

Explanatory variables	Reference	Model 1*			Model 2†			Model 3‡		
		Adjusted OR1	95% CI	P	Adjusted OR2	95% CI	P	Adjusted OR3	95% CI	P
Occurrence of KOA										
Component of MS										
OW	Yes vs no	2.36	1.28–4.34	0.006**	2.46	1.32–4.59	0.005**	1.71	0.88–3.33	0.114
HT	Yes vs no	3.02	1.47–6.23	0.003**	3.27	1.57–6.80	0.002**	2.74	1.30–5.78	0.008**
DL	Yes vs no	1.34	0.65–2.73	0.425	1.55	0.75–3.23	0.240	1.20	0.55–2.59	0.646
IGT	Yes vs no	2.42	1.37–4.27	0.002**	2.47	1.38–4.41	0.002**	1.94	1.05–3.59	0.033*
Progression of KOA										
Component of MS										
OW	Yes vs no	1.76	1.30–2.38	<0.001***	1.87	1.37–2.55	<0.001***	1.66	1.21–2.29	0.002**
HT	Yes vs no	1.75	1.26–2.42	0.001**	1.75	1.26–2.43	0.001**	1.54	1.10–2.17	0.012*
DL	Yes vs no	1.18	0.81–1.71	0.400	1.36	0.93–2.01	0.117	1.26	0.85–1.87	0.248
IGT	Yes vs no	1.42	1.04–1.94	0.029*	1.35	0.98–1.87	0.068	1.18	0.84–1.64	0.336

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Being OW was defined as BMI ≥ 25 kg/m^2, HT as systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 85 mm Hg, DL as serum HDL-cho level < 40 mg/dL, and IGT as serum HbA1c level ≥ 5.5%. Further, subjects being treated with medication for HT, DL, or IGT were regarded as having the respective disorder.

* Model 1 was obtained by a series of multivariate logistic regression analyses using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (being OW, HT, DL, or IGT) after adjusting for age and gender.

† Model 2 was obtained by a series of multivariate logistic regression analyses using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and each individual explanatory variable (being OW, HT, DL, and IGT) after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: current drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), and past history of knee injuries (0: no, 1: yes).

‡ Model 3 was obtained by multivariate logistic regression analysis using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and being OW, HT, DL, and IGT as explanatory variables, after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: current drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), past history of knee injuries (0: no, 1: yes), and other components of MS, mutually.

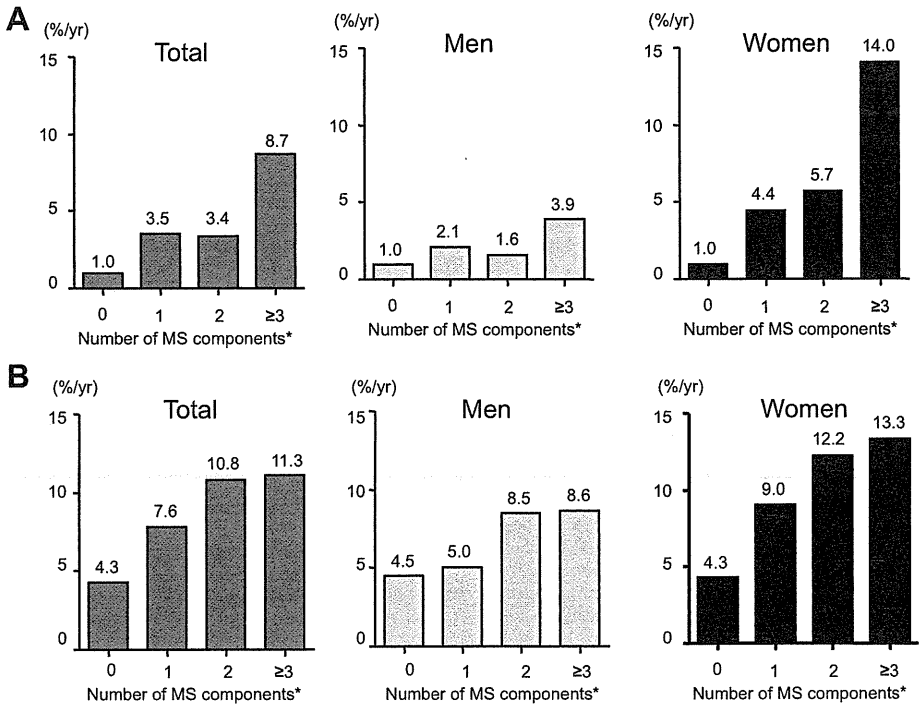
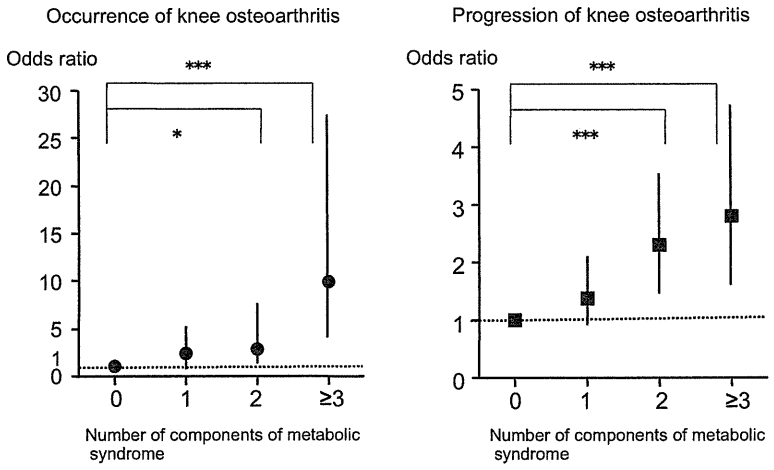


Fig. 2. Cumulative incidence (%/year) of KOA (A) and progression of the KL grade of either knee (%/year) (B) classified by the number of components of MS, including OW, HT, DL, and IGT.

for age and gender. The odds ratio (OR) and 95% CI for KOA occurrence were found to significantly increase with the number of MS components present (OR, 95% CI vs no component: one component, 2.16, 0.90–5.20, $P = 0.085$; two components, 2.49, 0.95–6.55, $P = 0.063$; ≥three components, 8.38, 3.12–22.5, $P < 0.001$). Similarly, KOA progression significantly increased with the number of MS components present (OR, 95% CI vs no component: one component, 1.41, 0.94–2.12, $P = 0.097$; two components, 2.25, 1.47–3.46, $P < 0.001$; ≥three components: 2.59, 1.57–4.27, $P < 0.001$).

Logistic regression model results obtained using KOA occurrence or progression as the objective variable and the number of MS components present as explanatory variables, after adjusting for age, gender, and the other potential risk factors listed in the Methods section, are shown in Fig. 3. The OR significantly increased with the number of MS components present after adjustment for



*:p < 0.05,***:p < 0.001

Multivariate logistic regression analysis using the occurrence or progression of KOA (over 3 years, 1: yes, 0: no) as the objective variable and the number of MS components as the explanatory variable, after adjusting for age, gender, region (0: coastal area, 1: mountainous area), smoking (0: ex- or non-smoker, 1: current smoker), alcohol consumption (0: ex- or non-drinker, 1: curre nt drinker), bicycling every day (0: no, 1: yes), regular exercise (0: no, 1: yes), and past history of knee injuries (0: no, 1: yes).

Fig. 3. ORs for occurrence and progression of KOA during the 3-year follow-up period vs the number of risk factors for MS.

other risk factors (OR, 95% CI vs no component: one component, 2.33, 0.96–5.65, $P = 0.065$; two components, 2.82, 1.05–7.54, $P = 0.039$; ≥three components, 9.83, 3.57–27.1, $P < 0.001$). Similarly, KOA progression significantly increased with the number of MS components present after adjustment for other risk factors (OR, 95% CI vs no component: one component, 1.38, 0.91–2.08, $P = 0.126$; two components, 2.29, 1.49–3.54, $P < 0.001$; ≥three components: 2.80, 1.68–4.68, $P < 0.001$). In both models, the OR for KOA occurrence significantly increased with the number of MS components present. Similar trends were observed for KOA progression with both models.

Discussion

In this study, we determined the cumulative incidence and progression rate of KOA diagnosed using the KL scale. We demonstrated that KOA occurrence and progression are associated with higher systolic BP, lower serum HDL-cho levels, and higher serum HbA1c levels, as well as higher BMI. Incorporating mutual adjustment for each MS component indicated that only BMI was significantly associated with KOA occurrence and progression. Regarding the risk factors for MS and KOA, even after adjusting for potential risk factors, multivariate analysis determined that HT and IGT were significantly associated with KOA occurrence, and OW and HT were significantly associated with KOA progression. The presence of a greater number of MS components was associated with a higher rate of KOA occurrence and progression. This tendency was much more pronounced in occurrence of KOA than in progression.

Numerous reports have presented an association between being OW or obese and KOA[1,7–12]. Lohmander *et al.* reported that being OW was associated with higher KOA incidence, and among measures of excess weight, BMI was observed to have the strongest relative risk gradient[28]. In the present study, we confirmed that BMI was the only continuous value significantly associated with KOA occurrence and progression among the MS risk factors (e.g., BMI, systolic BP, and serum levels of HDL-cho and HbA1c), consistent with previous studies. In contrast, several reports have shown that HT is associated with KOA presence, independent of OW[20,29–31]. In the present study, we confirmed a significant association between HT and IGT and KOA occurrence, and between OW and HT and KOA progression. Although several studies have found that obesity or increased BMI were risk factors for KOA onset[32–35], this appears to be the first report of associations between MS risk factors other than OW and KOA occurrence and progression.

There were differences between the results for continuous variables such as BMI, BP, and serum HDL-cho and HbA1c levels and those for categorical clinical criteria such as OW, HT, DL, and IGT. In analysis involving continuous variables, BMI was the only predictor of future KOA occurrence or progression. In contrast, clinical criteria-based analysis clearly showed associations between metabolic risk factors other than OW and KOA. This discrepancy suggests that the clinical criterion for OW (BMI ≥ 25 kg/m^2) may be less sensitive than continuous BMI values in reflecting the association of excess weight with KOA. We then performed additional analyses using KOA occurrence or progression as the objective variable and categorical risk factors for MS, such as HT, DL, and IGT, as explanatory variables. We also added continuous values for BMI at baseline rather than OW, after adjusting for multiple risk factors as listed for Model 2. The resulting overall ORs for HT, DL, and IGT adjusted for BMI on KOA occurrence or progression became smaller than those adjusted for OW. However, the association between HT and KOA occurrence remained significant (OR, 2.43; 95% CI, 1.14–5.18; $P = 0.021$), while IGT was no longer significant (OR, 1.70; 95% CI, 0.91–3.19; $P = 0.096$). Similarly, the association between HT and KOA progression remained significant (OR, 1.41; 95% CI, 1.00–2.00; $P = 0.049$). These results indicate that, even if associations between KOA and categorical MS components other than BMI are weak, if adjustments are made for OW using clinical criteria, then HT and IGT may be risk factors for KOA occurrence and HT may be a risk factor for KOA progression.

Regarding ethnic differences in KOA, we previously reported that KOA prevalence and incidence in the original ROAD study of 3,040 baseline participants was higher than those of Caucasians[36,37]. In contrast, with regard to ethnic differences in MS, Hoang *et al.* reviewed epidemiological studies and reported that MS prevalence in East Asians was lower than that in Caucasians[38]. MS prevalence in Asia may be increasing rapidly, as Nestel *et al.* reported a substantial increase in a cohort from Beijing from 9% in 1992 to 21% in 2002[39]. These ethnic differences have been suggested as resulting from genetic factors that modulate the association between KOA and obesity[40,41].

Regarding associations between risk factors of MS and KOA, Hart *et al.* attributed the effect of excess endogenous oestrogens to aromatization of oestrone in fat tissue[20]. Sowers *et al.* suggested that leptin and adiponectin levels influenced OA development[29]. Another hypothesis suggests that in obese subjects, metabolic changes in the striated muscles induced by interactions between insulin resistance and systemic inflammation may lead to fatigue and muscle weakness, influencing the balance between damage and repair mechanisms and ultimately leading to OA[42,43]. Inflammatory factors are suggested to be associated with both obesity and KOA[44,45]. Findlay evaluated the concept that vascular pathology might play a role in the initiation and/or progression of OA[46] and proposed that peripheral reduced blood flow associated with HT caused subchondral ischaemia. This ischaemia may in turn compromise nutrient and gas exchange into the articular cartilage and contribute to apoptosis of regional osteocytes of the subchondral bone. Furthermore, chondrocytes of OA exposed to high glucose concentrations exhibit impaired glucose transporter-1 downregulation[47]. Thus, impaired glucose transporter-1 downregulation may constitute an important pathogenic mechanism by which conditions characterized by hyperglycaemia may promote degenerative changes in chondrocytes, facilitating OA progression. However, in the present study, after adjustment for BMI, the effect of IGT was weak. Further studies are required to confirm whether IGT is a risk factor for KOA occurrence. Furthermore, because the present study aimed to identify associations between metabolic risk factors and future KOA occurrence or progression, we did not evaluate the effects of genetic factors and other risk factors potentially influencing MS and KOA. However, additional risk factors for both conditions should be addressed in further analysis of the ROAD study.

No previous studies have been performed on metabolic risk factor clustering and KOA occurrence or progression, although some cross-sectional epidemiological studies have evaluated the association between metabolic risk factor clustering and KOA presence[29,31]. In the present study, we demonstrated that KOA occurrence and progression are influenced not only by individual MS components but also by their clustering. An increase in the number of MS components significantly increases the risk of both KOA occurrence and progression. This effect of clustering was stronger for KOA occurrence than for KOA progression. Combining the present results with those of our previous report using the same analytical methods and adjustment factors[21], the ORs for ≥three components vs no components were 9.95, 2.79, and 2.72 for KOA occurrence, progression, and presence, respectively. Thus, preventing MS would aid in reducing every stage of KOA, including onset, worsening, and presence.

This study has several limitations. First, although it includes a relatively large number of participants, these participants do not

represent the entire general population because they were recruited from only two areas. Regarding potential selection bias of the ROAD study, we previously reported that no significant differences were identified between our participants and the general Japanese population, except that male participants aged 70–74 years in the ROAD study were significantly smaller in terms of body structure than the overall Japanese population ($P < 0.05$)[23]. Although we could locate and include baseline participants after 3 years with a high participation rate, this selection bias at baseline should be considered when generalising the results. Second, the definitions used for MS components were not completely identical to international criteria such as the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III, World Health Organization (WHO), or The American Association of Clinical Endocrinologists (AACE)[48]. As there has been considerable debate regarding abdominal circumference (≥85 cm in men, ≥90 cm in women) in the Japanese criteria[49], we decided to utilize BMI ≥ 25 kg/m^2 to indicate OW rather than abdominal circumference. Furthermore, because not all blood samples were obtained under fasting conditions, we did not use blood glucose and serum TG levels as indicators. Therefore, our results may underestimate the presence of MS components, especially DL and IGT. However, we used the alternative index for each condition, recommended by the National Health and Nutrition Survey for cases where collecting samples under fasting conditions is difficult[26], and thus our criteria likely reflect dysfunction in lipid and glucose metabolism. Finally, we used KL grade ≥ 2 for diagnosing KOA. However, the KL scale is a categorical index, and it is impossible to evaluate the minimum joint space and osteophytosis separately. To evaluate KOA severity using quantitative parameters, a KOA computer-assisted diagnostic system[50] measuring minimum joint space width and osteophytosis area is under development; this system will provide increased accuracy in determining the association between MS components and KOA development for early prevention of disability.

In conclusion, this study revealed that HT and IGT influence KOA occurrence and that OW and HT are associated with KOA progression. KOA occurred or worsened more frequently with increase in the number of MS components. Preventing MS may be useful in preventing both KOA occurrence and progression.

Author contributions

NY conceptualized the study, was primarily responsible for developing the protocol, and acts as the guarantor for this study. SM, HO, and TA conducted data collection and X-ray assessment. All authors reviewed the protocol and contributed to interpretation of the results. All authors were involved in drafting the article and approved the final version submitted for publication. All authors had full access to all of the data in the study and take responsibility for the integrity and accuracy of the data analyses.

Role of the funding source

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Conflict of interest

All authors declare that (1) no authors have received corporate support for the submitted work; (2) the authors have no relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) the authors' spouses, partners, or children do not have financial relationships that may be relevant to the submitted work; and (4) the authors have no non-financial interests that may be relevant to the submitted work.

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Does mild cognitive impairment affect the occurrence of radiographic knee osteoarthritis? A 3-year follow-up in the ROAD study

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Does mild cognitive impairment affect the occurrence of radiographic knee osteoarthritis? A 3-year follow-up in the ROAD study

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ABSTRACT

Objective: To determine whether mild cognitive impairment (MCI) increases the risk of occurrence or progression of radiographic knee osteoarthritis (KOA) in a general population.

Design: Population-based cohort study.

Setting: Residents in mountain and seaside areas of Wakayama Prefecture, Japan.

Participants: 1690 participants (596 men, 1094 women; mean age 65.2 years old) were enrolled from the large-scale cohort for the Research on Osteoarthritis (OA)/osteoporosis Against Disability (ROAD) study initiated in 2005 to investigate epidemiological features of OA in Japan. Of these, 1384 individuals (81.9%; 466 men, 918 women) completed the second survey including knee radiography 3 years later.

Primary outcome measures: Radiographic KOA was defined as Kellgren-Lawrence (KL) grade ≥ 2 using paired x-ray films. Incidence of KOA during follow-up defined on radiographs as KL grade ≥2, progression of KOA defined as a higher KL grade (either knee) at follow-up compared with baseline. MCI defined as a summary mini-mental state examination (MMSE) score ≤23. Associations between MCI and incidence or progression of KOA were analysed.

Results: The annual cumulative incidence of KOA was 3.3%; for progression of OA it was 8.0%. On logistic regression analysis adjusted for age, gender, regional differences, body mass index, grip strength (worse side), smoking, alcohol consumption, regular exercise and history of knee injury, baseline MMSE summary score was significantly associated with the incidence of KOA (+1 MMSE score; OR 0.83, p=0.010). Baseline MCI was also significantly associated with the incidence of KOA (vs non-occurrence of KOA; OR 4.90, p=0.027). There was no significant association between MMSE scores, the presence of MCI and progression of KOA (+1 MMSE score; OR 0.96, p=0.232; vs non-progression of KOA; OR 1.38, p=0.416).

Conclusions: MCI significantly increases the risk of incident radiographic KOA, but not the progression of KOA.

ARTICLE SUMMARY

Article focus

- Both cognitive impairment and osteoarthritis (OA) are top-ranked causes of disability requiring support, but there have been no previous reports on the association between cognitive impairment and OA.
- We aimed to investigate the association between mild cognitive impairment (MCI) and the occurrence and progression of radiographic knee osteoarthritis (KOA) among men and women who participated in the Research on Osteoarthritis/osteoporosis against Disability (ROAD) study.

Key messages

- Of 1690 participants at the baseline, 1384 individuals (81.9%; 466 men, 918 women) completed the second survey including knee radiography 3 years later.
- The annual cumulative incidence of radiographic KOA in these 1384 participants was 3.3%; for progression of KOA, it was 8.0%.
- The prevalence of MCI in the 1384 participants defined as summary mini-mental state examination score ≤23 was 4.5%.
- Baseline mini-mental state examination (MMSE) summary score was significantly associated with the incidence of radiographic KOA after adjustment for confounders (+1 score; OR0.83, p=0.010). Baseline MCI was also significantly associated with the incidence of radiographic KOA (vs non-occurrence of KOA; OR 4.90, p=0.027). There was no significant association between MMSE scores, the presence of MCI and the progression of radiographic KOA (+1 score; OR 0.96, p=0.232; vs non-progression of KOA; OR 1.38, p=0.416).

INTRODUCTION

Plural chronic diseases have a high prevalence in the elderly population. In the USA, about 77% of older adults have two or more chronic illnesses, and these can lead to

ARTICLE SUMMARY

Strengths and limitations of this study

- The present study includes a population-based design of a cohort, large number of participants with KOA, and a 3-year follow-up with a high participation rate of 81.9%.
- Substantial amount of detailed information, including an interviewer-administered questionnaire, dietary assessment, anthropometric measurements, neuromuscular function assessment, biochemical measurements, medical history, radiographic assessment and bone mineral density measurement, was collected at both the baseline and the second visit.
- We used KL grade ≥2 for the diagnosis of radiographic KOA, but the KL scale is a categorical index, and it might be impossible to evaluate the minimum joint space and osteophytosis separately.
- We used only the MMSE to diagnose MCI, and were unable to perform additional examinations such as MRI to improve the accuracy of the diagnosis.
- The small proportion of the population with MCI at risk of KOA onset detection might raise a bias in the results of the study.

severe and immediate disabilities.[1] According to the recent national livelihood survey by the Japanese Ministry of Health, Labour and Welfare, the leading causes of disability requiring support and long-term care were cardiovascular disease (CVD) followed by dementia, cognitive impairment, senility and osteoarthritis (OA).[2]

It is important to establish associations among these diseases causing disability, in order to reduce the risk of disability. In terms of CVD and dementia, the existence of vascular dementia, for example, indicates that there are links between CVD and dementia, and cardiovascular and metabolic risk factors such as hypertension and diabetes may play a role in the pathogenesis of Alzheimer's disease as well as in the development of vascular dementia.[3–6] Association between metabolic syndrome and risk of developing cognitive impairment has been demonstrated in older women, with a 23% age-adjusted increase in the risk of developing cognitive impairment in the number of components of metabolic syndrome.[7] Higher total cholesterol and low-density lipoprotein, and history of diabetes have been associated with faster cognitive decline in patients with incident Alzheimer's disease.[8]

However, as per our knowledge, there have been no previous reports on the association between OA and dementia. Mild cognitive impairment (MCI), a transitional state associated with memory impairment, has been associated with an increased risk of progression of Alzheimer's disease.[9 10] We aimed to investigate the association between MCI and the occurrence and progression of radiographic knee osteoarthritis (KOA) among men and women who participated in the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study.

PARTICIPANTS AND METHODS

Participants

Our analysis was based on data collected from cohorts established in 2005 for the ROAD study. Details of the cohort have been reported elsewhere.[11 12] In brief, we created a baseline database in 2005–2007, which included clinical and genetic information for 3040 residents of Japan (1061 men, 1979 women). Participants were recruited from resident registration listings in three communities, each with different characteristics, namely an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama.

For the present study, we enrolled 1690 participants (596 men, 1094 women) residing in the mountainous and coastal areas, where the mental test was performed at baseline. Participants provided written informed consent, and the study was conducted with the approval of the ethics committees of the University of Tokyo (approval number 1264).

Baseline procedures

Participants completed an interviewer-administered questionnaire comprising 400 items. These included lifestyle-related questions to obtain information about main occupation; smoking habits (0: exsmoker or never smoked, 1: current smoker); alcohol consumption (0: exdrinker or never drank, 1: current drinker); alcohol consumption; physical activity including cycling every day in the past 12 months (0: no, 1: yes); regular exercise, that is, football, tennis, baseball, golf or other sports after graduation from school (0: no, 1: yes); and medical history including history of knee injury (0: no, 1: yes).

Anthropometric measurements included height, weight, body mass index (BMI) calculated as weight (kg)/height (m^2) and grip strength of both hands. Experienced orthopaedic surgeons (SM and HO) collected medical information about pain, swelling and the range of motion in the knee.

All participants underwent a radiographic examination of both knees using an anteroposterior view with weight-bearing and foot map positioning. Fluoroscopic guidance with a horizontal anteroposterior x-ray beam was used to properly visualise the joint space.

Cognitive functioning was measured using the mini-mental state examination (MMSE).[13] This is a 30-item cognitive screening test that measures orientation, registration, short-term memory, attention and concentration, language and constructional capacity. The test–retest reliability of the original version of the MMSE is 0.83,[13] and the criterion validity is 0.66–0.79 with the Wechsler Adult Intelligence Scale, 0.83 with the Short Portable Mental Status Questionnaire and 0.88 with the Cognitive Capacity Screening Examination.[14 15] We used the validated Japanese version of the MMSE.[16] Summary scores from the MMSE were used to measure cognitive

functioning and the criterion for MCI was a summary score ≤23.

Three-year follow-up and definition of the occurrence and progression of radiographic Knee osteoarthritis

In 2008–2010, the 1690 participants were invited to attend the 3-year follow-up of the second ROAD survey, which involved a repeat of the baseline examinations. Knee radiographs obtained at baseline and follow-up were read in pairs without knowledge of the participant's clinical status by a single well-experienced orthopaedist (SM), and the Kellgren/Lawrence (K/L) grade was defined using the K/L radiographic atlas for overall knee radiographic grades.[17] To evaluate the intraobserver variability of the K/L grading, 100 randomly selected radiographs of the knee were scored by the same observer 1 month after the first reading. One hundred other radiographs were also scored by two experienced orthopaedic surgeons (SM and HO) using the same atlas for interobserver variability. The intravariabilities and intervariabilities evaluated for K/L grade (0–4) were confirmed by kappa analysis to be sufficient for assessment (κ=0.86 and 0.80, respectively). When a different grade was assigned to each knee, the participant was classified by the higher grade. A participant with a KL grade ≥2 was defined as having radiographic KOA. A new case of radiographic KOA was identified if the KL grade at baseline had been <2 for both knees, and if one or both knees were assigned grade ≥2 at follow-up. A higher KL grade for either knee at follow-up compared with the baseline was defined as progression of OA.

Statistical analysis

Statistical analyses were performed using STATA statistical software (STATA Corp, College Station, Texas, USA). Differences in proportions were compared using the χ^2 test. Differences in continuous variables were tested for significance using analysis of variance (ANOVA) for multiple groups or Scheffé's least significant difference test for pairs of groups. To test the association between occurrence or progression of radiographic KOA and the presence of MCI after adjustment for confounding factors, we performed two types of multivariate logistic regression analysis. For both, we entered the occurrence or progression of OA over 3 years (1: yes, 0: no) as the dependent variable, and the MMSE summary score or presence of MCI (1: presence, 0: absence) as the independent variable. In model 1, the analysis was performed after adjusting for age, gender, regional differences and BMI. In model 2, we adjusted for potential risk factors that had previously been identified in this cohort as significantly associated with the presence of KOA,,[9 18] namely age, gender, regional differences, BMI, grip strength (kg) on the worse side, smoking, alcohol consumption, regular exercise and history of knee injuries. All p values and 95% CI of two-sided analysis are presented.

RESULTS

Eligible participants

Of the all 1690 participants in the baseline survey performed in the mountainous and coastal regions, 251 individuals (14.9%; 104 men, 147 women) did not attend the 3-year follow-up. Among them, 40 (27 men, 13 women) had died, 97 (32 men, 65 women) did not attend follow-up due to bad health, 16 (5 men, 11 women) had moved away, 51 (24 men, 27 women) declined the invitation to attend the second survey, 8 (4 men, 4 women) were absent and 39 (12 men, 27 women) did not participate for other reasons. In addition, 55 participants in the second survey (3.3%; 26 men, 29 women) did not complete all the follow-up examinations, including the interviewer-administered questionnaire, anthropometric measurements, radiographic examination and blood tests. Thus, our analysis was based on the remaining 1384 subjects (81.9%; 466 men, 918 women) who completed all examinations at both the baseline and follow-up (figure 1).

Prevalence of MCI and its baseline characteristics

The prevalence of MCI and baseline characteristics of the 1384 participants are shown in table 1. Based on the MMSE summary score, 75 participants (30 men, 45 women) were diagnosed with MCI (prevalence, 4.5%; men, 5.1%, women, 4.2%). The prevalence of MCI was significantly higher in the older age groups (trend, p<0.001). The mean MMSE summary score was significantly lower in participants with MCI than in those without (21.2 vs 28.5). Participants with MCI tended to reside in mountainous areas, and they had significantly lower weight, height and grip strength; drank less alcohol and exercised less compared with those without MCI (table 1). In addition, the prevalence of radiographic KOA classified by presence of MCI was compared in table 1. In total, 75.7% of patients in the MCI group were observed to have KOA, which was

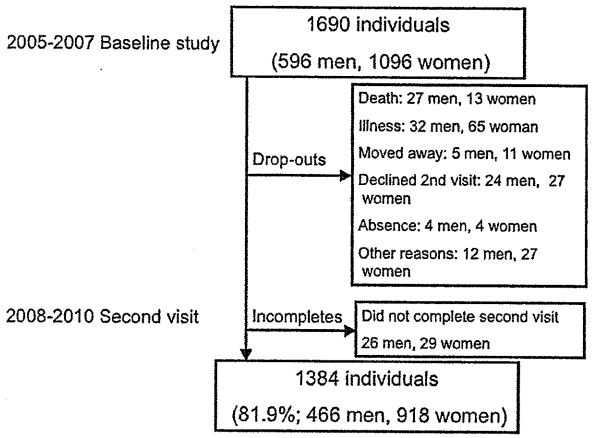

Figure 1 Flow diagram for participation in the baseline and follow-up Research on Osteoarthritis/osteoporosis Against Disability surveys.