



# Differences in prevalence and associated factors between mild and severe vertebral fractures in Japanese men and women: the third survey of the ROAD study

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## Abstract

Vertebral fracture (VF) is a common osteoporotic fracture, while its epidemiology varies according to regions and ethnicities, little is known about it in Japan. Using whole-spine radiographs from a population-based cohort study, the Research on Osteoarthritis/Osteoporosis Against Disability study 3rd survey performed in 2012–2013, we estimated the sex- and age-specific prevalence of VF in the Japanese. Genant's semiquantitative method (SQ) was used to define VF;  $SQ \geq 1$  as VF,  $SQ = 1$  as mild VF,  $SQ \geq 2$  as severe VF. We also revealed accurate site-specific prevalence, and associated factors with mild and severe VF. The participants were 506 men [mean age 66.3 years, standard deviation (SD):13.0] and 1038 women (mean age 65.3 years, SD: 12.6). The prevalence of VF in participants aged under 40, in their 40s, 50s, 60s, 70s, and  $\geq 80$  years was 17.4, 7.9, 18.5, 25.6, 26.3, and 41.5%, respectively, in men, and 2.9%, 2.4%, 7.3, 10.3, 27.1, and 53.0%, respectively, in women. Men had a significantly higher prevalence of mild VF (21.2%) than women (10.0%,  $p < 0.001$ ); whereas, severe VF was significantly more prevalent in women (9.1%) than in men (4.7%,  $p = 0.003$ ). VF was distributed with 2 peaks regarding site; one large peak at the thoracolumbar region, and another at the middle thoracic lesion. Low back pain and decreased walking ability were independently associated with severe VF, but not with mild VF, after adjustment for participant characteristics. Decreased walking ability was associated with multiple VFs in women, but not in men.

**Keywords** Vertebral fracture · Prevalence · Low back pain · Walking ability · ROAD study

## Introduction

Vertebral fracture (VF) is the most common among osteoporotic fractures [1]. VF not only affects activities of daily living (ADL) and health-related quality of life (HRQoL) [2–5], but also is related to high mortality [6, 7]. Johnell et al. reported higher 5-year mortality after clinical VF than other

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osteoporotic fractures or general population [6]. Therefore, preventing VF to improve life expectancy and to maintain HRQoL of the elderly is imperative.

The first step to prevent VF is to know its precise epidemiology. However, Cooper et al. reported that only about a third of all vertebral deformities noted on radiographs come to medical attention [8]. Hence, researches at medical institutions alone do not provide sufficient information; conducting a survey on the general population with radiographs to know its epidemiology is mandatory. Due to this complexity, studies on the epidemiology of VF are still very limited worldwide. The reported prevalence of VF varies from 12 to 37% [9–16] depending on the studied regions and the criteria used to define VF. Recent reports on the epidemiology of VF in Japan launched their baseline studies in mid–late 1990s [13, 15, 16], that is, the reported prevalence of VF was that of 2 decades ago. In addition, most reports were based on radiographs of the thoracic spine and of the lumbar spine taken and assessed separately; thus, the accurate site of fracture, especially at the thoracolumbar region, was difficult to be estimated. [17, 18].

This study aimed to determine the prevalence and site of morphometric VF by sex and age in Japan, using whole-spine radiographs, and to analyze associated factors of the presence of VF. The data of the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study 3rd survey performed in 2012–2013 were used in this study.

## Materials and methods

### Participants

The ROAD study is a large-scale population-based cohort study that started in 2005 in three communities in Japan: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama. Details of the study have been described previously [19, 20]. In the present study, we used the 3rd survey of the ROAD study from the mountainous region and the coastal region; hence, we describe the cohort in the 2 regions. This is a cross-sectional observational study.

After the baseline and 2nd surveys, a third survey was performed in the same communities from 2012 to 2013. Invitation letters were distributed to the inhabitants whose names were listed in the ROAD study baseline and 2nd survey database. In addition to the former participants, inhabitants aged  $\geq 40$  years from Hidakagawa and Taiji, who were willing to participate in the 2012–2013 ROAD survey, were included in the third survey. The inclusion criteria were as follows: ability to (1) walk to the clinic where the survey was performed, (2) provide self-reported data, and (3) understand and sign an informed consent form. No other exclusion

criteria were used. Thus, 1629 residents (mountainous area, Hidakagawa, Wakayama, 722 individuals; and coastal area, Taiji, Wakayama, 907 individuals) participated in the third survey. Of them, whole-spine X-ray examinations were performed on a total of 1544 participants (506 men and 1038 women, mean age 65.6 years). We did not perform the examination in participants who could not stand alone or who did not give their consent for the examination. We used the data obtained from 1544 participants in the present study.

The study was approved by the ethics committees of the University of Tokyo (nos. 1264 and 1326) and the Tokyo Metropolitan Institute of Gerontology (no. 5). Written informed consent was provided by all participants.

### Questionnaire, interview, and anthropometric measurements

Participants completed a 400-item interviewer-administered questionnaire that included lifestyle information such as occupational career, smoking habits, alcohol consumption, family history, medical history, physical activity, reproductive variables, and health-related quality of life. Anthropometric measurements included height, weight, arm length, and body mass index (BMI; weight [kg]/height<sup>2</sup> [m<sup>2</sup>]). Medical information was taken by well-experienced orthopedists on systemic, local, and mental status including information of low back pain. Low back pain was defined as pain on low back on most days during the past month.

### The 6-m walking time

The time of participants' walking a 6-m course at their usual speed was measured. The method of measurement of walking time was identical to that performed in the large-scale cohort study entitled "The Osteoporotic Fractures in Men (MrOS)", which started prior to the ROAD study [21]. In the present study, a cutoff value of 0.8 m/s was used [22, 23] to indicate decreased walking ability. In addition, participants who needed any support or assistance such as a cane, a walker, or a wheel chair in their usual walking were also defined as having decreased walking ability.

### Radiographic assessment

Stand-up lateral radiographs of the whole spine were taken for each subject by licensed radiography technicians using standard radiographic techniques. The radiographs were read by one spine surgeon (C.H.). VF and its severity were determined on all vertebrae from T4 to the most caudal vertebra of each participant, using the Genant semiquantitative (SQ) method [24] as indicated by the 2015 Official Position of International Society of Clinical Densitometry [25]. SQ is graded from 0 to 3, where 0 is normal; 1, mildly deformed;

2, moderately deformed; and 3, severely deformed. Morphometric VF was defined as  $SQ \geq 1$ , mild VF as  $SQ = 1$ , and severe VF as  $SQ \geq 2$ , respectively. Each participant was defined as having VF when at least 1 vertebra was determined as  $SQ \geq 1$ ; as mild VF when the maximum grade of  $SQ = 1$ ; and as severe VF when the maximum grade of  $SQ \geq 2$ .

Each vertebra was numbered on the principle of the most caudal vertebra being L5 and the cranial vertebra to L1 being T12. The most caudal vertebra was exceptionally numbered as L6 when all the vertebrae from C2 to C7 and from T1 to T12 were visible, and 6 vertebrae completely apart from the sacrum were recognized caudal to T12. Another exception included a case when all the vertebrae from C2 to C7 and from T1 to T12 were visible, and only 4 vertebrae were recognized caudal to T12. In that case, the most caudal vertebra was numbered as L4. Eleven participants were determined to have L6 as the most caudal vertebra, but L6 vertebrae were excluded from the analysis because all of them were scored as grade 0.

To investigate the intra- and inter-observer reliability of SQ grading, 50 randomly selected radiographs were scored by the same reader (C.H.) again with an interval of > 2 weeks and another orthopedist (T.I.) who was blinded to the scores graded by C.H. The percentage of agreement and kappa statistic were 98.1 and 0.70%, and 98.0 and 0.62% for the intra-observer reliability and inter-observer reliability, respectively.

### Bone mineral density measurement

Bone mineral density (BMD) was measured at the lumbar spine (L2–L4) and the proximal femur using dual-energy X-ray absorptiometry (DXA) (Hologic Discovery; Hologic, Waltham, MA, USA). To control quality, the same DXA equipment was used, and the same spine phantom was scanned daily to monitor the machine's performance in study populations at 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, the same physician (N.Y.) examined all participants to prevent observer variability.

### Statistical analysis

All statistical analyses were performed using STATA statistical software, version 15.1 (STATA, College Station, TX, USA). Differences in proportion were compared using Chi-square test unless frequency of at least one cell was 5 or less; Fisher's exact test was used instead. Differences in continuous variables were examined using non-paired Student's *t* test. A *p* value < 0.05 was regarded to suggest a significant difference.

To test the association between the presence of mild and severe VF with potential associated factors, multinomial logistic regression analysis was used. In the analysis, the presence of mild VF and severe VF was used as the objective variable (0, group without VF; 1, group with mild VF; 2, group with severe VF), and explanatory variables were selected in addition to the basic characteristics, such as sex, age, residing area, BMI, smoking, alcohol consumption, and BMD at L2–L4. Other explanatory variables included the presence of low back pain and decreased walking ability. After the multinomial logistic regression analysis, the relative risk ratios (RRRs) were evaluated. In addition, to determine associations of multiple VFs with low back pain and decreased walking ability in both sexes, multiple logistic regression analysis was used after adjustment for sex, age, residing area, BMI, smoking, alcohol consumption, and BMD at L2–L4 in the overall population and after adjustment for age, residing area, BMI, smoking, alcohol consumption, and BMD at L2–L4 in men and women.

## Results

### Characteristics of the participants

Table 1 shows the characteristics of the 1544 participants in the present study. The mean age was not significantly different between both sexes ( $p = 0.17$ ). The mean BMD of men was significantly higher than women at both L2–L4 and the femoral neck ( $p < 0.001$ , both).

### Sex- and age- specific prevalence

Table 2 shows the prevalence of VF, mild VF (the maximum grade of  $SQ = 1$ ), and severe VF (the maximum grade of  $SQ \geq 2$ ) in men and women, classified according to age. Number of patients with maximum of each grade is shown in Table 3. Men had significantly higher prevalence of VF than women in their 50s and 60s ( $p = 0.006$  and  $p < 0.001$ , respectively), but the difference was not significant in other age strata. As a whole, men had significantly higher prevalence of VF (25.9%) than women (19.1%) ( $p = 0.002$ ). VF increased in an age-dependent way in women, and > 50% of women aged 80 years or older had at least one VF. Severe VF increased in an age-dependent way in both men and women, and the prevalence of severe VF was significantly higher in women than in men in their 70s, at age 80 years or older, and as a whole. By contrast, the prevalence of mild VF was significantly higher in men than in women in their 50s, 60s, and as a whole.

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

	Total	Men	Women	<i>p</i> value
Age strata (years)				
–39	58	23	35	
40–49	122	38	84	
50–59	273	81	192	
60–69	433	133	300	
70–79	432	137	295	
80–	226	94	132	
Total	1544	506	1038	
Age (years)	65.6 (13.0)	66.3 (13.8)	65.3 (12.6)	0.17
Height (cm)	156.0 (9.9)	164.8 (7.3)	151.7 (7.9)	<0.001
Weight (kg)	55.8 (11.3)	63.8 (11.4)	51.9 (8.9)	<0.001
BMI (kg/m <sup>2</sup> )	22.8 (3.5)	23.4 (3.4)	22.5 (3.5)	<0.001
Residing in the coastal area (%)	54.5	51.8	55.9	0.13
Smoking (%)	8.6	20.4	2.9	<0.001
Alcohol consumption	39.7	66.4	26.7	<0.001
BMD (g/cm <sup>2</sup> )				
L2–L4	0.96 (0.21)	1.08 (0.21)	0.89 (0.18)	<0.001
Femoral neck	0.67 (0.24)	0.75 (0.13)	0.63 (0.27)	<0.001

*BMI* Body mass index, *BMD* bone mineral density

**Table 2** Prevalence (%) of vertebral fracture (VF), mild VF, and severe VF in men and women classified by age strata

Age strata (years)	VF			Mild VF			Severe VF		
	Men	Women	<i>p</i> value	Men	Women	<i>p</i> value	Men	Women	<i>p</i> value
–39	17.4	2.9	0.08	17.4	2.9	0.08	0.0	0.0	
40–49	7.9	2.4	0.17	5.3	1.2	0.23	2.6	1.2	0.53
50–59	18.5	7.3	0.006	18.5	5.7	0.001	0.0	1.6	0.56
60–69	25.6	10.3	<0.001	24.1	6.0	<0.001	1.5	4.3	0.17
70–79	26.3	27.1	0.85	20.5	14.6	0.13	5.8	12.5	0.03
80–	41.5	53.0	0.09	27.7	22.7	0.40	13.8	30.3	0.004
Total	25.9	19.1	0.002	21.2	10.0	<0.001	4.7	9.1	0.003

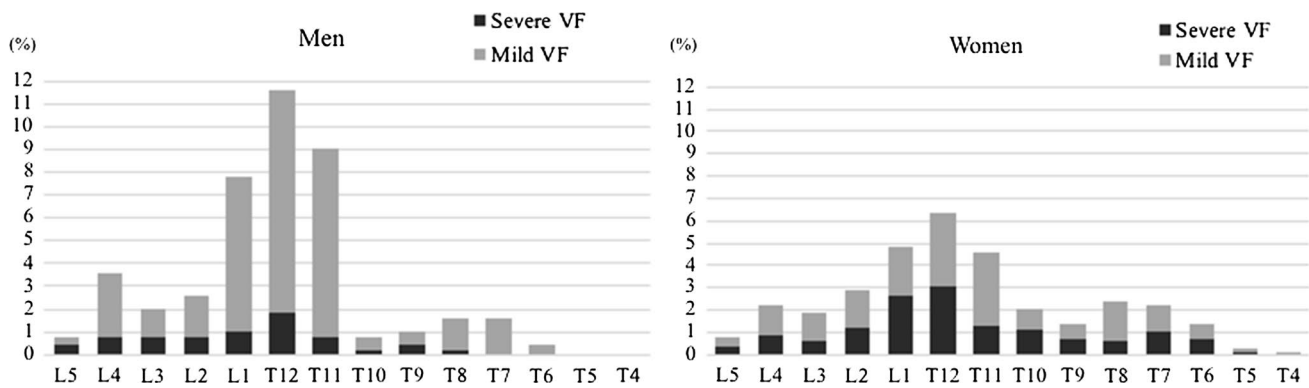
**Table 3** Number of participants with each grade classified by sex and age strata

Age strata (years)	Mild VF		Severe VF			
	Grade 1		Grade 2		Grade 3	
	Men	Women	Men	Women	Men	Women
–39	4	1	0	0	0	0
40–49	2	1	1	1	0	0
50–59	15	11	0	3	0	0
60–69	32	18	2	9	0	4
70–79	28	43	4	20	4	17
80–	26	30	7	20	6	20
Total	107	104	14	53	10	41

### Site-specific prevalence

Figure 1 shows the site-specific prevalence of mild and severe VF in men and women. T12 had the highest

prevalence of VF both in men (11.6%) and in women (6.4%). In both sexes, 2 peaks of the prevalence of VF were observed: one at the thoracolumbar lesion (T11–L1) and the other small peak at the middle thoracic lesion (T7–T8).



**Fig. 1** Prevalence (%) of mild vertebral fracture (VF) and severe VF in both sexes classified according to site

**Table 4** Characteristics of each group divided by maximum grade

	Maximum grade		
	0	1	2, 3
<i>N</i>	1215	211	118
Women (%)	69	49	80
Mean age (SD)	63.5 (12.6)	70.9 (11.9)	77.6 (9.2)
Residing in seacoast area (%)	53.7	59.7	53.4
Mean BMI (SD)	22.7 (3.5)	23.5 (3.5)	22.2 (3.6)
Smoking (%)	8.9	10.0	3.4
Alcohol consumption (%)	41.2	42.4	19.5
Mean BMD (SD)	0.96 (0.20)	0.99 (0.23)	0.82 (0.20)
Low back pain (%)	37.4	44.1	49.6
Decreased walking ability (%)	10.8	21.8	52.5

*SD* standard deviation, *BMI* bod mass index, *BMD* bone mineral density

Severe VF had similar peaks in women; whereas in men, it was almost evenly distributed at the lesion T8 or caudal with a small peak at T12.

### Associated factors for mild and severe VF

We next examined the associated factors for mild and severe VF. Table 4 shows the characteristics of each group; normal, mild VF, and severe VF. Table 5 shows the RRRs obtained from the multinomial logistic regression analysis using the presence of mild VF and severe VF as objective variables. All the variables in the left column in Table 5 were included as explanatory variables. As different tendency in prevalence of mild and severe VF between sexes was observed, this analysis was performed initially as a whole with sex as one of the explanatory variables, and then separately in men and women. After adjustment for basic characteristics, significant association was found between the presence of low back pain and decreased walking ability and severe VF, but none between the presence of low back pain and decreased walking ability

and mild VF. Especially, a strong relationship was observed between severe VF and decreased walking ability in women (RRR = 3.03, 95% confidence interval: 1.72–5.23).

### The prevalence of multiple VFs and their associated factors

Figure 2 shows the prevalence of single VF, multiple VFs, and multiple severe VFs in men and women, classified according to age. Men in their 50s and 60s had significantly higher prevalence of multiple VFs (3.7% and 8.3%, respectively) than women (0.0% and 3.0%, respectively) ( $p=0.03$ , 0.02, respectively). In men and women in their 70s and 80s or older, no significant difference was observed between sexes. The overall prevalence of multiple VFs was 10.7% and 8.0% in men and women, respectively, without significant difference ( $p=0.08$ ). In contrast, the prevalence of multiple severe VFs was significantly higher in women (3.0%) than in men (1.2%) ( $p=0.03$ ). In women aged 80 years or older, 20/132 participants (15.2%) had multiple severe VFs. We next examined the association of multiple VFs with low back pain and decreased walking ability by multiple logistic regression analysis as shown in Table 6. As different clinical significance of multiple morphometric VFs between sexes has been reported [26], the analysis was performed by sex. After adjustment for age, residing area, BMI, smoking, alcohol consumption, and BMD at L2–L4, no association was found between low back pain and multiple VFs in men or women; decreased walking ability was significantly associated with multiple VFs in the whole population and in women.

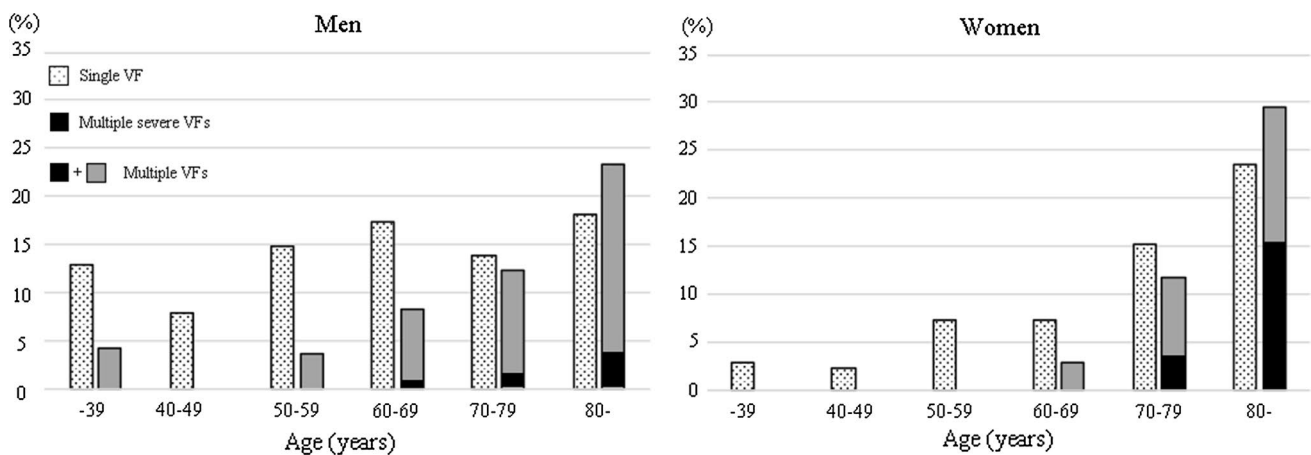
### Discussion

In the present study, we determined the latest prevalence and the accurate site of morphometric VF classified by severity in general population in Japan using whole-spine

**Table 5** Relative risk ratios (RRRs) of potentially associated factors for the presence of mild VF and severe VF vs. normal

	Reference	Mild VF			Severe VF		
		RRR	95% CI	<i>p</i> value	RRR	95% CI	<i>p</i> value
Women	Men	0.45	0.30–0.66	<0.001	1.11	0.60–2.07	0.74
Age	+1 Year	1.06	1.04–1.08	<0.001	1.11	1.08–1.14	<0.001
Men		1.04	1.01–1.06	<0.01	1.09	1.02–1.16	0.01
Women		1.10	1.07–1.13	<0.001	1.12	1.08–1.16	<0.001
Residing in seacoast area	Mountainous area	1.82	1.31–2.52	<0.001	1.69	1.09–2.64	0.02
Men		2.73	1.67–4.46	<0.001	2.38	0.89–6.41	0.09
Women		1.23	0.79–1.91	0.36	1.44	0.87–2.36	0.16
BMI	+1SD	1.29	1.10–1.52	<0.01	1.13	0.89–1.43	0.31
Men		1.16	0.90–1.50	0.24	0.97	0.52–1.81	0.91
Women		1.27	1.01–1.60	0.04	1.13	0.87–1.47	0.35
Smoking	Yes/no	1.38	0.79–2.40	0.26	1.53	0.48–4.82	0.47
Men		1.11	0.60–2.04	0.74	1.41	0.32–6.20	0.65
Women		1.39	0.29–6.62	0.68	1.00	0.11–8.91	1.00
Alcohol consumption	Yes/no	1.06	0.74–1.52	0.75	0.83	0.47–1.46	0.51
Men		1.15	0.70–1.89	0.57	0.37	0.13–1.08	0.07
Women		0.92	0.52–1.64	0.79	1.21	0.63–2.32	0.56
BMD at L2-L4	+1SD	0.92	0.77–1.09	0.33	0.55	0.41–0.73	<0.001
Men		1.01	0.80–1.28	0.95	0.41	0.23–0.74	<0.01
Women		0.93	0.70–1.23	0.60	0.63	0.45–0.88	0.01
Low back pain	Yes/no	1.32	0.97–1.81	0.08	1.64	1.07–2.53	0.02
Men		1.20	0.76–1.90	0.44	2.23	0.86–5.79	0.10
Women		1.42	0.92–2.20	0.12	1.52	0.93–2.49	0.09
Decreased walking ability	Yes/no	1.21	0.78–1.87	0.40	3.04	1.84–5.03	<0.001
Men		1.18	0.60–2.31	0.63	2.61	0.82–8.33	0.11
Women		1.12	0.63–1.99	0.70	3.03	1.72–5.33	<0.001

Upper: whole-cohort analysis  
 Middle: Men were analyzed separately  
 Lower: Women were analyzed separately



**Fig. 2** Prevalence (%) of single, multiple, and multiple severe vertebral fractures (VFs) classified according to age and sex. Single VF: participants with 1 VF only. Multiple VFs: participants with 2 or more VFs. Multiple severe VFs: participants with 2 or more severe VFs



**Table 6** Association of multiple vertebral fractures with low back pain and decreased walking ability

	Crude OR (95% CI)	Adjusted OR (95% CI)
Overall		
Low back pain	1.37 (0.96–1.96)	1.35 (0.92–1.97)
Decreased walking ability	6.60 (4.55–9.56)	2.53 (1.61–3.95)
Men		
Low back pain	1.37 (0.78–2.43)	1.29 (0.71–2.37)
Decreased walking ability	3.40 (1.83–6.31)	1.69 (0.80–3.59)
Women		
Low back pain	1.39 (0.89–2.19)	1.31 (0.79–2.17)
Decreased walking ability	9.88 (6.13–15.92)	2.77 (1.57–4.91)

OR Odds ratio, 95% CI 95% confidence interval

radiographs. The following were the major findings of this study: the prevalence of mild VF was significantly higher in men than in women, whereas the prevalence of severe VF was significantly higher in women than in men, and VF had the 2-peak distribution in both men and women. We also revealed that low back pain and decreased walking ability were significantly associated with severe VF, but not with mild VF. Multiple VFs were associated with decreased walking ability in women.

As mentioned above, surveys at medical institutions alone do not provide sufficient information about the epidemiology of VF; conducting a survey on general population with radiographs is mandatory. Due to this complexity, studies on the epidemiology of VF have been very limited in Japan. Based on population-based surveys involving both men and women, only 3 studies reporting the prevalence of VF in Japan have been conducted [12, 15, 16], except the present study. The reported prevalence of VF varies from 3.3% [15] to 20.5% [16]. A wide range of prevalence is reported even in a Japanese study. One of the supposed reasons for the variance is the difference in the definition and diagnostic methods of VF, resulting from lack of gold standards to

diagnose VF. Age of the participants can also be a reason for differences.

Fujiwara et al. [15] also used the Genant SQ method to determine VF, but their criteria of VF were set at  $SQ \geq 2$ , which corresponds to severe VF in the present study. Their reported prevalence of VF in men and women (3.3% and 10.3%, respectively) is comparable to the prevalence of severe VF in the present study (4.7% and 9.1%, respectively).

Two population-based studies worldwide have been conducted on the prevalence of VF, which was composed of both men and women, containing age stratification information and using Genant's SQ method to define VF. One was surveyed on Brazilian residents between 2005 and 2007 [27] and the other on Hong Kong residents between 2001 and 2003 [28]. To compare the results, the prevalence of VF and severe VF of the present study in men and women aged 65–69 years was calculated as follows: men VF, 24.6%; severe VF, 3.3%; women VF, 13.8%; and severe VF, 5.6%. Table 7 shows the comparison among the present study and the previous 2 studies. Compared to the results from the Hong Kong study, the prevalence of both VF and severe VF in the present study was generally higher, except severe VF in women aged 65–69 years and 70–70 years. Compared to the Brazilian study, the prevalence of VF was lower in younger generation (aged 65–69 years) and higher in older generation (aged 80 years or more). Because all 3 studies were population-based, were voluntary participated, and used the same diagnostic criteria, these differences are considered to reflect ethnic and regional differences.

To the best of our knowledge, this is the first study to report on the prevalence of VF using whole-spine radiographs, which enabled us to number each vertebra accurately. As Lian et al. reported, the whole-spine view was mandatory for accurate vertebral numbering. [17] We revealed site-specific prevalence of VF and 2-peak prevalence of VF with one main peak at the thoracolumbar lesion and the other small peak at the middle thoracic lesion. The same tendency was reported using thoracic and lumbar radiographs [12, 24, 29]. This tendency was confirmed with greater accuracy using whole-spine radiographs.

**Table 7** A comparison of age-specific vertebral fracture prevalence among the ROAD study and previous two reports

Age (years)	65–69			70–79			80–		
	ROAD	Hong Kong <sup>a</sup>	Brazil <sup>b</sup>	ROAD	Hong Kong <sup>a</sup>	Brazil <sup>b</sup>	ROAD	Hong Kong <sup>a</sup>	Brazil <sup>b</sup>
Men: VF	24.6	12.3	29.8	26.3	14.7	29.6	41.5	25.0	31.8
Men: Severe VF	3.3	2.9	N/A	5.8	5.2	N/A	13.8	11.1	N/A
Women: VF	13.8	10.8	19.1	27.1	17.4	26.4	53.0	29.5	50.0
Women: Severe VF	5.6	6.1	N/A	12.5	13.6	N/A	30.3	22.6	N/A

ROAD the Research on Osteoarthritis/Osteoporosis Against Disability study (the present study), N/A not available

<sup>a</sup>Mr. OS (Hong Kong) and Ms. OS (Hong Kong) studies [28]

<sup>b</sup>[27]

To confirm whether the participants of the present study are representative of the Japanese population, we compared anthropometric measurements and frequency of smoking and alcohol consumption between the participants and the general Japanese population. The details of the comparison are in Supplementary Tables 1 and 2. Briefly, the overall BMI of the participants was basically comparable to that of the broader Japanese population; whereas, the participants had healthier lifestyles than the general Japanese population in terms of smoking and alcohol consumption. Given that the results obtained from the present study were applicable to the total age–sex distribution derived from the Japanese census in 2015 [30], it would be assumed that 14,600,000 Japanese people (19.4%) [74,00,000 men (21.2%) and 71,00,000 women (18.0%)] aged 40 years and older would be affected by morphometric VF and that 4700,000 Japanese people (6.3%) [1,200,000 men (3.5%) and 3,500,000 women (8.8%)] aged 40 years and older would be affected by morphometric severe VF.

Our study showed that severe VF was significantly associated with low back pain after adjustment for basic characters (Table 5). The results are consistent with previous literature [11, 28]. Although the tendency was the same in both men and women when analyzed separately, the association between low back pain and severe VF was not significant in men or women in a sex-separate analysis; whereas, the association was significant in the whole-cohort model. The supposed reason for the discrepancy is the low number of participants with severe VF (men; 24, women; 94, shown in Table 3, as this model had 8 explanatory variables. Hence, the whole-cohort model is considered more plausible than the separate model. The association between VF and decreased walking ability has not been clearly demonstrated to date. Our results revealed that severe VF was significantly associated with decreased walking ability after adjustment for basic characters. As severe VF can be a cause of sagittal imbalance and sagittal imbalance has been reported to correlate with walking disability [31], it may be considered that severe VF associates with decreased walking ability through sagittal imbalance. However, Lafage et al. reported that the strongest correlation was observed between walking disability and pelvic tilt [31], which was a pelvic parameter not manifesting spinal deformity. Therefore, our results revealed a new aspect of the association between VF and walking disability.

In this study, multiple VFs were significantly associated with decreased walking ability in women, but not in men. Some studies have reported increased mortality with multiple VFs in women. [26, 32] Further, Mutikanen et al. reported that walking disability was associated with increased mortality in older community-dwelling women. [33]. The result of the current study corresponds with these reports. As walking disability is one of the major

risk factors for falls in elderly people [34] and falls are the biggest cause of VF, multiple VFs are considered to have the tendency to lead to the next VF. Several reports have supported that prevalent VF is a risk factor for incident VF [35–37]. Furthermore, vitamin D deficiency is considered to accelerate the reproducing cycle of VF through being a cause of osteoporosis [38, 39] and being a risk factor for falls [40].

Mild VF was not associated with low BMD, low back pain, or decreased walking ability, which indicates that mild VF lack characteristics specific to clinical VF [41]. Szulc et al. [42] and Kherad et al. [29] also reported low clinical relevance of mild VF in elderly men; however, both studies were conducted on only men. In the present study, we confirmed the same tendency both on men and women. Low clinical relevance of mild VF may partly be because of confusion between true VF and deformity, which is a non-osteoporotic condition, as Szulc et al. discussed. [42] This would be a limitation of morphometrical diagnosis of VF in a cross-sectional study. The clinical importance of mild VF is still obscure from the present study. However, Roux et al. reported that prevalent morphometric VF, even mild, was a significant risk factor for incidence of new VF in elderly women [43]. Pongchaiyakul et al. reported a higher rate of incident symptomatic fracture and higher mortality after a symptomatic fracture among those with prevalent morphometric VF [44]. Therefore, to clarify the significance of mild VF, following the same participants and analyzing following subsequent clinical and radiological outcomes are necessary. We will continue to follow the participants in the ROAD study 3rd visit and will clarify the subsequent outcomes of VF in the near future.

This study has several limitations. First, the present cohort may not be truly representative of the general population. Especially, participants aged  $\geq 80$  years of the present study were significantly smaller in BMI than the general Japanese population. This difference should be taken into consideration when estimating the prevalence of VF in people aged  $\geq 80$  years, since a small body build is associated with osteoporosis. Therefore, our results might represent an overestimation. Second, mild VF in the present study may include vertebral deformity, which is unrelated to osteoporosis, as discussed above. This is a limitation attributed to morphometrical diagnosis. Thus, prevalence of overall VF may be an overestimation; whereas, prevalence of severe VF would be reasonable. Third, the present study does not reveal a cause-and-effect link as it is a cross-sectional study. In addition, there is a possibility that measuring the change in vertebral height enables us to diagnose VF more accurately in a longitudinal study. However, we have one of the largest cohorts among recent Japanese studies of VF, and we can and will analyze the longitudinal results as the ROAD study is still ongoing.



Despite these limitations, we estimated age- and sex-specific prevalence of mild and severe VF with accurate site-specific distribution determined according to whole-spine radiographs in Japanese men and women. Our results suggested that the characteristics of mild and severe VF were different, such as mild VF had male dominancy, whereas severe VF had female dominancy; not mild VF but severe VF was significantly associated with low back pain and decreased walking ability. Further, we revealed that multiple VFs were associated with decreased walking ability in women.

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