

# Natto Intake is Inversely Associated with Osteoporotic Fracture Risk in Postmenopausal Japanese Women

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## ABSTRACT

**Background:** The direct association between intake of Japanese fermented soybeans, namely natto, and bone mineral density (BMD) is known. However, the association with osteoporotic fractures has not been studied.

**Objective:** This study aimed to investigate whether habitual natto intake is associated with a risk of osteoporotic fractures.

**Methods:** This prospective cohort study included 1417 postmenopausal Japanese women who were enrolled in the Japanese Population-Based Osteoporosis cohort study in 1996, 1999, 2002, and 2006 and were aged  $\geq 45$  y at baseline. The intake of natto, tofu, and other soybean products was surveyed with use of a FFQ at baseline. Fractures were ascertained in follow-up surveys conducted in 1999, 2002, 2006, and 2011/2012. Osteoporotic fracture was the primary outcome and was defined as a clinical fracture occurring without strong external force, diagnosed with radiographs by a medical doctor. HRs with 95% CIs were estimated with Cox proportional hazard models.

**Results:** During the 17,699 person-years of follow-up (median, 15.2 y), 172 women experienced osteoporotic fractures. After adjustment for age and BMD at the total hip, the HRs compared with those of  $< 1$  pack (approximately 40 g)/wk natto intake were 0.72 (95% CI: 0.52, 0.98) and 0.51 (95% CI: 0.30, 0.87) for 1–6 and  $\geq 7$  packs/wk, respectively. After further adjustment for BMI, history of osteoporotic fractures, history of myocardial infarction or stroke, diabetes mellitus, current smoking, alcohol intake, frequency of tofu and other soybean product intakes, and dietary calcium intake, the HRs were 0.79 (95% CI: 0.56, 1.10) and 0.56 (95% CI: 0.32, 0.99) for 1–6 and  $\geq 7$  packs/wk, respectively. Frequency of tofu or other soybean product intakes had no association with the risk of osteoporotic fractures.

**Conclusions:** Habitual natto intake may be associated with a reduced risk of osteoporotic fractures independent of confounding factors, including BMD, in Japanese postmenopausal women. This trial was registered at [umin.ac.jp](http://umin.ac.jp) as UMIN 000032869. *J Nutr* 2020;150:599–605.

**Keywords:** fermented soybeans, natto, osteoporotic fracture, prospective cohort study, postmenopausal women

## Introduction

Osteoporotic fractures are associated with an increased risk of subsequent fractures (1) and mortality (2), creating a considerable financial burden for healthcare systems worldwide (3). Japanese fermented soybeans, namely natto, are rich in vitamin K, which plays an important role in bone formation. Vitamin K acts as a cofactor for  $\gamma$ -glutamyl carboxylase, which is an enzyme that converts glutamate residues of osteocalcin into  $\gamma$ -carboxyglutamate residues. This  $\gamma$ -glutamyl carboxylase facilitates binding of carboxylated osteocalcin with calcium ions in the bone tissue; this is followed by binding to bone

hydroxyl apatite (4). Insufficiency of vitamin K increases serum undercarboxylated osteocalcin, as a result of the insufficient carboxylation of osteocalcin. Natto is particularly rich in menaquinone-7 (MK-7), a variant of vitamin K, which is synthesized by bacteria (5). One portion size of natto is usually 1 pack (approximately 40 g), which contains 350  $\mu$ g of MK-7 (6). A previous analysis in 517 postmenopausal women from our cohort found that natto intake was associated with a reduction in bone loss at the femoral neck during a follow-up period of 3 y (7). A cross-sectional study in Japanese men aged  $\geq 65$  y demonstrated that the bone mineral density

(BMD) at the femoral neck was significantly higher in those who had higher natto intake ( $\geq 7$  packs/wk compared with  $< 1$  pack/wk) (8).

An ecological study found an inverse association between natto intake and the incidence of hip fractures in Japan (9, 10). However, to our knowledge, no prospective cohort study has evaluated this association. The present study aimed to evaluate the association between habitual natto intake and the risk of osteoporotic fractures in Japanese postmenopausal women with data from a large prospective cohort study.

## Methods

### Participants

The present study was conducted as part of a large cohort study (the Japanese population-based osteoporosis study) (11) and involved 5 municipalities (Supplementary Figure 1). We recruited healthy women aged 15–79 y, randomly selected from the resident registry of each municipality in 1996. The follow-up surveys were conducted in 1999, 2002, 2006, and 2011/2012. The present study included women aged  $\geq 45$  y who were postmenopausal at enrollment, baseline, or during the follow-up surveys in 1999, 2002, and 2006 (Figure 1). Menopause was defined as the absence of menstruation for at least a year. Women with unclear timing of onset of menopause were included if they were aged  $\geq 53$  y at enrollment. Women with a history of total hysterectomy aged  $\geq 53$  y at enrollment were included. The age of 53 y was selected as the cutoff, as the median age of natural menopause (12). The exclusion criteria were as follows: women who were postmenopausal as a result of disease; those with missing data on total hip BMD, natto intake, frequency of tofu and other soybean product intake, and smoking habit; and those who were lost to follow-up ( $n = 144$ ). Finally, 1592 women were enrolled, as 1348, 47, 116, and 81 participants in 1996, 1999, 2002, and 2006, respectively (as shown in Figure 1).

### Osteoporotic fractures

Interviews at each follow-up survey in 1999, 2002, 2006, and 2011/2012 obtained details on every fracture event, including the skeletal site of fracture, situation in which the fracture occurred, and whether the fracture was diagnosed by radiography. In addition, supplemental mail surveys were conducted in 2006 and 2011/2012 for nonparticipants of the follow-up surveys to obtain data on the occurrence of clinical fractures. In 2011, a mail survey was conducted instead of a follow-up survey among all baseline participants in Miyakojima. Information provided on fracture events was confirmed by trained public health nurses through face-to-face interviews during follow-up surveys, or telephone interviews in those who responded to the supplemental mail surveys. We defined an osteoporotic fracture as a clinical fracture that was diagnosed by a medical doctor based on radiographic reports and occurred without strong external force at the

following skeletal sites: neck, clavicle, rib, proximal humerus, proximal or distal elbow joint, distal forearm, vertebra, pelvis, or hip. In cases of multiple fracture events, data on the first fracture during the follow-up period were used for analysis.

### Bone mass

The BMD was measured at enrollment in the right hip by certified radiological technologists through use of DXA (QDR 4500A, Hologic) (13). The short-term coefficient variation of the BMD measurement in vivo, as calculated on the basis of 5 measurements on different days for each of 5 volunteers, was 1.2% for the total hip (13).

### Body size

The height (cm) and weight (kg) of the participants were measured with an automatic scale (TK-11,868 h, Takei Kagaku). The BMI was calculated as weight divided by height squared ( $\text{kg}/\text{m}^2$ ).

### Interviews

Detailed interviews were conducted by trained public health nurses both at baseline and during follow-up surveys to confirm the questionnaire responses. The questionnaire included items on age at menopause, smoking habit (never, past, or current), frequency of alcohol intake (nondrinker,  $< 1$ , 1, 2, 3, 4, 5, 6, or  $\geq 7$  times/wk), milk intake (seldom, 200 mL/wk, 600–800 mL/wk, 200 mL/d, or  $\geq 400$  mL/d), history of disease, and present disease.

We used FFQ that were validated to estimate dietary calcium intake (14). Detailed interviews on the FFQ were conducted by trained dietitians. In the interviews, the usual amounts of intakes of natto, tofu, and other soybean products at 1 time were determined by comparison with reference food samples. The response options in the FFQ for these foods were seldom, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, 1 time/d, 2 times/d, or 3 times/d. Natto is sold in a plastic pack, which usually contains about 40 g; this is considered to be suitable for a meal in Japan. The portion sizes of tofu (bean curd), ground soybean, green soybeans, and boiled soybeans were 75, 17.5, 140, and 45 g/serving, respectively.

### Ethics

We individually obtained written informed consent for all study procedures before baseline and during every follow-up survey. The study protocol was approved by the Ethical Committee of the Kindai University, Faculty of Medicine.

### Statistics

The value of dietary calcium intake was log-transformed for data analysis and presented as a geometric mean with 95% CI. The characteristics of the categories of natto intake were tested with Cuzick's test for trends. Analysis of covariance was used to examine age-adjusted BMD at the total hip according to natto intake. The HRs with 95% CIs for the risk of osteoporotic fracture, the primary outcome of the present study, were estimated with the Cox proportional hazards regression model. The follow-up period was calculated from the date of baseline measurement to the date of the first fracture event, date of the last follow-up survey, the responded date for the mail survey in individual participants without fracture events, or the date of death. In the interview in the follow-up surveys, we asked for the age at which the event occurred (e.g., if a patient had a fracture at the age of 30 y, the age was 30.5 y). In the mail survey, which was conducted for nonparticipants of the follow-up surveys in 2006 and 2011/2012 and for all baseline participants in Miyakojima in 2011, we asked for the year and month in which the fracture event occurred. According to the response distribution data in the FFQ, the frequencies for consuming foods were classified into 3 categories. These variables were modeled with dummy terms;  $< 1$  pack/wk, 1–6 packs/wk, and  $\geq 7$  packs/wk for natto;  $\leq 2$  times/wk, 3–6 times/wk, and  $\geq 7$  times/wk for tofu; and  $< 1$  time/wk, 1–6 times/wk, and  $\geq 7$  times/wk for other soybean products with use of the lowest serving category as the reference group, respectively. A history of myocardial infarction (MI) or stroke was included in the models because patients with these diseases are prescribed anticoagulant medication which affects vitamin K function

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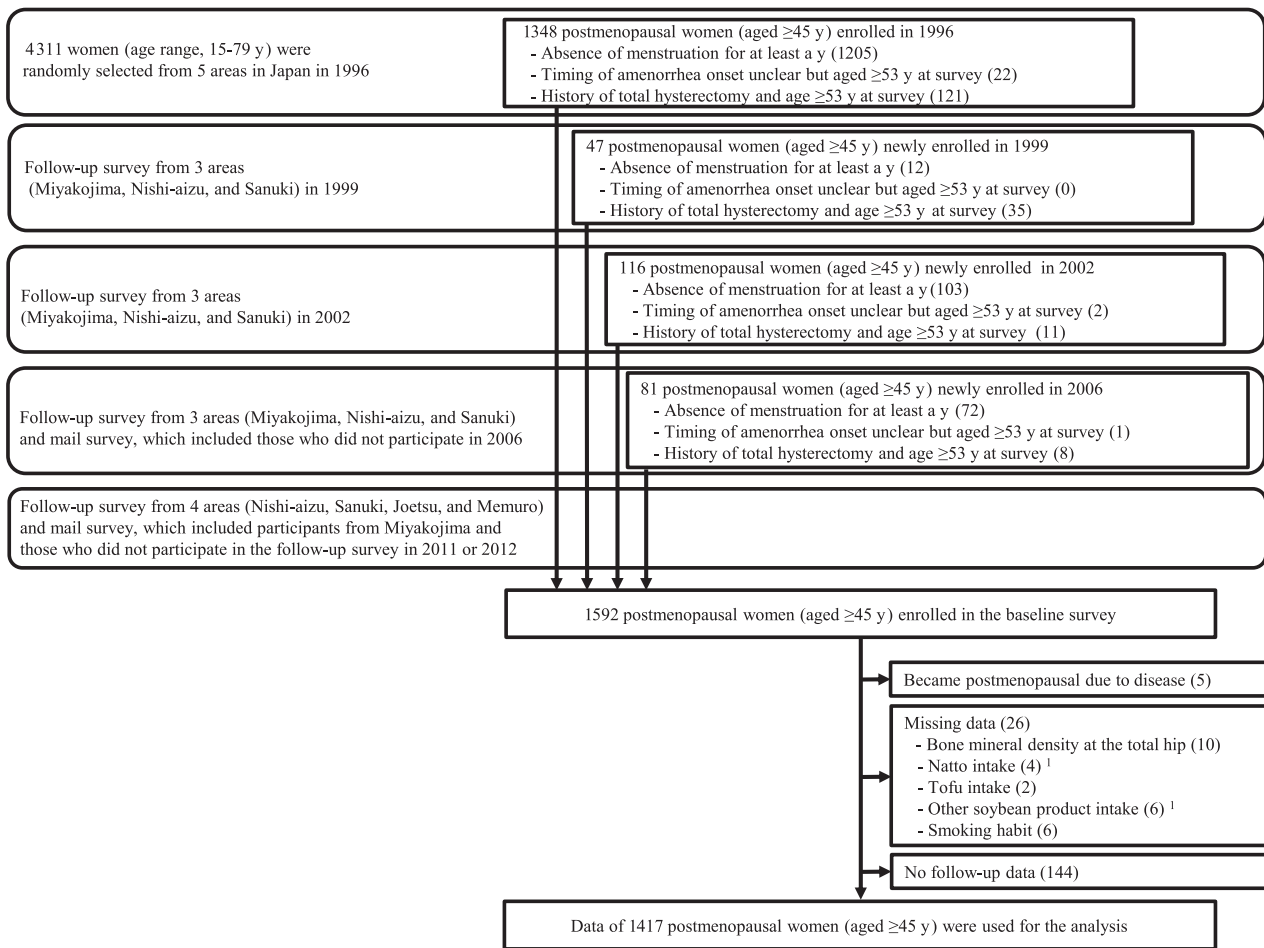
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Data sharing: Data described in the manuscript, code book, and analytic code will not be made available because we are still preparing other reports with the data set.

Supplementary Table 1 and Supplementary Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/jn>.

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Abbreviations used: BMD, bone mineral density; MI, myocardial infarction; MK-7, menaquinone-7.



**FIGURE 1** Flow chart of the participants in the Japanese population-based osteoporosis study. The figures in parentheses represent the number of participants. <sup>1</sup>Two women had unavailable data on both natto and other soybean product intake.

(15, 16); moreover, they are prohibited from eating natto (17). The presence of diabetes mellitus (yes/no), which is known to increase undercarboxylated osteocalcin (18, 19), was entered into the model. Smoking habits and the frequency of alcohol intake were classified into 2 categories: current smoker (yes/no) and alcohol intake  $\geq 3$  times/wk (yes/no).

A test to determine the trend of association between the risk of fractures and the categories of food intake frequency was conducted with factors of 1.0, 3.5, and 7.0 for natto (<1, 1-6, and  $\geq 7$  packs/wk); 1.5, 3.5, and 7.0 for tofu ( $\leq 2$ , 3-6, and  $\geq 7$  times/wk); and 1.0, 1.5, and 7.0 for other soybean products (<1, 1-6, and  $\geq 7$  times/wk).

We used the following models to investigate the relation with the risk of osteoporotic fractures. Models I-IV were used to evaluate the association of natto intake. Model I was adjusted for age and BMD. Model II was further adjusted for BMI, history of osteoporotic fractures, history of MI or stroke, and the presence of diabetes mellitus. Model III was additionally adjusted for current smoking, alcohol intake, and frequency of intake of tofu and other soy products. Model IV was additionally adjusted for dietary calcium intake. We used Models V and VI to evaluate for an association with the frequency of tofu intake. Model V was adjusted for current smoking, alcohol intake, and frequency of intake of natto and frequency of intake of other soybean products in addition to Model II. Model VI was further adjusted for dietary calcium intake. Models VII and VIII were used to evaluate for an association with the frequency of other soybean products intake. Model VII was adjusted for current smoking, alcohol intake, and intake of natto and frequency of tofu in addition to Model II. Model VIII was further adjusted for dietary calcium intake. The Stata statistical software (version 14; Stata Corporation) package was used for all statistical analyses and values of  $P < 0.05$  were considered significant.

## Results

During a median follow-up of 15.2 y (IQR: 10.1-15.4 y; total 17,699 person-years), 172 osteoporotic fractures occurred.

Table 1 shows the demographic and lifestyle characteristics according to the natto intake. The prevalence of natto intakes of < 1, 1-6, and  $\geq 7$  packs/wk were 37.5%, 49.2%, and 13.3%, respectively. Women with higher natto intake demonstrated a lower incident osteoporotic fracture rate, had higher BMD, and higher dietary calcium intake. Compared with women with natto intakes of < 1 pack/wk, women with intakes of  $\geq 7$  packs/wk demonstrated a higher prevalence of habitual intakes of milk ( $\geq 200$  mL/d), tofu ( $\geq 7$  times/wk), and other soybean products ( $\geq 7$  times/wk) (Table 1). The age-adjusted BMD values in women stratified by natto intake were  $0.746 \pm 0.005$  g/cm<sup>2</sup> (<1 pack/wk),  $0.763 \pm 0.004$  g/cm<sup>2</sup> (1-6 packs/wk), and  $0.763 \pm 0.008$  g/cm<sup>2</sup> ( $\geq 7$  times/wk) ( $P = 0.050$ ).

HRs for the risk of osteoporotic fractures based on natto intake are shown in Table 2. Natto intake was inversely associated with the risk of osteoporotic fractures. Compared with those consuming < 1 pack/wk, the age-adjusted HRs for those consuming 1-6 and  $\geq 7$  packs/wk were significantly lower. The HR for those consuming  $\geq 7$  packs/wk was still significant after adjusting for age, BMD, BMI, history of osteoporotic fractures, history of MI or stroke, the presence of diabetes mellitus, current smoking, alcohol intake, frequency of intake of tofu and other soy products, and dietary calcium intake (Model

**TABLE 1** Comparison of characteristics according to natto intake among postmenopausal women<sup>1</sup>

	All subjects	Frequency of natto intake			P-trend <sup>2</sup>
		< 1 pack/wk	1–6 packs/wk	≥7 packs/wk	
Number of participants	1417	531 (37.5)	697 (49.2)	189 (13.3)	—
Incident osteoporotic fractures	172 (12.1)	80 (15.1)	76 (10.9)	16 (8.5)	0.008
History of osteoporotic fractures	101 (7.1)	41 (7.7)	43 (6.2)	17 (9.0)	0.812
Age, y	63.5 ± 8.4	64.4 ± 8.5	62.5 ± 8.2	64.3 ± 8.5	0.298
BMI, kg/m <sup>2</sup>	24.0 ± 3.4	23.9 ± 3.4	24.0 ± 3.5	23.9 ± 3.2	0.849
Current smoker	53 (3.7)	20 (3.8)	28 (4.0)	5 (2.6)	0.584
Frequency of alcohol intake, ≥3 times/wk	108 (7.6)	29 (5.5)	64 (9.2)	15 (7.9)	0.112
Dietary calcium intake, mg/d	643 [630–656]	550 [533–567]	677 [659–695]	829 [787–875]	<0.001
Milk intake, <sup>3</sup> ≥200 mL/d	1108 (78.3)	373 (70.5)	568 (81.5)	167 (88.4)	<0.001
Frequency of tofu intake, ≥7 times/wk	419 (29.6)	158 (29.8)	172 (24.7)	89 (47.1)	<0.001
Frequency of other soybean product intake, <sup>4</sup> ≥7 times/wk	149 (10.5)	39 (7.3)	67 (9.6)	43 (22.8)	<0.001
Bone mineral density at the femoral neck, g/cm <sup>2</sup>	0.757 ± 0.123	0.739 ± 0.122	0.770 ± 0.119	0.757 ± 0.131	0.009
History of myocardial infarction or stroke <sup>5</sup>	22 (1.6)	4 (0.8)	14 (2.0)	4 (2.1)	0.112
Presence of diabetes mellitus <sup>6</sup>	50 (3.5)	23 (4.3)	21 (3.0)	6 (3.2)	0.334

<sup>1</sup>Values are arithmetic means ± SDs, geometric means [95% CI], or frequency (percentage), unless otherwise indicated, *n* = 1417.

<sup>2</sup>The characteristics of the categories of natto intake were tested with Cuzick's test for trends.

<sup>3</sup>Calculated among 1415 participants (529, 697, and 189 participants: < 1 pack/wk, 1–6 packs/wk, and ≥7 packs/wk, respectively).

<sup>4</sup>Soybean products other than natto and tofu.

<sup>5</sup>Participants with self-reported history of myocardial infarction or stroke from the questionnaire.

<sup>6</sup>Participants with self-reported present history of diabetes mellitus from the questionnaire.

IV). The frequency of intake of tofu or other soybean products was not associated with the risk of osteoporotic fractures (Table 2).

After exclusion of 22 participants with MI and stroke from the analysis, the statistical significance of the HR for those ≥7 packs/wk was attenuated, but a significant trend was still demonstrated (Supplementary Table 1).

## Discussion

This prospective cohort study demonstrated that a higher natto intake was associated with a reduced risk of osteoporotic fractures in Japanese postmenopausal women during a median follow-up period of 15.2 y. This association was independent of not only classical risk factors for fractures such as age, BMI, BMD at the total hip, history of osteoporotic fractures, current smoking, alcohol intake, and the presence of diabetes mellitus, but also potential confounding factors such as dietary calcium intake, the frequency of intake of tofu or other soy products, and history of MI or stroke. The findings in the present study also showed that a natto intake of ≥7 packs/wk was significantly associated with a 44% reduced risk of osteoporotic fractures, compared with a natto intake of < 1 pack/wk, after adjustments for the aforementioned covariates.

This was the first prospective cohort study to show the association between the intake of natto and the risk of osteoporotic fractures in community-dwelling women. MK-7 facilitates osteocalcin  $\gamma$ -carboxylation, which is a surrogate marker of bone turnover (20–22), damage accumulation (23), and mineralization (22). MK-7 supplementation for 3 y in Caucasian postmenopausal women showed that compared to placebo, MK-7 supplementation showed beneficial effects in cases of BMD loss after the second year, whereas MK-7 supplementation worked more effectively and faster in terms of the impact strength index from the first to the third year. Thus, MK-7 may affect fragility more than density (24). In addition to BMD, bone fragility is associated with bone quality, including microarchitecture (25, 26). Therefore, the benefits of natto in

preventing bone fragility may not only be mediated through preservation of bone mass, but also through maintenance of bone microarchitecture. MK-7 is known to maintain the bone microarchitecture including the number, spacing, and thickness of trabecular bone (27), which is a determinant of bone fragility (28). Menaquinones are also produced by the intestinal bacterial flora (29, 30). There may be a link between the microbiome and bone fragility through the production of menaquinones in the gut, based on some animal experiments (31, 32).

Natto is also rich in isoflavones, which have a beneficial effect on the reduction of bone loss (33) and stimulation of bone formation (34). In our cohort, the intakes of tofu and other soybean products, which were also rich in isoflavones, were not associated with the risk of osteoporotic fractures. This may be explained by the difference in the type of isoflavones contained in natto, tofu, and other soybean products. Natto contains more isoflavone aglycone than tofu or other soy products per 1 portion size (35). In humans, isoflavone aglycones are absorbed faster, and may be more bioavailable than isoflavone glycosides which are included in nonfermented foods such as tofu and other soybean products (36). One portion size of natto contains a 1.3–1.5-fold higher amount of isoflavone aglycones than that in tofu and green soybeans (37). Furthermore, natto is rich in genistein, a variant of isoflavone aglycone. In a randomized controlled trial, the BMD at lumbar spine and femoral neck had increased in the group with genistein of 54 mg/d for 2 y (38). Therefore, we speculate that in addition to the beneficial effects of MK-7, the rich isoflavone aglycone content of natto would contribute to prevent bone fragility.

This study has several limitations. First, we used an FFQ for estimating dietary calcium intake; therefore, we could not adjust for energy intake. It is possible that the participants who consumed larger amounts of natto may have had higher energy intake, which could have contributed to the protective effect against osteoporotic fractures. This possible confounding factor may have been controlled by the adjustments for BMI in the present analysis. However, we admit that the association found between higher intake of natto and a lower risk of osteoporotic fractures in this study should be interpreted with

**TABLE 2** HRs and 95% CIs of the risk of osteoporotic fractures according to natto intake, frequency of tofu intake, and intake of other soy products among postmenopausal women<sup>1</sup>

	Natto intake <sup>2</sup>			P-trend
	< 1 pack/wk HR (95% CI)	1–6 packs/wk HR (95% CI)	≥7 packs/wk HR (95% CI)	
Crude model	1	0.67 (0.49, 0.91)	0.50 (0.29, 0.85)	0.002
Age-adjusted model	1	0.70 (0.51, 0.96)	0.49 (0.29, 0.84)	0.003
Adjusted Model I <sup>3</sup>	1	0.72 (0.52, 0.98)	0.51 (0.30, 0.87)	0.005
Adjusted Model II <sup>4</sup>	1	0.73 (0.53, 1.00)	0.51 (0.30, 0.88)	0.006
Adjusted Model III <sup>5</sup>	1	0.75 (0.54, 1.03)	0.51 (0.30, 0.89)	0.009
Adjusted Model IV <sup>6</sup>	1	0.79 (0.56, 1.10)	0.56 (0.32, 0.99)	0.032
	Frequency of tofu intake			
	≤ 2 times/wk HR (95% CI)	3–6 times/wk HR (95% CI)	≥7 times/wk HR (95% CI)	P-trend
Crude model	1	0.84 (0.56, 1.25)	0.97 (0.63, 1.47)	0.841
Age-adjusted model	1	0.86 (0.58, 1.28)	0.95 (0.62, 1.45)	0.964
Adjusted Model I <sup>3</sup>	1	0.86 (0.58, 1.28)	0.95 (0.62, 1.45)	0.950
Adjusted Model II <sup>4</sup>	1	0.86 (0.58, 1.28)	0.92 (0.60, 1.41)	0.910
Adjusted Model V <sup>7</sup>	1	0.88 (0.59, 1.31)	0.95 (0.62, 1.46)	0.990
Adjusted Model VI <sup>8</sup>	1	0.93 (0.62, 1.41)	1.06 (0.67, 1.68)	0.655
	Frequency of intake of other soybean products			
	< 1 time/wk HR (95% CI)	1–6 times/wk HR (95% CI)	≥7 times/wk HR (95% CI)	P-trend
Crude model	1	0.76 (0.55, 1.05)	0.84 (0.50, 1.42)	0.810
Age-adjusted model	1	0.74 (0.54, 1.02)	0.79 (0.47, 1.34)	0.683
Adjusted Model I <sup>3</sup>	1	0.74 (0.54, 1.02)	0.81 (0.48, 1.36)	0.742
Adjusted Model II <sup>4</sup>	1	0.76 (0.55, 1.05)	0.86 (0.51, 1.45)	0.894
Adjusted Model VII <sup>8</sup>	1	0.81 (0.58, 1.12)	0.99 (0.57, 1.69)	0.754
Adjusted Model VIII <sup>6</sup>	1	0.85 (0.61, 1.20)	1.08 (0.62, 1.90)	0.527

<sup>1</sup> Values are HRs (95% CIs) obtained from Cox proportional hazards analysis; a total of 1417 women contributed 17,699 person-years to this analysis; the total fracture count was 172.

<sup>2</sup> The frequency for listed foods was classified into 3 categories, which were modeled with dummy terms with the lowest serving category as the reference group.

<sup>3</sup> Adjusted for age and bone mineral density at the total hip.

<sup>4</sup> Adjusted for all factors in Model I plus BMI, history of osteoporotic fractures, history of myocardial infarction or stroke, and presence of diabetes mellitus.

<sup>5</sup> Adjusted for all factors in Model II plus current smoking, alcohol intake (≥3 times/wk), and frequency of intake of tofu and other soybean products.

<sup>6</sup> Adjusted for all factors in Models III, V, or VII plus dietary calcium intakes.

<sup>7</sup> Adjusted for all factors in Model II plus current smoking, alcohol intake (≥3 times/wk), and frequency of intake of natto and other soybean products.

<sup>8</sup> Adjusted for all factors in Model II plus current smoking, alcohol intake (≥3 times/wk), and frequency of natto and tofu intake.

caution. Second, only information about dietary intake at the time of enrollment was used. There might be within-person variability over time during the relatively long follow-up period in this study. Third, because we obtained information with FFQs, the amounts of consumption for natto, tofu, and the other soybean products may have been wrongly reported. However, errors in natto intake were unlikely with this product, because natto is sold in standard pack sizes of 40 g. Regarding the frequency of intake of tofu and other soybean products, they are sold in various pack sizes, which could cause errors. These errors may have attenuated the true association between the frequency of intake of tofu and other soy products and the risk of osteoporotic fractures. Fourth, participants with MI or stroke may have been receiving warfarin for treatment and prevention of thromboembolic events, including venous thrombosis and pulmonary embolism. Patients prescribed warfarin are prohibited from eating natto, as the anticoagulant effect of warfarin may be suppressed by vitamin K. However, the results were similar after excluding participants with a history of MI and stroke. Fifth, because we did not investigate supplement intake, the intake of supplements may have affected our results. However, in Japan, the proportion of those who habitually took supplements was 20% in 2001, lower than that of Western countries (39–41); therefore, the effect of

vitamin K supplementation would be small in the present study. Sixth, the fracture events were self-reported and not based on medical records, but self-reports of forearm, spine, and hip fractures have been shown to be relatively accurate compared to the fracture registry based on medical records (42, 43).

The present study was superior to previous studies with respect to the study design. Participants in a baseline study included a large sample, including women selected randomly from 5 municipalities throughout Japan; the baseline participation rate was high at 87.6% (13).

The findings from the present study suggest that in Japanese postmenopausal women, habitual natto intake may be associated with a decreased risk of osteoporotic fractures, independent of confounding factors, including BMD. The beneficial effects of natto on fractures may also be attributed to the maintenance of bone quality.

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