

Calcium intake and the 10-year incidence of self-reported vertebral fractures in women and men: The Japan Public Health Centre-based Prospective Study

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The purpose of this study was to evaluate the effect of low Ca intake on the 10-year incidence of vertebral fractures in cohorts I and II of the Japan Public Health Centre-based Prospective Study. The baseline studies were conducted in 1990–1994, with the follow-up studies conducted after 10 years. We analysed 33 970 subjects aged 40–59 years in cohort I and 41 664 subjects aged 40–69 years in cohort II. At baseline, the intake of Ca was assessed as a predictor, using validated FFQ. A meta-analysis was performed to estimate a summary relative risk (RR) for the two cohort studies. The 10-year cumulative incidences of self-reported vertebral fractures were 0.38% for cohort I and 0.56% for cohort II. In women, lower Ca intake was associated with a higher incidence of vertebral fractures (P for trend=0.001), with the lowest quartile of Ca intake having a significantly higher incidence (0.89/1000 persons per year or RR 2.10 (95% CI 1.25, 3.55)) than that (0.42/1000 persons per year) of the highest. In addition, the RR calculated using energy-adjusted Ca intake (by the residual method) as an outcome was 1.92 (95% CI 1.28, 2.88). However, no such association was observed in men. An increase of Ca intake should be considered as a preventive strategy for vertebral fractures in peri- and post-menopausal women with a low Ca intake.

Calcium: Cohort studies: Japanese: Vertebral fractures

A bone fracture is the most tragic outcome of osteoporosis, an age-related disease characterized by generalized skeletal fragility⁽¹⁾. Some fractures decrease the levels of activities of daily living and the quality of life in the elderly. A vertebral fracture is one such fracture. Patients with vertebral fractures often have impaired mobility and/or suffer from back pain⁽²⁾. Vertebral fractures have been reported to be more common in Japan⁽³⁾ than in the USA⁽⁴⁾ and, as such, their prevention deserves a high priority.

Ca is a nutrient essential for the maintenance of normal bone metabolism and bone mass and its insufficient intake results in loss of bone and the eventual development of osteoporosis. Therefore, sufficient intake of Ca is considered to be the first step for preventing bone loss, osteoporosis and, presumably, osteoporotic fractures in adults. For example, high Ca intake (≥ 1000 – 1200 mg/d) is recommended as an adequate intake for adults in the USA⁽⁵⁾. Ca intake among the Japanese is generally low. The National Nutrition Survey of Japan reported that the average Ca intake in adults (aged 40–69 years) is estimated to be 492–602 mg/d⁽⁶⁾, even though Ca intake of 600–700 mg/d has been recommended as an adequate intake for this age group⁽⁷⁾. In spite of this, there have only been a few studies conducted in Japan that

have examined whether low Ca intake adversely affects bone-related parameters. A previous study reported that low dietary Ca intake in elderly women was significantly associated with high levels of bone resorption markers⁽⁸⁾. In addition, the bottom half of the population has been shown to have lower values on bone ultrasound characterization⁽⁹⁾. On the one hand, these reports suggest that low Ca intake in the Japanese population may affect the incidence of vertebral fractures. However, despite the lower Ca intake in the Japanese, the incidence of hip fractures in Japan has been reported to be lower than that of Europeans and North Americans^(10,11). This, on the other hand, may suggest that low Ca intake in the Japanese may only slightly, if at all, increase the incidence of vertebral fractures. Previously, there have been far fewer epidemiological studies on vertebral than on hip fractures. To our knowledge, no epidemiological studies on vertebral fractures have ever been conducted to test and clarify the effect of low Ca intake in East Asians, particularly the Japanese, in whom Ca intake is generally low.

The Japan Public Health Centre-based Prospective Study (JPHC Study) is a large, population-based cohort study, designed to reveal risk factors for chronic diseases, including cancers, CVD, diabetes and others. It targets around 117 000

Abbreviations: JPHC Study, Japan Public Health Centre-based Prospective Study; RR, relative risk.

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middle-aged and elderly Japanese women and men nationwide⁽¹²⁾. In the present study, we analysed the levels of Ca intake and the 10-year incidence of vertebral fractures. The purpose of this study was to test whether low Ca intake is associated with increased incidence of vertebral fractures in Japanese adults.

Subjects and methods

The JPHC Study consists of two cohorts, cohort I and cohort II, with the subjects selected from nationwide areas of Japan. The following participants met our exclusion criteria according to the baseline survey: (1) subjects who reported a history of vertebral fractures, diabetes mellitus or cancers (of the stomach, lung, colon, liver, breast or the uterus); (2) subjects who were undergoing corticosteroid therapy; (3) subjects who were taking medicine for suspected osteoporosis; (4) subjects who were taking female hormones. In addition, subjects whose reported dietary energy intake fell within the upper or lower 2.5% were excluded. It is the policy of the JPHC Study to exclude extreme values for dietary intake, because we consider these reports may be unreliable⁽¹³⁾. The energy cut-off points were 3255 and 9427 kJ (778 and 2253 kcal)/d for cohort I women, 4527 and 14 878 kJ (1082 and 3556 kcal)/d for cohort I men, 2423 and 7159 kJ (579 and 1711 kcal)/d for cohort II women and 3523 and 12 221 kJ (842 and 2921 kcal)/d for cohort II men. The present study protocol was approved by the institutional review board of the National Cancer Centre, Tokyo, Japan. Detailed information describing the study design, conduct and participant profiles has been published previously⁽¹²⁾. The follow-up surveys were conducted 10 years after the baseline survey.

Subjects of Japan Public Health Centre-based Prospective Study cohort I

The JPHC Study cohort I consisted of four public health centre-based cohorts in fourteen municipalities within four prefectures (Akita, Iwate, Nagano and Okinawa), which represent distinct geographical areas of Japan⁽¹⁴⁾, and a health check-up cohort in the Tokyo metropolitan district. The baseline survey for cohort I was conducted in 1990, except in Katsushika, where questionnaires were administered during health check-ups from 1990–1994. Among 61 595 residents (31 613 women and 29 982 men) between 40–59 years of age with a registered address, 50 245 (81.6% response rate) returned the questionnaire. Of the 50 245 subjects who completed the baseline survey, 37 861 (response rate 75.4%) returned the follow-up questionnaire in 2000. After excluding 1998 subjects who met our exclusion criteria and 1819 subjects whose dietary energy intake was within the extreme range, 34 044 subjects were included in the final analysis.

Subjects of Japan Public Health Centre-based Prospective Study cohort II

In 1993–1994, cohort II was added to the JPHC Study. The JPHC Study cohort II consisted of seven population-based cohorts in fourteen municipalities, in six prefectures (Niigata, Ibaraki, Osaka, Kochi, Nagasaki and Okinawa)⁽¹⁴⁾. Among 78 825 residents (40 085 women and 38 740 men) between

40–69 years of age with a registered address, 63 216 (response rate 80.2%) returned the questionnaire. Of the 63 216 subjects who completed the baseline survey, 48 615 (response rate 76.9%) returned the follow-up questionnaire in 2003–2004. After excluding 4457 subjects who met our exclusion criteria and 2323 subjects whose dietary energy intake was within the extreme range, 41 835 subjects were included in the final analysis.

Measurements at baseline

Demographic, lifestyle and nutritional information was obtained through a self-administered questionnaire. Subjects' age, sex, body height, body weight, past medical history and medications were recorded. BMI was calculated by dividing the weight (kg) by the square of the height (m²). Subjects were asked about the frequency at which they engage in sport activities and the answers were coded as 1 for less than once per month, 2 for one to three times per month, 3 for once or twice per week and 4 for three or more times per week. Smoking and alcohol use habits were also recorded. Dietary intake, including Ca, vitamin D and total energy, was assessed by two validated FFQ, a forty-four item FFQ for cohort I⁽¹⁵⁾ and a fifty-two item FFQ for cohort II⁽¹⁶⁾. Each participant was asked how often during the previous month he or she had consumed specific foods and beverages, on average. The amount of each food consumed was calculated by multiplying the frequency of consumption with the portion size. The appropriate portion size for each food was estimated separately for each cohort using a validation study conducted in a sub-sample of each cohort⁽¹⁷⁾. The individuals' daily intake of nutrients, including Ca, protein and vitamin D, was calculated using the *Standardized Tables of Food Composition*, 5th ed.⁽¹⁸⁾. The validity of the FFQ with regard to assessing intake was evaluated against 7 d dietary records collected as a reference during each of the four seasons. Regarding Ca intake, the Spearman's correlation coefficient between the forty-four item FFQ and the reference 7 d record was 0.46 for women and 0.56 for men, and that between the fifty-two item FFQ and the reference record was 0.50 for women and 0.53 for men.

Follow-up survey after 10-years

The subjects were asked to report previously developed fractures within the lumbar region (herein defined as a vertebral fracture) in the 10-year follow-up period. The question was posed in the following manner: 'Has your doctor(s) told you that you have a fracture at the lumbar region? If so, when was the fracture first diagnosed – in the past 10 years or earlier?' The subjects were also asked not to report vertebral fractures due to high-energy trauma, such as traffic and occupational accidents, as a vertebral fracture in this study.

Statistical analysis

Statistical analysis was performed separately in cohort I and cohort II. The cumulative incidence of vertebral fractures in the 10-year follow-up period was calculated for each quartile of continuous variables (except for age) and for each level of discrete variables. The relative risk (RR) of vertebral fractures

was calculated for continuous variables (except for age), for each quartile relative to the fourth quartile. RR for Ca and vitamin D intakes were also calculated using energy adjustment by the residual method⁽¹⁹⁾. The RR of vertebral fractures was calculated for discrete variables, for each level relative to the reference level. A test for linear trend was performed using logistic regression, with an occurrence of vertebral fracture as the outcome variable and each discrete variable as a predictor. RR adjusted for age, body weight, smoking, alcohol use, frequency of sports activity, area, vitamin D intake and energy were estimated using the OR yielded by multiple logistic regression analysis. The questionnaires used in JPHC Study cohort I and cohort II differed slightly with regard to food items and thus the following statistical methods (meta-analysis) were used to obtain summary RR in relation to Ca intake. We calculated separate estimates for cohort I and cohort II and then analysed the combined result using a fixed-effects model. That is:

$$\beta_c = \frac{(1/v_1)\beta_1 + (1/v_2)\beta_2}{(1/v_1) + (1/v_2)}, \quad RR_c = \exp(\beta_c);$$

β_c is the combined parameter estimate, v_1 is the variance of cohort I, β_1 is the parameter estimate of cohort I, v_2 is the variance of cohort II, β_2 is the parameter estimate of cohort II, RR_c is the combined RR⁽²⁰⁾. The weighted average procedure was also applied to the test-for-trend statistics by using $v_2 = (\log RR_c)^2((1/v_1) + (1/v_2))$. In the test for heterogeneity using an inverse variance method, the two cohorts were not heterogeneous ($P=0.439$). The population-attributable fraction (%) was estimated as $(pd(RR - 1))/RR$, where pd is the proportion of cases exposed to the risk factors⁽²¹⁾. The SAS (release 9.13; SAS Institute Inc., Cary, NC, USA) was used for computation. A P -value less than 0.05 was considered to be statistically significant.

Results

Baseline characteristics of the subjects in cohorts I and II, stratified by sex, are shown in Table 1. Overall, men tended to

have higher values than women, except for age and Ca intake in both cohort I and cohort II. Percentage frequency of smoking and drinking habits of the subjects is also shown in Table 1. The 10-year cumulative incidences of vertebral fractures were 0.38% for cohort I overall, 0.42% for cohort I women and 0.33% for cohort I men and 0.56% for cohort II overall, 0.66% for cohort II women and 0.44% for cohort II men. In total, the incidence was 0.55% for women and 0.39% for men ($P=0.001$).

Table 2 shows unadjusted RR of vertebral fractures occurring within 10 years in cohort I, with the values for each level calculated relative to a reference level. Age was the strongest predictor of vertebral fractures among the variables measured in this cohort (P for trend <0.001). The 10-year incidence of vertebral fractures was significantly higher in the 50–54 year group and the 55–59 year group than in the 40–44 year group for both sexes. Lower (energy-unadjusted) Ca intake and less frequent milk consumption in women was associated with a higher incidence of vertebral fractures, with the 'less than once per week' group having significantly higher incidence than the 'five or more times per week' group. Lower vitamin D intake in men was associated with lower incidence of vertebral fractures, with the first quartile having significantly lower incidence than the fourth quartile.

Table 3 shows unadjusted RR of vertebral fractures occurring within 10 years in cohort II, with each level being relative to the reference level of the respective predictor variable. Age was the strongest predictor of vertebral fractures among variables measured in this cohort. The 10-year incidence of vertebral fractures was significantly higher in any of the age groups in women (P for trend <0.001), as well as in the 60–64 and the 65–69 year groups in men, compared with the 40–44 year group (P for trend <0.001). Lower Ca intake in women was associated with higher incidence of vertebral fractures, with the first quartile having significantly higher incidence than the fourth quartile.

Table 4 shows adjusted RR of vertebral fractures occurring within 10 years for women and men according to quartiles of Ca intake in cohorts I and II. Lower Ca intake in women was significantly associated with higher incidence of vertebral

Table 1. Baseline characteristics of the subjects in cohorts I and II, stratified by sex* (Means and standard deviations or percentage)

	Cohort I				Cohort II			
	Women (n 18 524)		Men (n 15 520)		Women (n 22 596)		Men (n 19 239)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	49.3	5.9	49.2	6.0	53.6	8.7	53.0	8.6
Height (cm)	151.8	5.3	164.0	6.1	152.0	5.8	164.2	6.5
Weight (kg)	54.2	7.6	63.4	8.7	53.9	7.8	63.4	9.0
BMI (kg/m ²)	23.5	3.1	23.5	2.8	23.3	3.4	23.5	3.0
Total energy† (kJ/d)	5962	1255	9125	2284	4619	954	7284	1849
Total energy† (kcal/d)	1425	300	2181	546	1104	228	1741	442
Ca intake† (mg/d)	512	245	520	276	334	142	332	142
Vitamin D intake† (μg/d)	5.8	2.8	6.3	3.2	4.8	2.6	5.7	3.3
Proportion of current smokers (%)	5.2		51.7		5.6		50.2	
Proportion of frequent drinkers (five or more times per week) (%)	3.9		50.1		3.8		47.2	

* For details of subjects and procedures, see Subjects and methods.

† Nutritional parameters were assessed by two different FFQ for cohort I and cohort II.

Table 2. Unadjusted relative risk (RR) of vertebral fractures occurring within 10 years in cohort I*

	Women			Men		
	Cumulative incidence	Unadjusted RR	95% CI	Cumulative incidence	Unadjusted RR	95% CI
Age (years)						
40–44	7/4871	1 (reference)		6/4331	1 (reference)	
45–49	10/4182	1.66	0.63, 4.37	5/3463	1.04	0.32, 3.41
50–54	31/4944	4.36	1.92, 9.90	16/3827	3.02	1.18, 7.70
55–59	30/4527	4.61	2.03, 10.49	25/3899	4.63	1.90, 11.27
	<i>P</i> for trend<0.001			<i>P</i> for trend<0.001		
Weight						
Q1	16/4314	0.78	0.41, 1.48	13/3380	1.92	0.82, 4.48
Q2	14/3906	0.75	0.39, 1.47	15/4245	1.76	0.77, 4.02
Q3	26/5680	0.96	0.55, 1.70	15/3412	2.19	0.96, 5.00
Q4	22/4624	1 (reference)		9/4483	1 (reference)	
	<i>P</i> for trend=0.426			<i>P</i> for trend=0.210		
BMI						
Q1	15/4703	0.77	0.39, 1.52	14/3934	1.52	0.66, 3.50
Q2	20/4596	1.05	0.56, 1.97	15/3906	1.64	0.72, 3.74
Q3	24/4632	1.25	0.69, 2.28	14/3839	1.56	0.67, 3.59
Q4	19/4593	1 (reference)		9/3841	1 (reference)	
	<i>P</i> for trend=0.383			<i>P</i> for trend=0.358		
Smoking						
Non-smoker	71/17229	1 (reference)		12/3803	1 (reference)	
Ex-smoker	0/332	0	–	16/3685	1.38	0.65, 2.90
Current smoker						
< 20 cigarettes/d	5/685	1.77	0.72, 4.37	7/2282	0.97	0.38, 2.47
≥ 20 cigarettes/d	2/269	1.80	0.44, 7.32	17/5746	0.94	0.45, 1.96
	<i>P</i> for trend=0.566			<i>P</i> for trend=0.633		
Alcohol drinking						
< once/month	63/14009	1 (reference)		9/3039	1 (reference)	
1–3 times/month	7/2238	0.71	0.32, 1.54	4/1634	0.83	0.25, 2.68
1–4 times/week	7/1514	1.04	0.48, 2.28	15/3091	1.64	0.72, 3.74
≥ 5 times/week	2/722	0.63	0.15, 2.55	24/7780	1.04	0.48, 2.24
	<i>P</i> for trend=0.440			<i>P</i> for trend=0.640		
Frequency of sport activity						
< once/month	59/14187	1 (reference)		37/9924	1 (reference)	
1–3 times/month	6/1325	1.09	0.47, 2.52	5/2725	0.49	0.19, 1.25
1–2 times/week	7/1458	1.15	0.53, 2.52	5/1511	0.89	0.35, 2.25
≥ 3 times/week	5/1279	0.94	0.38, 2.34	4/1215	0.88	0.32, 2.47
	<i>P</i> for trend=0.907			<i>P</i> for trend=0.542		
Total energy						
Q1	24/4631	1.09	0.61, 1.94	12/3879	0.71	0.34, 1.48
Q2	22/4631	1	0.55, 1.80	11/3881	0.65	0.30, 1.38
Q3	10/4631	0.45	0.22, 0.96	12/3880	0.71	0.34, 1.48
Q4	22/4631	1 (reference)		17/3880	1 (reference)	
	<i>P</i> for trend=0.560			<i>P</i> for trend=0.322		
Ca intake						
Q1	24/4631	1.60	0.84, 3.05	11/3880	0.69	0.32, 1.48
Q2	25/4631	1.67	0.88, 3.16	12/3880	0.75	0.36, 1.58
Q3	14/4631	0.93	0.45, 1.93	13/3880	0.81	0.39, 1.69
Q4	15/4631	1 (reference)		16/3880	1 (reference)	
	<i>P</i> for trend=0.044			<i>P</i> for trend=0.321		
Energy-adjusted† Ca intake						
Q1	27/4631	1.93	1.01, 3.67	13/3880	1.00	0.46, 2.15
Q2	18/4631	1.29	0.64, 2.58	6/3880	0.46	0.18, 1.21
Q3	19/4631	1.36	0.68, 2.70	20/3880	1.54	0.77, 3.09
Q4	14/4631	1 (reference)		13/3880	1 (reference)	
	<i>P</i> for trend=0.055			<i>P</i> for trend=0.385		
Frequency of milk consumption						
< once/week	21/3670	1.78	1.00, 3.18	9/3702	0.66	0.30, 1.44
1–2 times/week	17/3339	1.58	0.86, 2.93	10/3311	0.82	0.39, 1.73
3–4 times/week	15/3625	1.29	0.68, 2.44	12/2743	1.18	0.58, 2.40
≥ 5 times/week	25/7778	1 (reference)		21/5684	1 (reference)	
	<i>P</i> for trend=0.037			<i>P</i> for trend=0.251		
Vitamin D intake						
Q1	23/4630	1.16	0.63, 2.14	6/3851	0.36	0.14, 0.90
Q2	24/4627	1.32	0.73, 2.39	11/3902	0.64	0.30, 1.37
Q3	11/4627	0.63	0.31, 1.30	18/3885	1.06	0.55, 2.05
Q4	21/4640	1 (reference)		17/3882	1 (reference)	
	<i>P</i> for trend=0.277			<i>P</i> for trend=0.015		

Table 2. Continued

	Women			Men		
	Cumulative incidence	Unadjusted RR	95 % CI	Cumulative incidence	Unadjusted RR	95 % CI
Energy-adjusted† vitamin D intake						
Q1	23/4631	1.05	0.58, 1.87	8/3880	0.50	0.21, 1.17
Q2	25/4631	1.14	0.64, 2.01	8/3880	0.50	0.21, 1.17
Q3	8/4631	0.36	0.16, 0.82	20/3880	1.25	0.65, 2.41
Q4	22/4631	1 (reference)		16/3880	1 (reference)	
	<i>P</i> for trend=0.311			<i>P</i> for trend=0.027		

Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

Cut-off values for quartiles are as follows:

Weight: 49, 53 and 59 kg for women; 57, 63 and 68 kg for men.

BMI: 21.4, 23.2 and 25.3 kg/m² for women; 21.6, 23.4 and 25.2 kg/m² for men.

Energy: 5075, 5874 and 6753 kJ (1213, 1404 and 1614 kcal)/d for women; 7351, 8962 and 10774 kJ (1757, 2142 and 2575 kcal)/d for men.

Ca intake: 326, 464 and 677 mg/d for women; 324, 452 and 673 mg/d for men.

Vitamin D intake: 3.7, 5.5 and 7.6 µg/d for women; 3.9, 5.9 and 8.1 µg/d for men.

* For details of subjects and procedures, see Subjects and methods.

† Adjusted by the residual method.

fractures in cohorts I and II (except for energy-adjusted Ca intake in cohort I), but there were no significant associations in men.

A meta-analysis was conducted to determine summary RR of Ca intake for vertebral fractures for cohorts I and II. Table 5 shows the results of the 10-year vertebral fracture RR analysis of each quartile relative to the fourth quartile for Ca intake in women and men. Lower Ca intake in women was associated with higher incidence of vertebral fractures, with the first quartile having significantly higher incidence (0.89/1000 persons per year) than the fourth quartile (0.42/1000 persons per year). The population-attributable fraction of a vertebral fracture in women relative to the fourth quartile (an unexposed group) was 27.0% (pd 0.81 and RR 1.5 for the first–third quartiles as an exposed group). By contrast, there were no significant associations between Ca intake and vertebral fractures in men.

A meta-analysis was conducted to determine summary associations between vitamin D intake and vertebral fractures for cohorts I and II, because there was a significant association between them in cohort I men (Table 3). However, no significant associations were found between vitamin D intake and vertebral fractures (adjusted *P* for trend=0.267) or between energy adjusted vitamin D intake and vertebral fractures (adjusted *P* for trend=0.398).

Discussion

This is the first cohort study exploring the risk of vertebral fractures in Asian women whose Ca intake is low. It demonstrated that women with lower Ca intake had a higher incidence of vertebral fractures. The National Nutrition Survey⁽²²⁾ reported that mean Ca intake of the Japanese aged between 40–70 years was 562 mg/d, on average, which is lower than that of people in many European and North American countries.

The present study used two different FFQ for the two large cohorts, which prevented us from directly analysing the combined data of cohorts I and II. Mean values of total energy measured by the FFQ used in cohort II were lower than those measured by the FFQ used in cohort I, while the mean values of anthropometric variables, such as weight and BMI, were almost the same in cohorts I and II. This, together with the

results of the National Nutrition Survey, indicates that the FFQ used in cohort II underestimated the values of nutritional parameters. Because there is little regional difference in Ca intake in Japan^(6,22), and because cohorts I and II were large enough, the actual Ca intakes of cohorts I and II were considered to be almost equivalent. This warranted our meta-analysis.

The meta-analysis of the current study demonstrated that the subjects in the first quartile of Ca intake had a twice higher risk of clinical vertebral fractures than those in the fourth quartile, but only in women. The FFQ used in this study may not necessarily give an accurate Ca intake, even though their rank correlations with the 7 d dietary record method were acceptable. The National Nutrition Survey of Japan (using a dietary record method) is expected to have provided more accurate data on Ca intake⁽⁶⁾. It showed that 25th, 50th and 75th percentiles of Ca intake in 50–69 year old women were 362, 532 and 716 mg/d, respectively. In general, peri- and early post-menopausal women with a Ca intake of 350 mg/d or lower have a significantly higher risk of vertebral fractures than those with a Ca intake of 700 mg/d or higher, which is an adequate Ca intake for post-menopausal women based on the 2005 *Dietary Reference Intakes for Japanese*⁽⁷⁾.

The accuracy of self-reported vertebral fractures is a major concern in the current study. A study in the USA reported that agreements between self-reports for single-site fractures and medical records were lower for clinical spine fractures than for fractures of the appendicular bones, such as hip and arm fractures⁽²³⁾. We believe, however, that the accuracy of self-reported fractures among the Japanese are better than previously thought. There have been no published data regarding this issue in Japanese populations. However, an ongoing cohort study (Muramatsu study) on fractures in elderly Japanese (aged 69 years and over)⁽²⁴⁾ indicates a high positive predictive value of self-reported vertebral fractures. In that study, among eight self-reported vertebral fractures in a 4-year follow-up, seven were radiographically diagnosed as vertebral fractures, as identified by orthopaedists using the diagnostic criteria of the Japanese Society of Bone and Mineral Metabolism (personal data)⁽²⁵⁾. Although this result was derived from a study with a shorter follow-up period and limited cases, it warrants high accuracy of self-reporting

Table 3. Unadjusted relative risk (RR) of vertebral fractures occurring within 10 years in cohort II*

	Women			Men		
	Cumulative incidence	Unadjusted RR	95% CI	Cumulative incidence	Unadjusted RR	95% CI
Age (years)						
40–44	4/4626	1 (reference)		11/4301	1 (reference)	
45–49	11/3146	4.04	1.29, 12.69	7/2925	0.94	0.36, 2.41
50–54	20/4291	5.39	1.84, 15.76	11/3658	1.18	0.51, 2.71
55–59	22/3630	7.01	2.42, 20.32	16/3045	2.05	0.95, 4.42
60–64	44/3837	13.26	4.77, 36.88	20/3059	2.56	1.23, 5.33
65–69	49/3066	18.48	6.68, 51.16	19/2251	3.30	1.57, 6.92
	<i>P</i> for trend<0.001			<i>P</i> for trend<0.001		
Weight						
Q1	39/5628	1.14	0.74, 1.78	26/4461	1.22	0.70, 2.12
Q2	40/4813	1.37	0.88, 2.13	12/4790	0.52	0.26, 1.05
Q3	32/5712	0.93	0.58, 1.48	22/4961	0.93	0.52, 1.65
Q4	39/6443	1 (reference)		24/5027	1 (reference)	
	<i>P</i> for trend=0.281			<i>P</i> for trend=0.838		
BMI						
Q1	38/5800	0.99	0.63, 1.55	23/4977	0.93	0.52, 1.64
Q2	34/5646	0.91	0.57, 1.45	18/4752	0.76	0.41, 1.40
Q3	41/5560	1.11	0.72, 1.73	19/4704	0.81	0.44, 1.47
Q4	37/5590	1 (reference)		24/4806	1 (reference)	
	<i>P</i> for trend=0.749			<i>P</i> for trend=0.754		
Smoking						
Non-smoker	137/21044	1 (reference)		20/4817	1 (reference)	
Ex-smoker	2/248	1.24	0.31, 4.98	18/4761	0.91	0.48, 1.72
Current smoker						
< 20 cigarettes/d	8/839	1.46	0.72, 2.98	16/2437	1.58	0.82, 3.05
≥ 20 cigarettes/d	2/415	0.74	0.18, 2.98	30/7203	1.00	0.57, 1.76
	<i>P</i> for trend=0.462			<i>P</i> for trend=0.823		
Alcohol drinking						
< once/month	126/17749	1 (reference)		20/4208	1 (reference)	
1–3 times/month	7/1906	0.52	0.24, 1.11	2/1512	0.28	0.07, 1.19
1–4 times/week	6/1895	0.45	0.20, 1.01	23/4112	1.18	0.65, 2.14
≥ 5 times/week	8/843	1.34	0.66, 2.72	35/8792	0.84	0.48, 1.45
	<i>P</i> for trend=0.035			<i>P</i> for trend=0.519		
Frequency of sport activity						
< once/month	117/16136	1 (reference)		64/12206	1 (reference)	
1–3 times/month	9/1685	0.74	0.37, 1.45	4/3022	0.25	0.09, 0.69
1–2 times/week	7/2285	0.42	0.20, 0.90	8/1835	0.83	0.40, 1.73
≥ 3 times/week	16/2240	0.99	0.59, 1.66	8/2007	0.76	0.37, 1.58
	<i>P</i> for trend=0.215			<i>P</i> for trend=0.202		
Total energy						
Q1	34/5649	0.97	0.61, 1.56	23/4809	0.92	0.52, 1.62
Q2	43/5649	1.23	0.79, 1.92	15/4810	0.60	0.32, 1.14
Q3	38/5648	1.09	0.69, 1.72	21/4810	0.84	0.47, 1.50
Q4	35/5650	1 (reference)		25/4810	1 (reference)	
	<i>P</i> for trend=0.941			<i>P</i> for trend=0.558		
Ca intake						
Q1	45/5649	1.67	1.04, 2.68	21/4809	1.50	0.76, 2.95
Q2	42/5649	1.56	0.96, 2.52	23/4810	1.64	0.85, 3.19
Q3	36/5649	1.33	0.81, 2.19	26/4809	1.86	0.97, 3.55
Q4	27/5649	1 (reference)		14/4811	1 (reference)	
	<i>P</i> for trend=0.029			<i>P</i> for trend=0.379		
Energy-adjusted† Ca intake						
Q1	50/5649	1.92	1.20, 3.08	23/4810	1.57	0.80, 3.07
Q2	36/5649	1.38	0.84, 2.29	25/4810	1.79	0.93, 3.43
Q3	38/5649	1.46	0.89, 2.40	23/4810	1.64	0.85, 3.19
Q4	26/5649	1 (reference)		14/4809	1 (reference)	
	<i>P</i> for trend=0.011			<i>P</i> for trend=0.205		
Frequency of milk consumption						
Rarely	31/3162	1.67	1.08, 2.60	19/3315	1.62	0.87, 3.01
Occasionally	29/4147	1.19	0.76, 1.87	27/4858	1.57	0.89, 2.78
1–2 times/week	10/2325	0.73	0.37, 1.44	6/2428	0.70	0.28, 1.73
3–4 times/week	21/3251	1.10	0.67, 1.82	9/2363	1.08	0.49, 2.35
≥ 5 times/week	54/9222	1 (reference)		21/5946	1 (reference)	
	<i>P</i> for trend=0.052			<i>P</i> for trend=0.060		
Vitamin D intake						
Q1	38/5615	0.94	0.60, 1.45	25/4807	1.04	0.60, 1.82
Q2	33/5667	0.80	0.51, 1.27	13/4787	0.54	0.28, 1.07
Q3	38/5647	0.93	0.60, 1.44	22/4832	0.91	0.51, 1.63
Q4	41/5667	1 (reference)		24/4813	1 (reference)	
	<i>P</i> for trend=0.631			<i>P</i> for trend=0.780		

Table 3. Continued

	Women			Men		
	Cumulative incidence	Unadjusted RR	95 % CI	Cumulative incidence	Unadjusted RR	95 % CI
Energy-adjusted† vitamin D intake						
Q1	41/5649	0.98	0.64, 1.50	24/4810	1.09	0.61, 1.94
Q2	35/5649	0.83	0.53, 1.30	17/4810	0.77	0.41, 1.45
Q3	32/5649	0.76	0.48, 1.21	21/4810	0.95	0.53, 1.73
Q4	42/5649	1 (reference)		22/4809	1 (reference)	
	<i>P</i> for trend=1.000			<i>P</i> for trend=0.923		

Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

Cut-off values for quartiles are as follows:

Weight: 49, 53 and 58 kg for women; 57, 63 and 69 kg for men.

BMI: 21.2, 23.0 and 25.1 kg/m² for women; 21.5, 23.4 and 25.3 kg/m² for men.

Energy: 3954, 4581 and 5238 kJ (945, 1095 and 1252 kcal)/d for women; 5895, 7100 and 8556 kJ (1409, 1697 and 2045 kcal)/d for men.

Ca intake: 213, 329 and 445 mg/d for women; 219, 309 and 436 mg/d for men.

Vitamin D intake: 2.9, 4.4 and 6.3 µg/d for women; 3.3, 5.1 and 7.7 µg/d for men.

* For details of subjects and procedures, see Subjects and methods.

† Adjusted by the residual method.

in the present study, which targeted a younger population. In Japan, vertebral fractures are more common than other fractures, such as hip fractures, and are more prevalent in Japan than in Western countries^(4,26). Consequently, both patients and orthopaedists in Japan are more likely to be attentive to this type of fracture.

Several cohort studies have examined the association between Ca intake and incident vertebral fractures, but none has demonstrated a significant relationship. No association between Ca intake and morphometric vertebral fractures was

reported by Cummings *et al.*⁽²⁷⁾, whose study targeted Caucasian women in the USA aged 65 years and over (mean Ca intake 714 mg/d). Similarly, the Rotterdam Study⁽²⁸⁾, targeting Dutch men and women aged 55 years and over (mean Ca intake 1131 mg/d), found no such association either. In addition, the European Prospective Osteoporosis Study reported no association between frequency of milk consumption and morphometric vertebral fractures in men and women aged 50–79 years (mean Ca intake 1136 mg/d)⁽²⁹⁾. A lack of association between Ca intake and vertebral fracture in these three reports

Table 4. Adjusted relative risk (RR) of vertebral fractures occurring within 10 years for women and men according to quartiles of calcium intake in cohorts I and II*

	Women		Men	
	Adjusted RR†	95 % CI	Adjusted RR†	95 % CI
Ca intake in cohort I				
Q1	2.77	1.13, 6.78	0.90	0.32, 2.54
Q2	2.30	1.10, 4.84	0.79	0.34, 1.80
Q3	1.02	0.45, 2.28	0.96	0.44, 2.09
Q4	1 (reference)		1 (reference)	
	<i>P</i> for trend=0.021		<i>P</i> for trend=0.916	
Energy-adjusted‡ Ca intake in cohort I				
Q1	2.06	1.06, 4.02	1.05	0.44, 2.53
Q2	1.20	0.59, 2.45	0.53	0.20, 1.46
Q3	1.47	0.73, 2.94	1.70	0.83, 3.47
Q4	1 (reference)		1 (reference)	
	<i>P</i> for trend=0.054		<i>P</i> for trend=0.622	
Ca intake in cohort II				
Q1	1.82	0.91, 3.63	1.13	0.47, 2.73
Q2	1.60	0.91, 2.79	1.69	0.83, 3.43
Q3	1.55	0.89, 2.70	2.01	1.03, 3.94
Q4	1 (reference)		1 (reference)	
	<i>P</i> for trend=0.019		<i>P</i> for trend=0.278	
Energy-adjusted‡ Ca intake in cohort II				
Q1	1.84	1.11, 3.07	1.89	0.87, 4.12
Q2	1.36	0.81, 2.28	1.72	0.88, 3.38
Q3	1.51	0.91, 2.52	1.65	0.84, 3.26
Q4	1 (reference)		1 (reference)	
	<i>P</i> for trend=0.018		<i>P</i> for trend=0.174	

Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

* For details of subjects and procedures, see Subjects and methods.

† Adjusted for age, body weight, smoking, alcohol drinking, frequency of sport activity, area, vitamin D intake and total energy.

‡ Adjusted by the residual method.

Table 5. Meta-analysis* of relative risk (RR) of vertebral fractures occurring within 10 years for women and men according to quartiles of calcium intake in cohorts I and II†

	Unadjusted RR	95 % CI	Adjusted RR	95 % CI
Ca intake in women				
Q1	1.65	1.12, 2.42	2.13	1.23, 3.67
Q2	1.60	1.09, 2.35	1.82	1.17, 2.85
Q3	1.19	0.79, 1.80	1.35	0.86, 2.14
Q4	1 (reference)		1 (reference)	
	<i>P</i> for trend=0.004		<i>P</i> for trend=0.001	
Energy-adjusted‡ Ca intake in women				
Q1	1.93	1.32, 2.83	1.92	1.28, 2.88
Q2	1.35	0.90, 2.04	1.30	0.86, 1.98
Q3	1.43	0.95, 2.14	1.50	0.99, 2.26
Q4	1 (reference)		1 (reference)	
	<i>P</i> for trend=0.001		<i>P</i> for trend=0.002	
Ca intake in men				
Q1	1.07	0.64, 1.77	1.03	0.53, 2.01
Q2	1.16	0.71, 1.91	1.22	0.71, 2.09
Q3	1.29	0.79, 2.10	1.46	0.88, 2.44
Q4	1 (reference)		1 (reference)	
	<i>P</i> for trend=0.936		<i>P</i> for trend=0.515	
Energy-adjusted‡ Ca intake in men				
Q1	1.29	0.78, 2.15	1.46	0.82, 2.61
Q2	1.17	0.68, 2.01	1.20	0.68, 2.09
Q3	1.60	0.98, 2.58	1.68	1.02, 2.74
Q4	1 (reference)		1 (reference)	
	<i>P</i> for trend=0.646		<i>P</i> for trend=0.450	

Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile.

* Calculated from the weighted average of results from separate logistic regressions fitted to the individual cohorts.

† For details of subjects and procedures, see Subjects and methods.

‡ Adjusted by the residual method.

may be partly due to the relatively high baseline Ca intake of their target populations, as compared with the population in the JPHC Study. A meta-analysis of randomized controlled trials examining the effect of Ca supplementation showed that RR of vertebral fracture was 0.77 (95 % CI 0.54, 1.09), suggesting that Ca supplementation was providing a statistically insignificant trend toward reduction in vertebral fractures⁽³⁰⁾. Given the results of these previous studies, which studied mainly Caucasian populations with a relatively high Ca intake, Ca intake may not be a major predictor of incident vertebral fractures.

A positive result of the present study may be interpreted as lower Ca intake being associated with a higher incidence of vertebral fractures in peri- and post-menopausal populations with an already low Ca intake. There has been a similar large cohort study on hip fractures in Japan⁽³¹⁾, which reported that those who drank milk less than once per week had 1.7 times higher risk of hip fractures than those who drank milk five or more times per week. These results, much like the present study results, suggest that low Ca intake may adversely affect the incidence of fractures among the Japanese, especially in women.

Some epidemiological studies on fractures among Chinese populations have been conducted. Lau *et al.*⁽³²⁾ conducted a case-control study in the late 1980s, which showed an inverse association between Ca intake and hip fractures. Chan *et al.*⁽³³⁾ reported an OR of 2.1 (95 % CI 1.1, 3.9) for vertebral fracture, comparing the lowest quartile relative to the highest quartile. These results are consistent with the findings of the present study.

The incidence of vertebral fractures in this study was low. This may be due to the fact that the present study relied on self-reported vertebral fractures, which does not capture underlying vertebral fractures that can only be diagnosed by radiography. Fujiwara *et al.*⁽³⁴⁾ reported that the annual incidence of radiographically diagnosed vertebral fractures in Japanese women in their 50s was five per 1000 person-years. In contrast, the current study found a 10-year cumulative incidence of 0.55 % for self-reported vertebral fractures in women in the same age range, a value equivalent to about one-tenth that of the Fujiwara study. Radiographically diagnosed vertebral fractures include both symptomatic and asymptomatic fractures. It has been reported that more than 80 % of elderly Japanese women with radiographically diagnosed vertebral fractures are asymptomatic⁽³⁵⁾. On the other hand, self-reported vertebral fractures are more likely to be symptomatic. In the above-mentioned Muramatsu cohort study, all seven self-reported vertebral fractures were symptomatic. This has an important implication, suggesting that increased Ca intake may prevent symptomatic vertebral fractures in women whose habitual intake of Ca is low.

The 10-year incidence of self-reported vertebral fractures in the present study was higher in women than men with a female:male ratio of 1.4 (0.55 %:0.39 %). A study in Japanese people on the incidence of vertebral fractures, using radiographic methods that can detect asymptomatic fractures, showed that the age-adjusted incidence is twice as high in women as in men⁽³⁴⁾. Although there is a real sex difference in the incidence of vertebral fractures, the magnitude of the difference varies according to the method used to identify fractures. It has been suggested that asymptomatic vertebral fractures may be more prevalent in women than men.

The population-attributable fraction of a vertebral fracture in women for the first quartile relative to the fourth was as high as 27 %. This has important implications for vertebral fracture prevention, given the high prevalence of low Ca intake among Japanese women with high prevalence of underlying vertebral fractures.

The FFQ used in cohort II apparently underestimated nutrient intakes. The major reason for this may be that the portion sizes in the FFQ were too small⁽¹²⁾. Validation of this FFQ was conducted by comparing the FFQ data with the 7 d diet record of a subset of the sample⁽¹⁶⁾ in a standardized manner⁽¹⁷⁾. Thus, although the FFQ may give low absolute values, it is still useful in terms of the ranking of subjects.

The present study has several strengths. The JPHC Study is the largest nationwide population-based cohort study in Japan. Furthermore, a large sample size enabled us to detect vertebral fractures in middle-aged and early elderly women and men. Therefore, the results of this study can be generalized to middle-aged and early elderly people in Japan whose Ca intake is generally low. Nevertheless, the current study has some limitations. First, we used a self-report method for identifying fracture cases. Although the self-reported vertebral fractures were considered to be highly specific, they may not have been very highly sensitive. Consequently, the present results may have been biased by misclassification in identifying vertebral fractures. If the misclassification was undifferentiated, the association between Ca intake and the occurrence of vertebral fractures would be expected to attenuate towards the null. This was the major limitation of the current study. Second, like other FFQ-based studies, the accuracy (correlation with a 7 d record method) of estimating Ca intake by FFQ in this study was not high and, therefore, its potential measurement bias may have attenuated the association between Ca intake and the occurrence of vertebral fractures. Furthermore, there may have been an unknown third factor that yielded a spurious association. This possible third factor may have been physical activity level, which we did not evaluate sufficiently, and which should be further examined in future studies. Third, the present results may have been influenced by selection bias because approximately 24 % of the subjects did not return the follow-up questionnaire. On average, the difference in Ca intake between subjects who remained in the study and subjects who did not return the follow-up questionnaire was slight (6 mg/d lower for the dropouts). Therefore, the impact of selection bias in terms of Ca intake may be minimal. Fourth, we could not evaluate Ca supplementation. However, the proportion of subjects who use Ca supplements in the present population is only 0.4 % (unpublished results) and thus the effects of Ca supplementation in the present study were considered to be negligible. Finally, the present study used an observational design, which cannot eliminate all confounders. We considered many demographic and lifestyle factors as possible confounding variables; however, many other factors, including genetic factors, were not taken into account. Ideally, intervention studies are needed to remedy this problem.

The present study first demonstrated that there is an inverse association between Ca intake and clinical vertebral fractures. Our findings indicate that Japanese women, aged 40–69 years, with the lowest (approximately <350 mg/d) quartile of Ca intake had a two-fold higher risk than those with high Ca

intake (approximately ≥ 700 mg/d). This suggests that increasing the Ca intake could prevent vertebral fractures in peri- and post-menopausal female populations with low Ca intake. It then follows that Ca supplementation could be considered to increase Ca intake. Prior evidence has shown that Ca supplementation of 1000–1200 mg (plus 20 μ g vitamin D) daily reduces fracture incidence⁽³⁶⁾. However, such a high amount of Ca supplementation may prove to be too high for a low-Ca-intake population, resulting in an increase of side effects. Whether the increase of Ca intake with a lower dose of Ca could prevent vertebral fracture warrants future studies.

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