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Vitamin K intake levels are associated with bone health in people aged over 50 years: a NHANES-based survey

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Background: Bone health is important for older adults, and vitamin K (VK) is central to regulating bone formation and promoting bone health. However, whether VK can reduce the risk of osteoporosis and bone loss is unclear. This study hypothesized that different levels of VK intake exert varying effects on bone health in people aged over 50 years.

Methods: Individuals aged above 50 years were recruited from the National Health and Nutrition Examination Survey. VK intake, based on 24-h dietary recall, was divided into three groups, namely the high, medium, and low groups, by sex and tertile. Weighted multiple logistic regression was used to investigate the effects of VK intake on the risk of osteoporosis and bone loss at the femoral neck, trochanter, intertrochanter, total femur, lumbar spine, and overall.

Results: This study included 5,075 individuals. Of them, 1,001 (18%) had osteoporosis (808 women, 83%) and 2,226 (46%) had osteopenia (1,076 women, 54%). Overall, a medium level of VK intake was associated with a reduced risk of bone loss. In women, medium- [odds ratio, OR (95% confidence interval, CI): 0.66(0.47, 0.93)] and high-level [OR (95% CI): 0.71(0.52, 0.98)] VK intake were associated with a decreased risk of osteoporosis. In contrast, only medium-level VK intake was associated with a reduced risk of bone loss [OR (95% CI): 0.58(0.41, 0.81)]. Similar results were obtained for the trochanter, intertrochanter, total femur, and lumbar spine. In men, only medium-level VK intake was associated with a reduced risk of bone loss at the femoral neck [OR (95% CI): 0.66(0.48, 0.90)], whereas high-level VK intake corresponded to a reduced risk of bone loss to the lumbar spine [OR (95% CI): 0.68(0.47, 0.99)]. Nonetheless, VK intake levels did not affect the risk of osteoporosis.

Conclusion: This study demonstrates sex- and bone-site-specific variations in the associations between VK intake levels and bone health in individuals aged over 50 years. Further large-scale cohort studies or randomized controlled trials are warranted to explore the effects of different VK intake levels on bone health in people regardless of their sex and bone site.

KEYWORDS

vitamin K, osteoporosis, bone loss, bone health, National Health and Nutrition Examination Survey, NHANES

1 Introduction

Osteoporosis is a common multifactorial systemic metabolic skeletal disorder. It is characterized by low bone mass, degraded skeletal tissue microstructure, bone fragility, and susceptibility to fracture (1–3). As an age-increasing disease, osteoporosis is one of the key causes of disability and mortality in older adults. Its incidence is gradually increasing in older adults, imposing an enormous economic and health burden (4–7). In Europe, osteoporosis affects approximately 32 million people aged over 50 years, resulting in an average of one fracture every 3 s (8, 9). In the US, 10.3% of people aged over 50 years have osteoporosis and 43.9% have osteopenia, with higher rates in women. One in two women and one in four men experience an osteoporosis-related fracture (10–12). Each year, approximately 700,000 osteoporotic vertebral compression fractures are reported in the US alone, imposing economic burdens of approximately \$13.8 billion, which will increase with an aging population (13–15).

Osteoporosis is the culmination of multiple factors, such as genetics, individual lifestyle, and nutrition (5). Of them, diet is an important factor affecting bone health. Vitamin K (VK) is a series of derivatives of 2-methyl-1,4-naphthoquinone, which is essential for maintaining normal blood clotting and inhibiting vascular calcification in the body. Moreover, it is central to bone metabolism (16).

Bone metabolism is a repetitive process of bone resorption and formation, termed “bone remodeling.” The appearance and apoptosis of osteoblasts and osteoclasts are essential for maintaining bone remodeling and ensuring bone strength (17). With age, osteoblast production and the bioavailability of testosterone and estradiol decrease, causing the apoptosis of osteoblasts and osteocytes. This results in an imbalance in bone remodeling and progressive bone loss, eventually leading to reduced bone mass and osteoporosis (18). After menopause in women, estrogen levels decrease, which stimulates osteoclast differentiation and activity and inhibits osteoblasts, thereby accelerating bone loss (17, 19). However, VK stimulates osteoblasts and inhibits osteoclasts, thereby promoting bone calcification, which is beneficial for delaying bone loss and reducing the risk of osteoporotic fractures (20). Osteoblasts synthesize VK-dependent gamma-carboxyglutamic acid (Gla) protein, bone Gla protein (BGP or osteocalcin), a low-molecular-weight protein in the region of rapid bone growth. It induces osteoblastic progenitors and regulates calcium phosphate ossification, which serves as a marker of bone formation (21, 22). As a cofactor, VK is required for the γ -carboxylation of osteocalcin. Moreover, the glutamate in osteocalcin undergoes γ -carboxylation for osteocalcin to bind calcium ions and hydroxyapatite to mineralize bone and promote bone formation (22–24).

However, the impact of VK on bone health is controversial. VK supplementation maintains bone mineral density (BMD) in postmenopausal women; however, it has also been found that VK supplementation reduces BGP undercarboxylation without affecting BMD (25–29). Additionally, VK supplementation is associated with BGP carboxylation in a dose–response manner; the higher the VK supplementation, the lower the BGP undercarboxylation (30, 31). However, the associations between VK intake levels and the risk of osteoporosis and bone loss are unclear. Therefore, in this cross-sectional study, we hypothesized that different VK intake levels will exert varying effects on osteoporosis or bone loss in individuals aged over 50 years, where higher VK intake promotes or maintains bone health and contributes to a reduced risk of osteoporosis and bone loss.

2 Materials and methods

2.1 Study participants

The National Health and Nutrition Examination Survey (NHANES) is a complex, multistage, cross-sectional study based on probability sampling. It is updated every 2 years to assess the health and nutritional status of the US population. The NHANES conducts household interviews and physical examinations through the mobile examination center (MEC) throughout the US to collect information on sociodemographics, lifestyle, dietary intake, behavioral status, and medical conditions. The NHANES was approved by the National Center for Health Statistics Ethics Review Board, and all participants signed informed consent forms.

For this study, data from four NHANES cycles (2007–2008, 2009–2010, 2013–2014, and 2017–2020 Prepandemic) were extracted and analyzed (BMD data were unavailable for the 2011–2012 and 2015–2016 cycles). People aged over 50 years with complete dietary and BMD data were included. The exclusion criteria were as follows: missing individuals or who refused to respond to questions about age, sex, income level, education, hypertension, diabetes, smoking status, alcohol consumption, and so on. A total of 46,421 individuals were enrolled in the four cycles. After the screening, 5,075 individuals were finally included. Figure 1 illustrates the flow chart of sample screening. This study used publicly available deidentified data from NHANES; therefore, ethical approval was not needed.

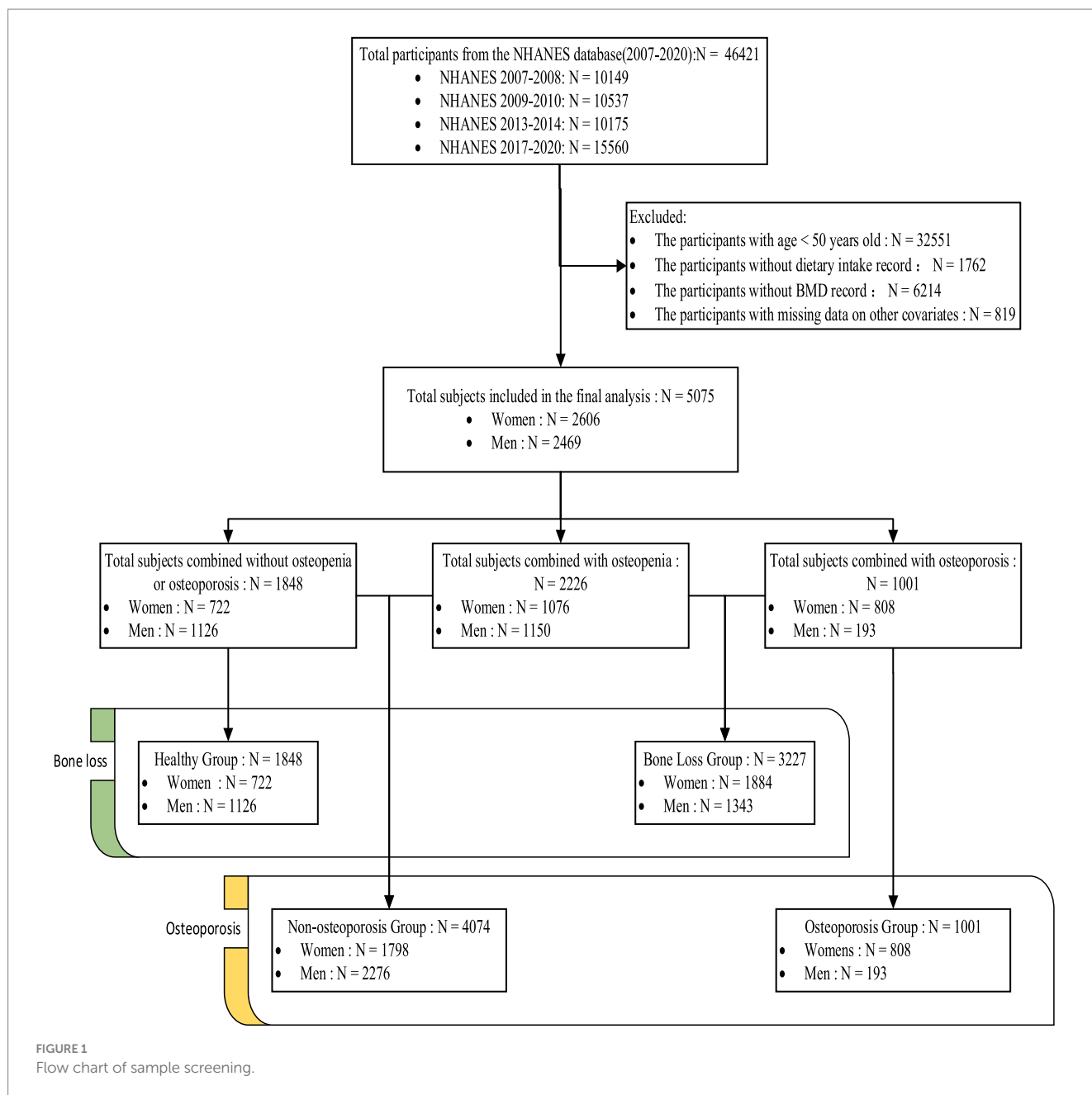
2.2 Dietary intake

The NHANES uses the 24-h dietary recall method to investigate the dietary and supplement intake of all participants. The participants received their first 24-h dietary survey at the MEC and completed a second survey via telephonic follow-up within 3 to 10 days. The responses were processed through the US Department of Agriculture's Food and Nutrition Database for Dietary Studies to calculate the nutrient intake.

Daily intake included dietary and nutritional supplement intake. The average intake over 2 days was calculated as the intake of the participant who responded to 2 days of the dietary survey; the intake over day 1 was calculated as the intake otherwise. Additionally, VK intake was defined as the major exposure factor; vitamin D (VD), vitamin C (VC), calcium, phosphorus, sodium, energy, protein, and caffeine were considered potential confounders for further analysis. Moreover, considering the differences in recommended VK and dietary intake between men and women, VK intake was divided into three levels according to sex and tertile as follows: low (<65.95 mcg/d for women, <69.85 mcg/d for men), medium (\geq 65.95 mcg/d and <129.40 mcg/d for women, \geq 69.85 mcg/d and <128.75 mcg/d for men), and high (\geq 129.40 mcg/d for women, \geq 128.75 mcg/d for men) (32).

2.3 Defining osteoporosis/osteopenia

Dual-energy X-ray absorptiometry (DXA) was utilized in the NHANES to measure BMD. The examination was conducted via a Hologic QDR-4500A sector beam densitometer (Hologic; Bedford, MA, USA), and all data were analyzed via Hologic APEX software (version 4.0).



The participants were diagnosed as healthy or with osteopenia/osteoporosis. All participants were defined as having osteoporosis/osteopenia based on osteoporosis (OSQ) questionnaires and the BMD of the femoral neck, trochanter, intertrochanter, total femur, and lumbar spine. The lumbar spine BMD was determined by calculating the mean BMD from L1 to L4. The participants were diagnosed with osteoporosis/osteopenia if they met the diagnostic criteria for osteoporosis/osteopenia at any site, and the remaining were considered healthy. Osteoporosis/osteopenia was diagnosed according to the WHO's recommendation, with the mean BMD of non-Hispanic white people aged 20–29 years in NHANES III used as the reference value (33–35). A BMD ≥ 2.5 standard deviations (SD) below the reference value indicated osteoporosis, whereas a BMD between 1 and 2.5 SD of the reference value indicated osteopenia (36). Participants with osteoporosis were also defined as those who reported an osteoporosis

diagnosis in the OSQ questionnaire. The participants were divided into osteoporosis and non-osteoporosis (including healthy and osteopenia) groups to analyze the associations between VK intake and the risk of osteoporosis; and they were divided into the healthy and bone loss (including osteopenia and osteoporosis) groups to analyze the associations between VK intake and the risk of bone loss.

2.4 Covariates

Considering the potential influence of other factors, the following covariates were included: age (50–59, 60–69, 70–79, ≥ 80 years), race (non-Hispanic White, non-Hispanic Black, Mexican American, other Hispanic, and other race/multiracial), education level (less than college, college or above), income level (based on the ratio of family

income to poverty: low (<1.3), medium (≥ 1.3 and <3.5), and high (≥ 3.5), body mass index (BMI; underweight, normal, overweight, and obesity), smoking status (never smoked, ever smoked, and current smoker), drinking status (never drank, nondrinking past 12 months, ≤ 1 drink per month, and >1 drink per month), diabetes status (diabetes, prediabetes, and healthy), hypertension status (yes, no), sedentary time (<8 h, ≥ 8 h), family history of osteoporosis (yes, no), history of prednisone or cortisone use (yes, no), history of estrogen use (yes, no), and dietary intake of VD (mcg/d), VC (mg/d), calcium (mg/d), phosphorus (mg/d), sodium (mg/d), energy (kcal/d), protein (g/d), and caffeine (mg/d).

In the NHANES, data were collected at all study sites by trained personnel with standardized procedures. Dietary intake data were obtained from the Dietary Interview - Total Nutrient Intakes, First/Second Day (DR1TOT/DR2TOT) and the Dietary Supplement Use 24-Hour - Total Dietary Supplements, First/Second Day (DS1TOT/DS2TOT) documents. They were processed and included in the model as continuous variables for subsequent analysis. Age, race, education, and income level were collected from the Demographic Variables and Sample Weights (DEMO) file; BMI from the Body Measures (BMX) file; smoking status from the Smoking - Cigarette Use (SMQ) file; drinking status from the Alcohol Use (ALQ) file; diabetes status from the Diabetes (DIQ) file; hypertension status from the Blood Pressure and Cholesterol (BPQ) file; sedentary time from the Physical Activity (PAQ) file; family history of osteoporosis and a history of prednisone or cortisone use from the OSQ file; and history of estrogen use from the Reproductive Health (RHQ) file. These data were categorized according to the preceding text and included as categorical variables.

2.5 Statistical analysis

For all calculations and analyses, the NHANES sample weights were used. The weights were selected according to the NHANES database instructions (37). They were adjusted for the weight of the first day 24-h dietary recall (WTDRD1) because this study was based on data from the first day of the dietary recall. Four NHANES periods were combined, totaling 9.2 years. Continuous variables are reported as *median* (P_{25} , P_{75}), and categorical variables are reported as unweighted numbers and weighted proportions. Sex was used for the subgroup analysis. A restricted cubic spline (RCS) analysis was conducted to explore the association between VK intake and bone health with a node number of 5. Weighted multiple logistic regression was used to explore the associations between different VK intake levels and the overall risk of osteoporosis or bone loss and that at specific sites. Five sets of models were constructed with osteoporosis or bone loss as the dependent variable, the nonosteoporosis or healthy group as the reference, and the VK intake level as the predictor. Model 1 was unadjusted; Model 2 was adjusted for age and race; Model 3 included Model 2 and was additionally adjusted for education, poverty, BMI, sedentary behavior, a history of smoking, and a history of alcohol use; Model 4 included Model 3 and was additionally adjusted for a family history of osteoporosis and a history of cortisone use, diabetes mellitus, and hypertension, and estrogen use in women; Model 5 added dietary variables, including the intake of VD, VC, calcium, phosphorus, sodium, energy, protein, and caffeine, to Model 4.

All statistical analyses were conducted with R software (version 4.2.3, Vienna, Austria). A $p < 0.05$ indicated statistical significance; the

Bonferroni correction was used for multiple comparisons. The Strengthening the Reporting of Observational Studies in Epidemiology-Nutritional Epidemiology (STROBE-NUT) guidelines were followed (38).

3 Results

3.1 Baseline information

A total of 5,075 participants were finally analyzed; of them, 2,606 (55%) were women, 1,001 (18%) had osteoporosis, and 2,226 (46%) had osteopenia. The baseline characteristics, such as age and other confounders, differed between the participants with different bone health (healthy, osteopenia, and osteoporosis) ($p < 0.05$) (Supplementary Table A), in addition to sex differences in bone health, baseline information, and confounders ($p < 0.05$) (Supplementary Table B). The RCS results demonstrated a non-linear association between VK intake levels and bone health (Supplementary Figure 1). The baseline conditions overall and by sex after generalized grouping by bone health (nonosteoporosis vs. osteoporosis, healthy vs. bone loss) are presented follows (Tables 1, 2).

3.1.1 Osteoporosis and nonosteoporosis groups

The nonosteoporosis group had a younger age, a higher proportion of men, better education levels, a higher percentage of high-income earners, a higher proportion of participants with overweight and obesity, longer sedentary period, and a higher intake of phosphorus, sodium, energy, protein, caffeine, and VK ($p < 0.05$) (Table 1). In contrast, the osteoporosis group had a higher proportion of never-smokers and nonalcohol drinkers; a higher proportion of participants with a family history of osteoporosis and a history of estrogen or glucocorticoid drugs use, and a higher intake of VD ($p < 0.05$) (Table 1). Among men, the nonosteoporosis group was younger and more likely to be overweight or obese, to have never drink alcohol, to have a family history of osteoporosis, and to use glucocorticoids at a higher proportion ($p < 0.05$) (Table 1). The remaining factors did not differ between the groups ($p > 0.05$) (Table 1). In contrast, among women, the between-group differences for the remaining indicators were consistent with the overall results. However, the smoking history, a history of estrogen use, and the intake of VD, VC, calcium, and phosphorus did not differ between the groups ($p > 0.05$). The proportion of women with overweight was lower in the nonosteoporosis group than in the osteoporosis group ($p < 0.05$) (Table 1).

3.1.2 Bone loss and healthy groups

The healthy group had a younger age, a higher proportion of men, a higher proportion of high-income earners, a higher proportion of participants with obesity, and higher intakes of phosphorus, sodium, energy, and protein ($p < 0.05$) (Table 2). In contrast, the bone loss group had a higher proportion of nonalcohol drinkers, a higher percentage of participants without diabetes and hypertension, a higher proportion of participants with a family history of osteoporosis, and higher proportions of estrogen or glucocorticosteroid use ($p < 0.05$) (Table 2). VK intake levels did not differ between the groups ($p > 0.05$) (Table 2). Among men, the healthy group was younger and more likely to be nonsmokers and have obesity, but the osteoporosis group was

TABLE 1 Baseline characteristics of participants in the osteoporosis and non-osteoporosis groups.

Characteristic	Overall ¹	Bone health groups		P ²
		Nonosteoporosis ¹	Osteoporosis ¹	
All participants				
N (n, %)	5,075 (100%)	4,074 (82%)	1,001 (18%)	
Age (n, %)				<0.001
50–59 years	2,011 (50%)	1,760 (55%)	251 (31%)	
60–69 years	1,837 (30%)	1,481 (30%)	356 (33%)	
70–79 years	873 (14%)	623 (12%)	250 (24%)	
80+ years	354 (5.2%)	210 (3.6%)	144 (12%)	
Gender (n, %)				<0.001
Men	2,469 (45%)	2,276 (52%)	193 (17%)	
Women	2,606 (55%)	1,798 (48%)	808 (83%)	
RACE (n, %)				0.008
Non-Hispanic White	2,316 (73%)	1,807 (73%)	509 (74%)	
Non-Hispanic Black	1,072 (9.7%)	940 (10%)	132 (6.6%)	
Mexican American	705 (5.4%)	564 (5.4%)	141 (5.6%)	
Other Hispanic	524 (4.6%)	420 (4.4%)	104 (5.1%)	
Other race/multiracial	458 (7.0%)	343 (6.5%)	115 (9.2%)	
Education level (n, %)				<0.001
Less than college	2,428 (40%)	1,892 (38%)	536 (47%)	
College or above	2,647 (60%)	2,182 (62%)	465 (53%)	
Income level (n, %)				<0.001
Low income	1,337 (16%)	1,022 (15%)	315 (23%)	
Middle income	1,910 (31%)	1,520 (30%)	390 (36%)	
High income	1,828 (52%)	1,532 (55%)	296 (41%)	
Smoke (n, %)				<0.001
Never smoking	2,658 (54%)	2,083 (53%)	575 (58%)	
Used smoking	1,605 (32%)	1,349 (33%)	256 (24%)	
Now smoking	812 (15%)	642 (14%)	170 (17%)	
Drink (n, %)				<0.001
Never drinking	677 (11%)	461 (9.3%)	216 (16%)	
Non-drink Past 12 Mon	1,238 (19%)	972 (18%)	266 (27%)	
≤1 Drink/mon	1,301 (26%)	1,033 (26%)	268 (26%)	
>1 Drink/mon	1,859 (44%)	1,608 (47%)	251 (31%)	
BMI (n, %)				<0.001
Normal	1,312 (27%)	916 (23%)	396 (40%)	
Underweight	82 (1.4%)	43 (0.7%)	39 (4.4%)	
Overweight	1,939 (38%)	1,589 (39%)	350 (36%)	
Obesity	1,742 (34%)	1,526 (37%)	216 (19%)	
Sedentary time (n, %)				0.023
< 8 h	3,606 (66%)	2,877 (66%)	729 (71%)	
≥8 h	1,469 (34%)	1,197 (34%)	272 (29%)	
Diabetes (n, %)				0.704
Healthy	3,988 (83%)	3,186 (83%)	802 (83%)	
Prediabetes	165 (3.0%)	138 (3.1%)	27 (2.4%)	

(Continued)

TABLE 1 (Continued)

Characteristic	Bone health groups			P ²
	Overall ¹	Nonosteoporosis ¹	Osteoporosis ¹	
Diabetes	922 (14%)	750 (14%)	172 (14%)	
Hypertension (n, %)				0.463
Healthy	2,555 (56%)	2,069 (56%)	486 (54%)	
Hypertension	2,520 (44%)	2,005 (44%)	515 (46%)	
Family history of osteoporosis (Yes, n, %)	706 (18%)	487 (16%)	219 (28%)	<0.001
History of prednisone or cortisone use (Yes, n, %)	317 (6.4%)	213 (5.4%)	104 (11%)	<0.001
History of estrogen use (Yes, n, %)	899 (21%)	621 (19%)	278 (31%)	<0.001
VD (mcg/d)	9.7 (3.2, 26.0)	8.8 (3.1, 24.5)	13.7 (3.7, 31.6)	<0.001
VC (mg/d)	107.4 (46.9, 198.0)	106.5 (48.3, 195.4)	111.3 (41.3, 212.0)	0.812
Calcium (mg/d)	1,027.9 (688.0, 1454.8)	1,028.5 (688.0, 1,434.6)	1,017.2 (723.7, 1562.5)	0.121
Phosphorus (mg/d)	1,253.0 (959.0, 1575.5)	1,290.0 (980.5, 1614.0)	1,114.9 (885.9, 1417.2)	<0.001
Sodium (mg/d)	3,011.5 (2300.8, 3929.9)	3,097.2 (2390.6, 4040.0)	2,659.2 (2051.6, 3412.7)	<0.001
Energy(kcal/d)	1,863.5 (1,466.3, 2384.1)	1,921.5 (1,496.0, 2446.1)	1,673.8 (1334.5, 2086.4)	<0.001
Protein (g/d)	73.1 (56.3, 94.0)	74.8 (57.7, 95.7)	63.9 (50.3, 79.8)	<0.001
Caffeine (mg/d)	145.5 (57.5, 257.0)	154.0 (63.0, 267.6)	107.5 (37.0, 228.0)	<0.001
VK (mcg/d)	93.8 (57.1, 162.8)	96.1 (59.6, 165.9)	87.2 (51.3, 141.0)	<0.001
Level of VK intake (n, %)				<0.001
Low	2,044 (33%)	1,599 (31%)	445 (40%)	
Medium	1,558 (33%)	1,273 (34%)	285 (29%)	
High	1,473 (34%)	1,202 (35%)	271 (30%)	
Men				
N (n, %)	2,469 (100%)	2,276 (93%)	193 (6.9%)	
Age (n, %)				<0.001
50–59 years	995 (53%)	942 (54%)	53 (39%)	
60–69 years	887 (29%)	826 (29%)	61 (30%)	
70–79 years	426 (13%)	381 (13%)	45 (20%)	
80+ years	161 (4.1%)	127 (3.6%)	34 (11%)	
Race (n, %)				0.416
Non-Hispanic White	1,106 (74%)	1,006 (73%)	100 (74%)	
Non-Hispanic Black	544 (9.8%)	514 (10%)	30 (7.4%)	
Mexican American	356 (5.8%)	333 (5.8%)	23 (5.8%)	
Other Hispanic	249 (4.3%)	232 (4.3%)	17 (3.2%)	
Other race/multiracial	214 (6.6%)	191 (6.4%)	23 (9.4%)	
Education level (n, %)				0.253
Less than college	1,226 (41%)	1,127 (40%)	99 (46%)	
College or above	1,243 (59%)	1,149 (60%)	94 (54%)	
Income level (n, %)				0.160
Low income	641 (16%)	577 (15%)	64 (22%)	
Middle income	909 (29%)	844 (30%)	65 (25%)	
High income	919 (55%)	855 (55%)	64 (53%)	
Smoke (n, %)				0.161
Never smoking	1,037 (46%)	964 (46%)	73 (44%)	
Used smoking	975 (38%)	904 (38%)	71 (33%)	

(Continued)

TABLE 1 (Continued)

Characteristic	Overall ¹	Bone health groups		P ²
		Nonosteoporosis ¹	Osteoporosis ¹	
Now smoking	457 (16%)	408 (15%)	49 (22%)	
Drink (n, %)				0.007
Never drinking	158 (5.7%)	142 (5.4%)	16 (10.0%)	
Non-drink past 12 mon	648 (20%)	587 (19%)	61 (34%)	
≤1 Drink/Mon	533 (20%)	490 (20%)	43 (18%)	
>1 Drink/Mon	1,130 (54%)	1,057 (56%)	73 (38%)	
BMI (n, %)				<0.001
Normal	611 (23%)	513 (21%)	98 (49%)	
Underweight	34 (0.8%)	28 (0.5%)	6 (5.0%)	
Overweight	1,038 (42%)	982 (43%)	56 (26%)	
Obesity	786 (35%)	753 (36%)	33 (20%)	
Sedentary time (n, %)				0.484
< 8 h	1,740 (66%)	1,613 (66%)	127 (62%)	
≥8 h	729 (34%)	663 (34%)	66 (38%)	
Diabetes (n, %)				0.115
Healthy	1,885 (80%)	1,742 (80%)	143 (74%)	
Prediabetes	89 (3.1%)	84 (3.2%)	5 (2.2%)	
Diabetes	495 (17%)	450 (16%)	45 (24%)	
Hypertension (n, %)				0.821
Healthy	1,288 (55%)	1,186 (55%)	102 (56%)	
Hypertension	1,181 (45%)	1,090 (45%)	91 (44%)	
Family history of osteoporosis (Yes, n, %)	238 (11%)	208 (11%)	30 (20%)	0.013
History of prednisone or cortisone use (Yes, n, %)	116 (5.3%)	97 (4.7%)	19 (12%)	0.002
VD (mcg/d)	7.5 (3.1, 18.0)	7.1 (3.1, 17.4)	10.3 (3.0, 30.8)	0.052
VC (mg/d)	106.7 (45.7, 189.9)	104.8 (45.0, 185.6)	129.5 (60.1, 247.0)	0.107
Calcium (mg/d)	1,022.0 (697.2, 1402.8)	1,022.0 (694.0, 1385.9)	1,009.8 (733.4, 1622.5)	0.249
Phosphorus (mg/d)	1,432.0 (1,117.6, 1764.8)	1,433.6 (1,123.5, 1767.4)	1,385.0 (1,003.2, 1699.8)	0.106
Sodium (mg/d)	3,507.0 (2,739.9, 4479.7)	3,519.9 (2,741.4, 4476.6)	3,431.4 (2,688.2, 4493.7)	0.576
Energy(kcal/d)	2,176.6 (1,728.7, 2700.3)	2,185.1 (1,730.5, 2703.6)	2,033.8 (1,658.4, 2691.6)	0.281
Protein (g/d)	84.9 (64.4, 107.9)	85.1 (65.4, 107.7)	76.7 (55.4, 108.7)	0.068
Caffeine (mg/d)	171.5 (68.5, 294.9)	173.0 (70.5, 297.5)	119.8 (29.1, 275.3)	0.051
VK (mcg/d)	95.2 (59.5, 163.7)	95.2 (59.8, 163.4)	92.7 (57.5, 165.8)	0.979
Level of VK intake (n, %)				0.621
Low	1,008 (33%)	921 (32%)	87 (36%)	
Medium	760 (33%)	709 (33%)	51 (29%)	
High	701 (34%)	646 (34%)	55 (35%)	
Women				
N (n, %)	2,606 (100%)	1798 (72%)	808 (28%)	
Age (n, %)				<0.001
50-59 years	1,016 (48%)	818 (55%)	198 (29%)	
60-69 years	950 (31%)	655 (30%)	295 (34%)	
70-79 years	447 (15%)	242 (12%)	205 (25%)	
80+ years	193 (6.1%)	83 (3.6%)	110 (12%)	

(Continued)

TABLE 1 (Continued)

Characteristic	Bone health groups			p ²
	Overall ¹	Nonosteoporosis ¹	Osteoporosis ¹	
Race (n, %)				0.012
NON-Hispanic White	1,210 (73%)	801 (73%)	409 (73%)	
NON-Hispanic Black	528 (9.6%)	426 (11%)	102 (6.4%)	
Mexican American	349 (5.1%)	231 (4.9%)	118 (5.5%)	
Other Hispanic	275 (4.8%)	188 (4.6%)	87 (5.4%)	
Other race/multiracial	244 (7.4%)	152 (6.7%)	92 (9.2%)	
Education level (n, %)				<0.001
Less than college	1,202 (39%)	765 (36%)	437 (47%)	
College or above	1,404 (61%)	1,033 (64%)	371 (53%)	
Income level (n, %)				<0.001
Low income	696 (17%)	445 (14%)	251 (23%)	
Middle income	1,001 (33%)	676 (31%)	325 (39%)	
High income	909 (50%)	677 (55%)	232 (38%)	
Smoke (n, %)				0.130
Never smoking	1,621 (60%)	1,119 (59%)	502 (61%)	
Used smoking	630 (26%)	445 (28%)	185 (23%)	
Now smoking	355 (14%)	234 (13%)	121 (16%)	
Drink (n, %)				<0.001
Never drinking	519 (15%)	319 (14%)	200 (17%)	
Non-drink past 12 mon	590 (19%)	385 (16%)	205 (26%)	
≤1 Drink/Mon	768 (31%)	543 (32%)	225 (28%)	
>1 Drink/Mon	729 (36%)	551 (39%)	178 (29%)	
BMI (n, %)				<0.001
Normal	701 (30%)	403 (27%)	298 (38%)	
Underweight	48 (1.9%)	15 (0.9%)	33 (4.3%)	
Overweight	901 (35%)	607 (34%)	294 (39%)	
Obesity	956 (33%)	773 (39%)	183 (19%)	
Sedentary time (n, %)				0.027
< 8 h	1,866 (67%)	1,264 (65%)	602 (72%)	
≥8 h	740 (33%)	534 (35%)	206 (28%)	
Diabetes (n, %)				0.728
Healthy	2,103 (86%)	1,444 (86%)	659 (85%)	
Prediabetes	76 (2.9%)	54 (3.1%)	22 (2.5%)	
Diabetes	427 (11%)	300 (11%)	127 (12%)	
Hypertension (n, %)				0.195
Healthy	1,267 (57%)	883 (58%)	384 (54%)	
Hypertension	1,339 (43%)	915 (42%)	424 (46%)	
Family history of osteoporosis (Yes, n, %)	468 (23%)	279 (21%)	189 (29%)	0.002
History of prednisone or cortisone use (Yes, n, %)	201 (7.3%)	116 (6.0%)	85 (11%)	<0.001
History of estrogen use (Yes, n, %)	899 (39%)	621 (39%)	278 (38%)	0.568
VD (mcg/d)	12.9 (3.5, 29.7)	12.2 (3.4, 29.2)	14.3 (3.8, 31.7)	0.148
VC (mg/d)	108.1 (48.3, 210.3)	107.5 (51.0, 212.1)	108.3 (40.8, 204.6)	0.199
Calcium (mg/d)	1034.1 (687.0, 1516.1)	1035.3 (680.5, 1504.0)	1027.0 (719.1, 1550.7)	0.567

(Continued)

TABLE 1 (Continued)

Characteristic	Overall ¹	Bone health groups		<i>p</i> ²
		Nonosteoporosis ¹	Osteoporosis ¹	
Phosphorus (mg/d)	1125.0 (885.1, 1404.8)	1144.0 (890.1, 1,418.0)	1092.6 (868.5, 1352.6)	0.053
Sodium (mg/d)	2692.4 (2091.3, 3398.6)	2754.7 (2153.3, 3461.6)	2491.7 (1978.5, 3214.9)	<0.001
Energy(kcal/d)	1,653.4 (1,346.2, 2061.0)	1693.0 (1351.3, 2086.2)	1617.1 (1307.0, 1994.0)	0.026
Protein (g/d)	64.0 (50.9, 81.4)	65.3 (51.2, 82.8)	62.2 (50.1, 76.0)	0.012
Caffeine (mg/d)	129.5 (50.0, 234.8)	139.5 (54.7, 240.0)	104.5 (37.5, 218.3)	0.006
VK (mcg/d)	92.7 (54.8, 161.0)	96.7 (59.4, 171.1)	83.3 (49.9, 140.7)	<0.001
Level of VK intake (<i>n</i> , %)				<0.001
Low	1,036 (33%)	678 (30%)	358 (41%)	
Medium	798 (33%)	564 (34%)	234 (29%)	
High	772 (34%)	556 (36%)	216 (30%)	

¹Median (P25, P75) for continuous; *n* (%) for categorical. ²Chi-squared test with Rao and Scott's second-order correction; Wilcoxon rank-sum test for complex survey samples. BMI, body mass index; VD, vitamin D; VC, vitamin C; VK, vitamin K. Bold values indicate *p* < 0.05.

more likely to be without hypertension and have a family history of osteoporosis (*p* < 0.05) (Table 2). However, VK intake levels did not differ between the groups (*p* > 0.05) (Table 2). Among women, the healthy group was younger and more likely to have a high income, obesity, and a greater intake of phosphorus, sodium, energy, and protein, and a medium-level VK intake (*p* < 0.05) (Table 2). In contrast, the osteoporosis group was more likely to be without diabetes and have a family history of osteoporosis (*p* < 0.05) (Table 2).

3.2 Association between VK intake levels and bone health

3.2.1 Association between VK intake levels and bone health among all participants

High-level VK intake was associated with a reduced risk of osteoporosis in Models 1 and 2. After adjustment for Models 3 and 4, medium-level VK intake was associated with a reduced risk of osteoporosis. However, this association was not observed in Model 5. Nevertheless, medium-level VK intake was associated with a lower risk of bone loss in all five models (Figure 2).

3.2.2 Sex-specific association between VK intake levels and osteoporosis

Weighted multiple logistic regression suggested that medium- and high-level VK intakes were associated with a reduced risk of osteoporosis in women aged over 50 years even after adjustment for covariates. In Model 5, women with medium- [odds ratio, OR (95% confidence interval, CI): 0.66(0.47, 0.93)] and high-level [OR (95% CI): 0.71(0.52, 0.98)] VK intake demonstrated a reduced risk of osteoporosis than women with low-level VK intake (Figure 3). However, VK intake was not associated with osteoporosis in men aged over 50 years (Figure 3).

3.2.3 Sex-specific association between VK intake levels and bone loss

Weighted multiple logistic regression suggested that medium-level VK intake was associated with a reduced risk of bone loss in women aged over 50 years in all five models [OR (95% CI): 0.59(0.43,

0.81); 0.55(0.39, 0.77); 0.54(0.38, 0.76); 0.55(0.40, 0.77); 0.58(0.41, 0.81)] (Figure 4). In contrast, high-level VK intake was not associated with bone loss (Figure 4). Moreover, VK intake was not associated with bone loss in men aged over 50 years (Figure 4).

3.2.4 Site-specific association between VK levels and osteoporosis

For all participants, high-level VK intake was associated with a reduced risk of osteoporosis at all bone sites. Upon considering only VK intake levels with age and race, medium-level VK intake was associated with a reduced risk of osteoporosis at the lumbar spine, femoral neck, intertrochanter, and total femur; however, these associations disappeared upon adjusting all variables (Supplementary Table C). Among women, medium-level VK intake was associated with a reduced risk of osteoporosis at the lumbar spine [OR (95% CI): 0.70(0.49, 0.99)] and high-level VK intake was at the femoral neck [OR (95% CI): 0.67(0.45, 1.00)], respectively, even after adjusted for all variables (Supplementary Table C). In Model 4, which excluded dietary intake, high-level VK intake was associated with a reduced risk of osteoporosis at all five sites (Supplementary Table C). In contrast, among men, VK intake levels were not associated with osteoporosis at all sites (Supplementary Table C).

3.2.5 Site-specific association between VK and bone loss

For all participants, medium-level VK intake was associated with a reduced risk of bone loss at all sites in Model 2, which considered only age and race. Moreover, medium-level VK intake was associated with a reduced risk of bone loss at the lumbar spine [OR (95% CI): 0.79(0.63, 0.99)] and femoral neck [OR (95% CI): 0.77(0.59, 1.00)] in Model 5 (Supplementary Table D). Among men, medium-level VK intake was associated with a reduced risk of bone loss at the femoral neck [OR (95% CI): 0.66(0.48, 0.90)]; high-level VK intake was associated with a reduced risk of bone loss at the lumbar spine [OR (95% CI): 0.68(0.47, 0.99)] only in Model 5 (Supplementary Table D). Among women, in Model 5, medium-level VK intake was associated with a reduced risk of bone loss at the lumbar spine [OR (95% CI): 0.60(0.43, 0.83)], trochanter [OR (95% CI): 0.66(0.48, 0.91)], intertrochanter [OR (95% CI): 0.66(0.50,

TABLE 2 Baseline characteristics of the participants in the bone loss and healthy groups.

Characteristic	Overall ¹	Bone Health Groups		P ²
		Healthy ¹	Bone loss ¹	
All participants				
N (n, %)	5,075 (100%)	1,848 (36%)	3,227 (64%)	
Age (n, %)				<0.001
50–59 years	2,011 (50%)	912 (61%)	1,099 (44%)	
60–69 years	1,837 (30%)	652 (28%)	1,185 (32%)	
70–79 years	873 (14%)	224 (9.0%)	649 (17%)	
80+ years	354 (5.2%)	60 (2.0%)	294 (7.0%)	
Gender (n, %)				<0.001
Men	2,469 (45%)	1,126 (59%)	1,343 (38%)	
Women	2,606 (55%)	722 (41%)	1,884 (62%)	
Race (n, %)				<0.001
NON-Hispanic White	2,316 (73%)	719 (70%)	1,597 (75%)	
NON-Hispanic Black	1,072 (9.7%)	571 (15%)	501 (6.9%)	
Mexican American	705 (5.4%)	262 (5.6%)	443 (5.3%)	
Other Hispanic	524 (4.6%)	178 (3.7%)	346 (5.0%)	
Other Race/Multiracial	458 (7.0%)	118 (5.7%)	340 (7.8%)	
Education level (n, %)				0.458
Less than college	2,428 (40%)	864 (41%)	1,564 (39%)	
College or above	2,647 (60%)	984 (59%)	1,663 (61%)	
Income level (n, %)				0.038
Low income	1,337 (16%)	450 (15%)	887 (17%)	
Middle income	1,910 (31%)	673 (29%)	1,237 (33%)	
High income	1,828 (52%)	725 (56%)	1,103 (50%)	
Smoke (n, %)				0.080
Never smoking	2,658 (54%)	966 (55%)	1,692 (53%)	
Used smoking	1,605 (32%)	598 (33%)	1,007 (31%)	
Now smoking	812 (15%)	284 (12%)	528 (16%)	
Drink (n, %)				<0.001
Never drinking	677 (11%)	186 (8.6%)	491 (12%)	
Non-drink past 12 mon	1,238 (19%)	435 (17%)	803 (21%)	
≤1 Drink/Mon	1,301 (26%)	466 (25%)	835 (26%)	
>1 Drink/Mon	1,859 (44%)	761 (50%)	1,098 (41%)	
BMI (n, %)				<0.001
Normal	1,312 (27%)	239 (12%)	1,073 (35%)	
Underweight	82 (1.4%)	5 (0.1%)	77 (2.1%)	
Overweight	1,939 (38%)	685 (38%)	1,254 (38%)	
Obesity	1,742 (34%)	919 (50%)	823 (25%)	
Sedentary time (n, %)				0.738
< 8 h	3,606 (66%)	1,304 (67%)	2,302 (66%)	
≥8 h	1,469 (34%)	544 (33%)	925 (34%)	
Diabetes (n, %)				0.008
Healthy	3,988 (83%)	1,399 (80%)	2,589 (85%)	
Prediabetes	165 (3.0%)	74 (4.0%)	91 (2.5%)	

(Continued)

TABLE 2 (Continued)

Characteristic	Bone Health Groups			P ²
	Overall ¹	Healthy ¹	Bone loss ¹	
Diabetes	922 (14%)	375 (16%)	547 (12%)	
Hypertension (n, %)				0.015
Healthy	2,555 (56%)	878 (52%)	1,677 (58%)	
Hypertension	2,520 (44%)	970 (48%)	1,550 (42%)	
Family history of osteoporosis (Yes, n, %)	706 (18%)	202 (12%)	504 (21%)	<0.001
History of prednisone or cortisone use (Yes, n, %)	317 (6.4%)	85 (4.7%)	232 (7.3%)	0.009
History of estrogen use (Yes, n, %)	899 (21%)	229 (15%)	670 (25%)	<0.001
VD (mcg/d)	9.7 (3.2, 26.0)	8.0 (3.2, 21.8)	10.7 (3.2, 27.4)	0.069
VC (mg/d)	107.4 (46.9, 198.0)	107.8 (46.6, 185.1)	107.0 (47.4, 203.7)	0.620
Calcium (mg/d)	1,027.9 (688.0, 1,454.8)	1,028.5 (693.3, 1,406.3)	1,022.0 (686.2, 1,484.5)	0.680
Phosphorus (mg/d)	1,253.0 (959.0, 1,575.5)	1,346.9 (1,021.5, 1,659.5)	1,199.8 (935.0, 1,523.2)	<0.001
Sodium (mg/d)	3,011.5 (2,300.8, 3,929.9)	3,211.0 (2,520.8, 4,200.3)	2,909.4 (2,228.5, 3,756.2)	<0.001
Energy(kcal/d)	1,863.5 (1,466.3, 2,384.1)	2,011.0 (1,575.0, 2,506.1)	1,802.0 (1,411.5, 2,291.3)	<0.001
Protein (g/d)	73.1 (56.3, 94.0)	78.3 (60.0, 98.3)	69.3 (53.9, 90.2)	<0.001
Caffeine (mg/d)	145.5 (57.5, 257.0)	156.0 (57.1, 272.0)	142.0 (57.5, 249.0)	0.151
VK (mcg/d)	93.8 (57.1, 162.8)	96.1 (62.5, 157.2)	92.6 (53.3, 166.0)	0.394
Level of VK intake (n, %)				0.084
Low	2,044 (33%)	730 (30%)	1,314 (34%)	
Medium	1,558 (33%)	600 (36%)	958 (31%)	
High	1,473 (34%)	518 (34%)	955 (34%)	
Men				
N (n, %)	2,469 (100%)	1,126 (46%)	1,343 (54%)	
Age (n, %)				<0.001
50–59 years	995 (53%)	529 (62%)	466 (46%)	
60–69 years	887 (29%)	408 (27%)	479 (31%)	
70–79 years	426 (13%)	143 (8.5%)	283 (17%)	
80+ years	161 (4.1%)	46 (2.5%)	115 (5.5%)	
Race (n, %)				<0.001
NON-Hispanic White	1,106 (74%)	439 (71%)	667 (76%)	
NON-Hispanic Black	544 (9.8%)	326 (13%)	218 (6.7%)	
Mexican American	356 (5.8%)	168 (5.9%)	188 (5.8%)	
Other Hispanic	249 (4.3%)	116 (4.0%)	133 (4.5%)	
Other Race/Multiracial	214 (6.6%)	77 (6.2%)	137 (6.9%)	
Education level (n, %)				0.512
Less than college	1,226 (41%)	562 (42%)	664 (40%)	
College or above	1,243 (59%)	564 (58%)	679 (60%)	
Income level (n, %)				0.892
Low income	641 (16%)	279 (16%)	362 (16%)	
Middle income	909 (29%)	399 (29%)	510 (30%)	
High income	919 (55%)	448 (56%)	471 (55%)	
Smoke (n, %)				0.016
Never smoking	1,037 (46%)	526 (51%)	511 (42%)	
Used smoking	975 (38%)	409 (35%)	566 (40%)	

(Continued)

TABLE 2 (Continued)

Characteristic	Overall ¹	Bone Health Groups		P ²
		Healthy ¹	Bone loss ¹	
Now smoking	457 (16%)	191 (14%)	266 (18%)	
Drink (n, %)				0.188
Never Drinking	158 (5.7%)	70 (5.3%)	88 (6.0%)	
Non-Drink Past 12 Mon	648 (20%)	279 (18%)	369 (23%)	
≤1 Drink/Mon	533 (20%)	240 (21%)	293 (19%)	
>1 Drink/Mon	1,130 (54%)	537 (56%)	593 (53%)	
BMI (n, %)				<0.001
Normal	611 (23%)	162 (12%)	449 (32%)	
Underweight	34 (0.8%)	4 (0.1%)	30 (1.4%)	
Overweight	1,038 (42%)	467 (42%)	571 (42%)	
Obesity	786 (35%)	493 (46%)	293 (25%)	
Sedentary time (n, %)				0.400
< 8 h	1,740 (66%)	798 (67%)	942 (65%)	
≥8 h	729 (34%)	328 (33%)	401 (35%)	
Diabetes (n, %)				0.674
Healthy	1,885 (80%)	844 (79%)	1,041 (81%)	
Prediabetes	89 (3.1%)	46 (3.4%)	43 (2.9%)	
Diabetes	495 (17%)	236 (18%)	259 (16%)	
Hypertension (n, %)				0.011
Healthy	1,288 (55%)	551 (52%)	737 (58%)	
Hypertension	1,181 (45%)	575 (48%)	606 (42%)	
Family history of osteoporosis (Yes, n, %)	238 (11%)	97 (8.3%)	141 (14%)	0.001
History of prednisone or cortisone use (Yes, n, %)	116 (5.3%)	42 (4.1%)	74 (6.2%)	0.103
VD (mcg/d)	7.5 (3.1, 18.0)	6.9 (3.1, 16.8)	7.9 (2.9, 19.1)	0.585
VC (mg/d)	106.7 (45.7, 189.9)	107.8 (41.0, 174.1)	104.7 (50.7, 198.9)	0.248
Calcium (mg/d)	1,022.0 (697.2, 1,402.8)	1,033.7 (716.2, 1,352.5)	1,006.9 (688.0, 1,422.5)	0.770
Phosphorus (mg/d)	1,432.0 (1,117.6, 1,764.8)	1,439.5 (1,140.0, 1,758.7)	1,424.5 (1,100.8, 1,777.0)	0.289
Sodium (mg/d)	3,507.0 (2,739.9, 4,479.7)	3,505.4 (2,715.2, 4,503.5)	3,508.8 (2,750.0, 4,407.3)	0.805
Energy(kcal/d)	2,176.6 (1,728.7, 2,700.3)	2,217.5 (1,757.2, 2,704.6)	2,147.8 (1,693.4, 2,697.8)	0.152
Protein (g/d)	84.9 (64.4, 107.9)	86.1 (65.8, 109.4)	83.3 (63.3, 106.1)	0.169
Caffeine (mg/d)	171.5 (68.5, 294.9)	173.0 (65.5, 297.9)	170.0 (70.2, 294.0)	0.812
VK (mcg/d)	95.2 (59.5, 163.7)	94.5 (60.5, 161.7)	97.3 (58.8, 164.6)	0.871
Level of VK intake (n, %)				0.716
Low	1,008 (33%)	462 (32%)	546 (33%)	
Medium	760 (33%)	350 (34%)	410 (32%)	
High	701 (34%)	314 (33%)	387 (35%)	
Women				
N (n, %)	2,606 (100%)	722 (27%)	1884 (73%)	
Age (n, %)				<0.001
50–59 years	1,016 (48%)	383 (61%)	633 (43%)	
60–69 years	950 (31%)	244 (28%)	706 (32%)	
70–79 years	447 (15%)	81 (9.7%)	366 (17%)	
80+ years	193 (6.1%)	14 (1.3%)	179 (7.9%)	

(Continued)

TABLE 2 (Continued)

Characteristic	Overall ¹	Bone Health Groups		P ²
		Healthy ¹	Bone loss ¹	
Race (n, %)				<0.001
NON-Hispanic White	1,210 (73%)	280 (70%)	930 (74%)	
NON-Hispanic Black	528 (9.6%)	245 (17%)	283 (7.0%)	
Mexican American	349 (5.1%)	94 (5.3%)	255 (5.0%)	
Other Hispanic	275 (4.8%)	62 (3.3%)	213 (5.4%)	
Other Race/Multiracial	244 (7.4%)	41 (5.0%)	203 (8.3%)	
Education level (n, %)				0.980
Less than college	1,202 (39%)	302 (39%)	900 (39%)	
College or above	1,404 (61%)	420 (61%)	984 (61%)	
Income level (n, %)				0.014
Low income	696 (17%)	171 (14%)	525 (18%)	
Middle income	1,001 (33%)	274 (29%)	727 (34%)	
High income	909 (50%)	277 (57%)	632 (48%)	
Smoke (n, %)				0.104
Never smoking	1,621 (60%)	440 (60%)	1,181 (60%)	
Used smoking	630 (26%)	189 (29%)	441 (25%)	
Now smoking	355 (14%)	93 (11%)	262 (15%)	
Drink (n, %)				0.078
Never drinking	519 (15%)	116 (13%)	403 (15%)	
Non-drink past 12 mon	590 (19%)	156 (16%)	434 (20%)	
≤1 Drink/Mon	768 (31%)	226 (31%)	542 (31%)	
>1 Drink/Mon	729 (36%)	224 (40%)	505 (34%)	
BMI (n, %)				<0.001
Normal	701 (30%)	77 (13%)	624 (36%)	
Underweight	48 (1.9%)	1 (<0.1%)	47 (2.6%)	
Overweight	901 (35%)	218 (32%)	683 (36%)	
Obesity	956 (33%)	426 (55%)	530 (25%)	
Sedentary time (n, %)				0.839
< 8 h	1,866 (67%)	506 (67%)	1,360 (67%)	
≥8 h	740 (33%)	216 (33%)	524 (33%)	
Diabetes (n, %)				0.009
Healthy	2,103 (86%)	555 (81%)	1,548 (88%)	
Prediabetes	76 (2.9%)	28 (4.7%)	48 (2.2%)	
Diabetes	427 (11%)	139 (15%)	288 (10%)	
Hypertension (n, %)				0.217
Healthy	1,267 (57%)	327 (53%)	940 (58%)	
Hypertension	1,339 (43%)	395 (47%)	944 (42%)	
Family history of osteoporosis (Yes, n, %)	468 (23%)	105 (16%)	363 (26%)	<0.001
History of prednisone or cortisone use (Yes, n, %)	201 (7.3%)	43 (5.5%)	158 (8.0%)	0.126
History of estrogen use (Yes, n, %)	899 (39%)	229 (35%)	670 (40%)	0.104
VD (mcg/d)	12.9 (3.5, 29.7)	12.2 (3.5, 28.5)	13.1 (3.5, 30.9)	0.361
VC (mg/d)	108.1 (48.3, 210.3)	107.3 (53.5, 220.0)	108.2 (45.1, 204.6)	0.385
Calcium (mg/d)	1,034.1 (687.0, 1,516.1)	1,007.4 (687.6, 1,449.2)	1,043.2 (682.1, 1,539.1)	0.496

(Continued)

TABLE 2 (Continued)

Characteristic	Overall ¹	Bone Health Groups		P ²
		Healthy ¹	Bone loss ¹	
Phosphorus (mg/d)	1,125.0 (885.1, 1,404.8)	1,188.3 (907.9, 1,483.8)	1,105.3 (873.6, 1,366.6)	0.014
Sodium (mg/d)	2,692.4 (2,091.3, 3,398.6)	2,898.2 (2,187.5, 3,675.0)	2,631.5 (2,049.5, 3,286.0)	0.002
Energy (kcal/d)	1,653.4 (1,346.2, 2,061.0)	1,718.0 (1,425.4, 2,122.4)	1,630.1 (1,317.0, 2,029.1)	0.006
Protein (g/d)	64.0 (50.9, 81.4)	68.6 (53.7, 86.7)	62.9 (50.5, 78.5)	0.004
Caffeine (mg/d)	129.5 (50.0, 234.8)	144.9 (48.0, 249.0)	124.6 (51.0, 224.4)	0.153
VK (mcg/d)	92.7 (54.8, 161.0)	99.3 (63.2, 151.0)	90.2 (52.0, 168.5)	0.190
Level of VK intake (n, %)				0.039
Low	1,036 (33%)	268 (27%)	768 (35%)	
Medium	798 (33%)	250 (39%)	548 (31%)	
High	772 (34%)	204 (34%)	568 (34%)	

¹Median (P25, P75) for continuous; n (%) for categorical. ²Chi-squared test with Rao and Scott's second-order correction; Wilcoxon rank-sum test for complex survey samples. BMI, body mass index; VD, vitamin D; VC, vitamin C; VK, vitamin K.

086)], and total femur [OR (95% CI): 0.68(0.51, 0.91)]; In contrast, high-level VK intake was associated with a reduced risk of bone loss at the intertrochanter [OR (95% CI): 0.72(0.54, 0.96)] only (Supplementary Table D). In Model 4, high-level VK intake was associated with a reduced risk of bone loss at the lumbar spine [OR (95% CI): 0.70(0.51, 0.96)] and total femur [OR (95% CI): 0.71(0.52, 0.98)] (Supplementary Table D). Additionally, only in unadjusted Model 1 [OR (95% CI): 0.73(0.54, 1.00)] and age- and race-adjusted Model 2 [OR (95% CI): 0.68(0.49, 0.95)], medium-level VK intake was associated with a reduced risk of bone loss at the femoral neck in women (Supplementary Table D).

4 Discussion

This study describes the associations between VK intake levels and the risk of osteoporosis and bone loss in people aged over 50 years. Higher levels of VK intake may be associated with a reduced risk of osteoporosis, whereas only medium-level VK intake was associated with a reduced risk of bone loss in all participants. The associations between VK intake levels and both osteoporosis and bone loss were consistent in women and all participants. However, VK intake levels were not associated with osteoporosis in men, with only medium and high levels of VK intake associated with a reduced risk of bone loss at the femoral neck and lumbar spine, respectively.

To the best of our knowledge, this is the first study to examine the association of VK intake levels with sex and bone health (both osteoporosis and bone loss) in a nationally representative sample. Most studies have focused on the association between VK supplementation and BMD, without considering the total VK intake; they have primarily focused on women. A 3-year-long randomized controlled trial suggested that VK₂ reduced the rate of decline in BMD at the femoral neck and lumbar spine in postmenopausal women, similar to the current findings (39). A meta-analysis reported that VK₂ supplementation exerted a protective effect on BMD at the lumbar spine but not at the femoral neck in postmenopausal women (40). Low VK intake, particularly low VK₁ intake, has been associated with an increased risk of hip fracture but not with reduced BMD (41, 42). A double-blind, placebo-controlled trial demonstrated that VK

supplementation reduced serum carboxylated osteocalcin but did not affect the BMD at the lumbar spine or proximal femur (27). In summary, the effects of VK differ according to sex and bone site, confirmed by the current results. In this study, medium- and high-level VK intakes were associated with a reduced risk of osteoporosis in all participants and only women; medium-level VK intake was associated with a reduced risk of bone loss. However, among men, only medium-level VK intake was associated with bone loss at the femoral neck; high-level VK intake was associated with bone loss at the lumbar spine.

In this study, the average VK intake was 95.2 mcg/d for men, which is below the intake (120 mcg/d) recommended by the American Dietetic Association. For women, it was 92.7 mcg/d, which meets the recommended intake (90 mcg/d) (32). Upon grouping VK intake levels based on sex and tertiles, medium-level VK intake (men: 69.85–128.75 mcg/d; women: 65.96–129.40 mcg/d) was close to the recommended intake. Regression analysis results suggested that medium-level VK intake was associated with a reduced risk of bone loss and osteoporosis in all participants and women aged over 50 years. High-level VK intake was associated with a reduced risk of osteoporosis in only women. This finding could be attributed to delayed bone loss or moderately increased BMD at different sites because of VK; however, these changes will not reverse the change in bone health status and may only postpone the age of osteoporosis diagnosis (25, 26, 39). In this study, VD intake level was higher in the osteoporosis group than in the non-osteoporosis group, which may be attributed to additional VD supplementation after osteoporosis diagnosis, thus reversing causality. VK intake levels may follow a similar trend, in which patients consume medically prescribed or self-administered VK supplementation after osteoporosis diagnosis, thus increasing VK intake levels in the osteoporosis group. This aspect potentially masks the effects of high-level VK intake on bone health. Additionally, the physiological effects of nutrients may interact with each other, with synergistic or antagonistic effects. The intake of different nutrients may affect the effects of VK on bone health (43). Therefore, dietary factors were considered continuous covariates for analysis. After controlling for these factors and other covariates, VK intake remained associated with bone health. However, it did not exert a causal effect, thus

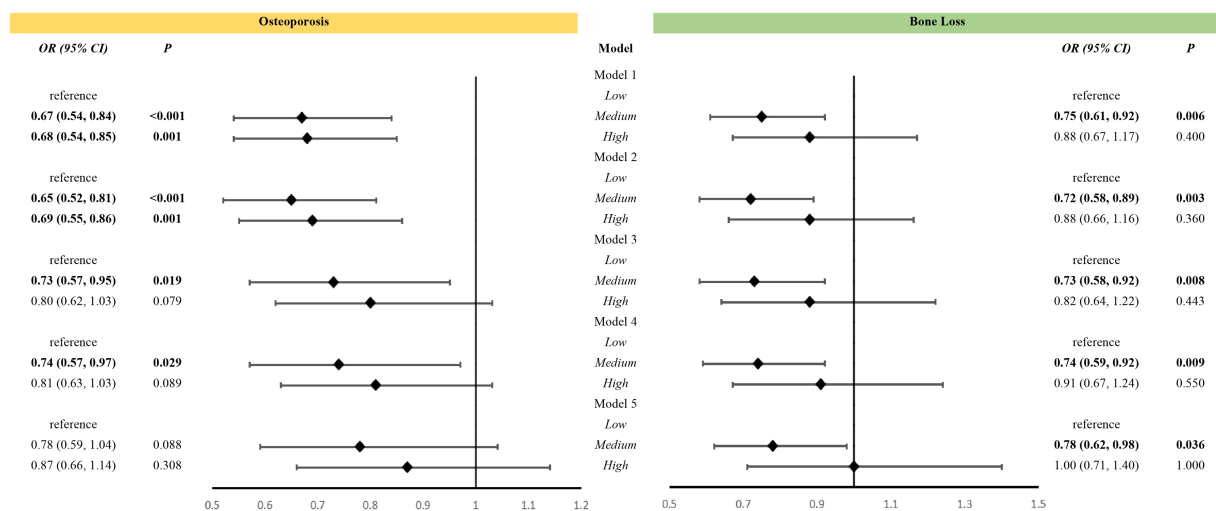


FIGURE 2 Association between vitamin K intake levels and bone health among all participants. Models: Model 1 was an unadjusted model; Model 2 was adjusted for age and race; Model 3 was further adjusted for education, poverty, BMI, sedentary behavior, history of smoking, and history of alcohol use based on Model 2; Model 4 included Model 3 and was further adjusted for family history of osteoporosis, and history of cortisone use, diabetes mellitus, and hypertension, and for estrogen use in women; Model 5 added dietary variables, including intake of vitamin D, vitamin C, calcium, phosphorus, sodium, energy, protein, and caffeine, to Model 4. Levels: LOW level: <65.95 mcg/d for women, <69.85 mcg/d for men; Medium level: 265.95 mcg/d and <129.40 mcg/d for women, 269.85 mcg/d and <128.75 mcg/d for men; High level: 2129.40 mcg/d for women, 2128.75 mcg/d for men.

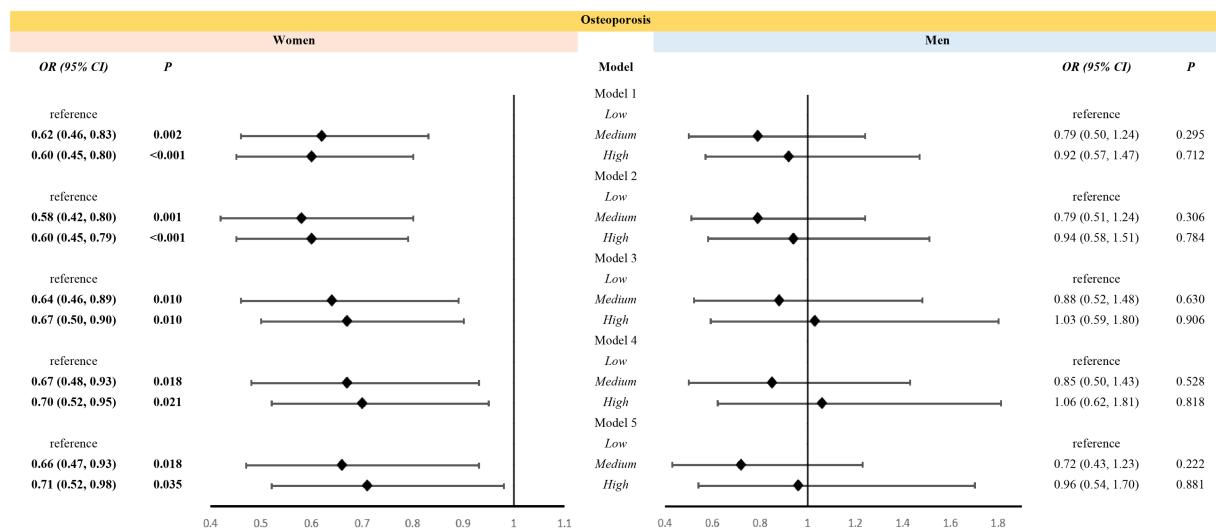


FIGURE 3 Association between levels of vitamin K intake and osteoporosis in different sexes. Models: Model 1 was an unadjusted model; Model 2 was adjusted for age and race; Model 3 was further adjusted for education, poverty, BMI, sedentary behavior, history of smoking, and history of alcohol use based on Model 2; Model 4 included Model 3 and was further adjusted for family history of osteoporosis, and history of cortisone use, diabetes mellitus, and hypertension, and for estrogen use in women; Model 5 added dietary variables, including intake of vitamin D, vitamin C, calcium, phosphorus, sodium, energy, protein, and caffeine, to Model 4. Levels: LOW level: <65.95 mcg/d for women, <69.85 mcg/d for men; Medium level: 265.95 mcg/d and <129.40 mcg/d for women, 269.85 mcg/d and <128.75 mcg/d for men; High level: 2129.40 mcg/d for women, 2128.75 mcg/d for men.

warranting further studies. Meanwhile, uncarboxylated osteocalcin decreases upon increasing VK intake. Nonetheless, the magnitude of the decrease reduces upon increasing the dose of VK intake, suggesting a physiological saturation effect. Therefore, high-level VK intake is not always beneficial, despite the absence of adverse effects. These findings do not highlight the benefits of high-level VK intake (30, 31, 44). Additionally, the current dose recommendation,

determined primarily based on maintaining the physiological function of coagulation, is inadequate for promoting bone health, particularly in postmenopausal women. This necessitates additional studies to determine the appropriate intake of different types of VK (43).

Osteoporosis is most commonly observed in older women. In the US, its prevalence is approximately four times higher in women aged

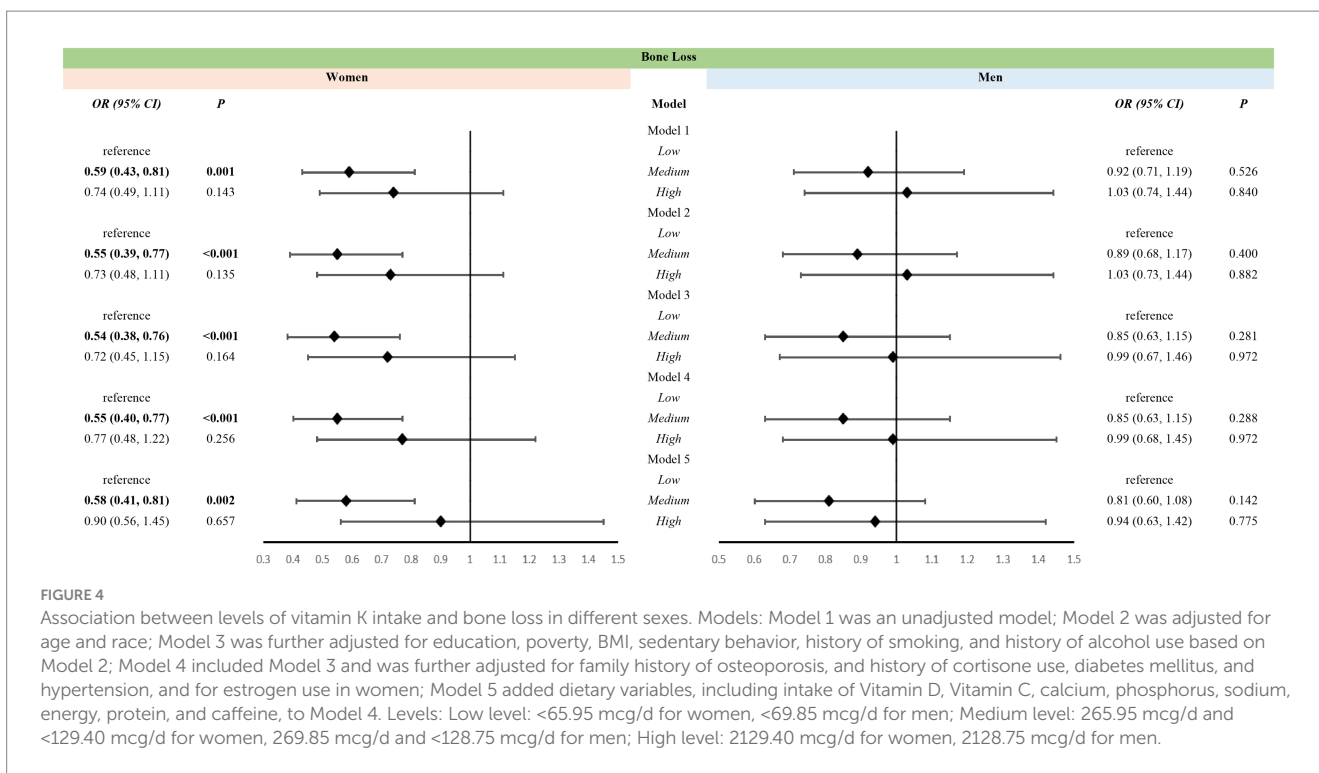


FIGURE 4 Association between levels of vitamin K intake and bone loss in different sexes. Models: Model 1 was an unadjusted model; Model 2 was adjusted for age and race; Model 3 was further adjusted for education, poverty, BMI, sedentary behavior, history of smoking, and history of alcohol use based on Model 2; Model 4 included Model 3 and was further adjusted for family history of osteoporosis, and history of cortisone use, diabetes mellitus, and hypertension, and for estrogen use in women; Model 5 added dietary variables, including intake of Vitamin D, Vitamin C, calcium, phosphorus, sodium, energy, protein, and caffeine, to Model 4. Levels: Low level: <65.95 mcg/d for women, <69.85 mcg/d for men; Medium level: 265.95 mcg/d and <129.40 mcg/d for women, 269.85 mcg/d and <128.75 mcg/d for men; High level: 2129.40 mcg/d for women, 2128.75 mcg/d for men.

over 50 years (28%) than in age-matched men (6.9%). Additionally, a study based on the Framingham Heart Study (1996–2000) reported that low dietary intake of VK is associated with low BMD in women but not in men, similar to the current findings (45). A study in China demonstrated that VK₂ supplementation reduced bone loss at the femoral neck in postmenopausal women; however, similar results were not observed at the lumbar spine or hip joints in women, or at any sites in men (44). The present study suggested that medium and high levels of VK intake were associated with a reduced risk of osteoporosis and bone loss in women, but only with a reduced risk of bone loss at the femoral neck and lumbar spine in men. In women, osteoporosis is primarily attributed to physiological changes, mostly due to an imbalance between bone formation and bone resorption caused by reduced postmenopausal estrogen. In contrast, osteoporosis in men is more commonly secondary, caused by various factors, such as metabolic diseases, low body weight, alcohol consumption, and low physical activity (18, 46–48). Differences in osteoporosis between men and women may stem from differences in bone biology and morphology (49). During the early decades of life, bone mass increases because of genetic and environmental factors, which determine the risk of osteoporosis (18). Owing to the differences in hormonal regulation and other aspects between sexes, men have higher peak bone mass and larger bone diameters than women (48, 49). Additionally, unlike women whose estrogen deficiency accelerates bone loss, men do not have hypogonadism, maintain stable hormone levels, and lack a phase of accelerated bone loss. In men, bone remodeling remains low at midlife and lower with age than in women (50, 51). Men experience age-related bone loss; however, the amount is smaller, and the primary mechanism is reduced bone formation (47). A decline in testosterone is the key cause of osteoporosis in men, with the slow age-related decline in

bone mass associated with a slow decline in androgen levels. Adequate intake of VK appears to promote the complete carboxylation of osteocalcin, partially inhibiting osteoclasts and promoting osteoblasts, thus partially correcting the imbalance in bone remodeling caused by estrogen reduction in women. This phenomenon may explain the varying effects of VK on the risk of osteoporosis and bone loss in both sexes (23, 52, 53).

To the best of our knowledge, this is the first study to demonstrate that medium-level VK intake is associated with a reduced risk of osteoporosis and bone loss in women aged over 50 years, providing further evidence for the sex-specific recommended VK intake level and subsequent studies on its association with bone health. However, this study has several limitations. First, it was a cross-sectional study, which does not provide sufficient evidence for a causal association between VK intake and bone health, thus warranting a long-term prospective study. Second, because of the differences in the indicators in each cycle of the NHANES database, biochemical indicators were not included. Moreover, the mechanisms between VK and bone metabolism cannot be completely demonstrated. Particularly, the varying effects of different VK intake levels on osteoporosis and bone loss in men and women cannot be entirely clarified, thus warranting further research. Third, owing to the limitations of the database, all types of VK were grouped into one for statistical analysis. Hence, the roles of each type of VK in bone health could not be elucidated, thereby necessitating further studies. Finally, the NHANES used the 24-h dietary recall method for dietary surveys. This method is the gold standard for dietary surveys; however, it is difficult to avoid bias, such as recall deviation and estimation error. The NHANES has collected and checked the data through training and supervision to control its quality. Additionally, data of the dietary surveys in NHANES have been proven reliable (54–58).

5 Conclusion

Medium-level VK intake (approximately 65–130 mcg/d) was associated with a reduced risk of osteoporosis and bone loss in people aged over 50 years, particularly women, and with a reduced risk of bone loss at the femoral neck in men. High-level VK intake was associated with a reduced risk of osteoporosis only in women and with a reduced risk of bone loss at the lumbar spine in men. Large prospective cohort studies or randomized controlled trials are warranted to elucidate the effects of varying VK intake levels on bone health at different sites based on sex. Additional studies will facilitate determining appropriate VK intake levels for different populations.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: <https://www.cdc.gov/nchs/nhanes/index.htm>.

Ethics statement

The studies involving humans were approved by the National Center for Health Statistics Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JGu: Writing – original draft, Visualization, Software, Methodology, Formal analysis. ZZ: Writing – review & editing, Formal analysis. JGo: Writing – review & editing, Validation. WH: Writing – review & editing, Supervision, Project administration. YL: Writing – review & editing, Project administration, Data curation, Conceptualization.

References

- Kanis JA, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporosis Int.* (2019) 30:3–44. doi: 10.1007/s00198-018-4704-5
- Qaseem A, Forciea MA, McLean RM, Denberg TD, Barry MJ, Cooke M, et al. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. *Ann Intern Med.* (2017) 166:818–39. doi: 10.7326/m15-1361
- Ravazzano L, Colaianni G, Tarakanova A, Xiao YB, Grano M, Libonati F. Multiscale and multidisciplinary analysis of aging processes in bone. *NPJ Aging.* (2024) 10:156. doi: 10.1038/s41514-024-00156-2
- Clynes MA, Harvey NC, Curtis EM, Fuggle NR, Dennison EM, Cooper C. The epidemiology of osteoporosis. *Br Med Bull.* (2020) 133:105–17. doi: 10.1093/bmb/ldaa005
- Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. *Am J Obstet Gynecol.* (2006) 194:S3–S11. doi: 10.1016/j.ajog.2005.08.047
- Praveen AD, Aspelund T, Ferguson SJ, Sigurdsson S, Gudnason V, Pálsson H, et al. Refracture and mortality risk in the elderly with osteoporotic fractures: the ages-Reykjavik study. *Osteoporosis Int.* (2024) 35:1231–41. doi: 10.1007/s00198-024-07096-3
- Khandelwal S, Lane NE. Osteoporosis: review of etiology, mechanisms, and approach to management in the aging population. *Endocrinol Metab Clin N Am.* (2023) 52:259–75. doi: 10.1016/j.ecl.2022.10.009
- Kanis JA, Norton N, Harvey NC, Jacobson T, Johansson H, Lorentzon M, et al. Scope 2021: a new scorecard for osteoporosis in Europe. *Arch Osteoporos.* (2021) 16:82. doi: 10.1007/s11657-020-00871-9
- Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporosis Int.* (2006) 17:1726–33. doi: 10.1007/s00198-006-0172-4
- Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res Off Am Soc Bone Miner Res.* (2014) 29:2520–6. doi: 10.1002/jbmr.2269
- LeBoff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporosis Int.* (2022) 33:2049–102. doi: 10.1007/s00198-021-05900-y
- Vásquez E, Alam MT, Murillo R. Race and ethnic differences in physical activity, osteopenia, and osteoporosis: results from Nhanes 2009–2010, 2013–2014, 2017–2018. *Arch Osteoporos.* (2023) 19:1356. doi: 10.1007/s11657-023-01356-1
- Yildiz Potter I, Rodriguez EK, Wu J, Nazarian A, Vaziri A. An automated vertebrae localization, segmentation, and osteoporotic compression fracture detection pipeline for computed tomographic imaging. *J Imaging Inf Med.* (2024) 37:2428–43. doi: 10.1007/s10278-024-01135-5
- Lou Y, Wang W, Wang C, Fu R, Shang S, Kang Y, et al. Clinical features and burden of osteoporotic fractures among the elderly in the USA from 2016 to 2018. *Arch Osteoporos.* (2022) 17:78. doi: 10.1007/s11657-022-01113-w
- Wu CH, Kao IJ, Hung WC, Lin SC, Liu HC, Hsieh MH, et al. Economic impact and cost-effectiveness of fracture liaison services: a systematic review of the literature. *Osteoporosis Int.* (2018) 29:1227–42. doi: 10.1007/s00198-018-4411-2

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmed.2024.1485095/full#supplementary-material>

16. Mladěnka P, Macáková K, Kujovská Krčmová L, Javorská L, Mrštná K, Carazo A, et al. Vitamin K - sources, physiological role, kinetics, deficiency, detection, therapeutic use, and toxicity. *Nutr Rev.* (2022) 80:677–98. doi: 10.1093/nutrit/nuab061
17. Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. *Endocr Rev.* (2000) 21:115–37. doi: 10.1210/edrv.21.2.0395
18. Vilaca T, Eastell R, Schini M. Osteoporosis in men. *Lancet Diab Endocrinol.* (2022) 10:273–83. doi: 10.1016/S2213-8587(22)00012-2
19. D'Ippolito G, Schiller PC, Ricordi C, Roos BA, Howard GA. Age-related osteogenic potential of mesenchymal stromal stem cells from human vertebral bone marrow. *J Bone Miner Res.* (1999) 14:1115–22. doi: 10.1359/jbmr.1999.14.7.1115
20. Weber P. Vitamin K and bone health. *Nutrition.* (2001) 17:880–7. doi: 10.1016/S0899-9007(01)00709-2
21. Hauschka PV, Lian JB, Cole DE, Gundberg CM. Osteocalcin and matrix Gla protein: vitamin K-dependent proteins in bone. *Physiol Rev.* (1989) 69:990–1047. doi: 10.1152/physrev.1989.69.3.990
22. Stock M, Schett G. Vitamin K-dependent proteins in skeletal development and disease. *Int J Mol Sci.* (2021) 22:9328. doi: 10.3390/ijms22179328
23. Yamaguchi M, Weitzmann MN. Vitamin K2 stimulates osteoblastogenesis and suppresses osteoclastogenesis by suppressing NF- κ B activation. *Int J Mol Med.* (2011) 27:3–14. doi: 10.3892/ijmm.2010.562
24. Palermo A, Tuccinardi D, D'Onofrio L, Watanabe M, Maggi D, Maurizi AR, et al. Vitamin K and osteoporosis: myth or reality? *Metabolism.* (2017) 70:57–71. doi: 10.1016/j.metabol.2017.01.032
25. Moschonis G, Kanellakis S, Papaioannou N, Schaafsma A, Manios Y. Possible site-specific effect of an intervention combining nutrition and lifestyle counselling with consumption of fortified dairy products on bone mass: the postmenopausal health study II. *J Bone Miner Metab.* (2011) 29:501–6. doi: 10.1007/s00774-010-0256-2
26. Braam LAJLM, Knapen MHJ, Geusens P, Brouns F, Hamulyák K, Gerichhausen MJW, et al. Vitamin K1 supplementation retards bone loss in postmenopausal women between 50 and 60 years of age. *Calcif Tissue Int.* (2003) 73:21–6. doi: 10.1007/s00223-002-2084-4
27. Binkley N, Harke J, Krueger D, Engelke J, Vallarta-Ast N, Gemar D, et al. Vitamin K treatment reduces undercarboxylated osteocalcin but does not alter bone turnover, density, or geometry in healthy postmenopausal north American women. *J Bone Miner Res.* (2009) 24:983–91. doi: 10.1359/jbmr.081254
28. Booth SL, Dallal G, Shea MK, Gundberg C, Peterson JW, Dawson-Hughes B. Effect of vitamin K supplementation on bone loss in elderly men and women. *J Clin Endocrinol Metab.* (2008) 93:1217–23. doi: 10.1210/jc.2007-2490
29. Fang Y, Hu C, Tao X, Wan Y, Tao F. Effect of vitamin K on bone mineral density: a meta-analysis of randomized controlled trials. *J Bone Miner Metab.* (2012) 30:60–8. doi: 10.1007/s00774-011-0287-3
30. K Giri T, Newton D, Chaudhary O, Deych E, Napoli N, Villareal R, et al. Maximal dose-response of vitamin-K2 (Menaquinone-4) on undercarboxylated osteocalcin in women with osteoporosis. *Int J Vitamin Nutr Res.* (2020) 90:42–8. doi: 10.1024/0300-9831/a000554
31. Inaba N, Sato T, Yamashita T. Low-dose daily intake of vitamin K(2) (Menaquinone-7) improves osteocalcin Γ -carboxylation: a double-blind, randomized controlled trials. *J Nutr Sci Vitaminol.* (2015) 61:471–80. doi: 10.3177/jnsv.61.471
32. Storz MA, Ronco AL. Nutrient intake in low-carbohydrate diets in comparison to the 2020–2025 dietary guidelines for Americans: a cross-sectional study. *Br J Nutr.* (2022) 129:1–14. doi: 10.1017/s0007114522001908
33. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO study group. *Osteoporosis Int.* (1994) 4:368–81. doi: 10.1007/bf01622200
34. Kanis JA, Glüer CC. An update on the diagnosis and assessment of osteoporosis with densitometry. *Osteoporosis Int.* (2000) 11:192–202. doi: 10.1007/s001980050281
35. Binkley N, Bilezikian JP, Kendler DL, Leib ES, Lewiecki EM, Petak SM. Official positions of the international society for clinical densitometry and executive summary of the 2005 position development conference. *J Clin Densitometry.* (2006) 9:4–14. doi: 10.1016/j.jocd.2006.05.002
36. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ, Khaltaev N. A reference standard for the description of osteoporosis. *Bone.* (2008) 42:467–75. doi: 10.1016/j.bone.2007.11.001
37. Centers for Disease Control and Prevention. Weighting module: Centers for Disease Control and Prevention (2024) Available at: <https://www.cdc.gov/nchs/nhanes/tutorials/weighting.aspx> (Accessed July 11, 2024).
38. Lachat C, Hawwash D, Ocké MC, Berg C, Forsum E, Hörnell A. Strengthening the reporting of observational studies in epidemiology - nutritional epidemiology (Strobe-nut): an extension of the Strobe statement. *Nutr Bull.* (2016) 41:240–51. doi: 10.1111/nu.12217
39. Knapen MHJ, Drummen NE, Smit E, Vermeer C, Theuvsen E. Three-year low-dose Menaquinone-7 supplementation helps decrease bone loss in healthy postmenopausal women. *Osteoporosis Int.* (2013) 24:2499–507. doi: 10.1007/s00198-013-2325-6
40. Ma ML, Ma ZJ, He YL, Sun H, Yang B, Ruan BJ, et al. Efficacy of vitamin K2 in the prevention and treatment of postmenopausal osteoporosis: a systematic review and meta-analysis of randomized controlled trials. *Front Public Health.* (2022) 10:979649. doi: 10.3389/fpubh.2022.979649
41. Apalset EM, Gjesdal CG, Eide GE, Tell GS. Intake of vitamin K1 and K2 and risk of hip fractures: the Hordaland health study. *Bone.* (2011) 49:990–5. doi: 10.1016/j.bone.2011.07.035
42. Booth SL, Tucker KL, Chen H, Hannan MT, Gagnon DR, Cupples LA, et al. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. *Am J Clin Nutr.* (2000) 71:1201–8. doi: 10.1093/ajcn/71.5.1201
43. Adams J, Pepping J. Vitamin K in the treatment and prevention of osteoporosis and arterial calcification. *AJHP.* (2005) 62:1574–81. doi: 10.2146/ajhp040357
44. Zhang Y, Liu Z, Duan L, Ji Y, Yang S, Zhang Y, et al. Effect of low-dose vitamin K2 supplementation on bone mineral density in middle-aged and elderly Chinese: a randomized controlled study. *Calcif Tissue Int.* (2020) 106:476–85. doi: 10.1007/s00223-020-00669-4
45. Booth SL, Broe KE, Gagnon DR, Tucker KL, Hannan MT, McLean RR, et al. Vitamin K intake and bone mineral density in women and men. *Am J Clin Nutr.* (2003) 77:512–6. doi: 10.1093/ajcn/77.2.512
46. Noh J-W, Park H, Kim M, Kwon YD. Gender differences and socioeconomic factors related to osteoporosis: a cross-sectional analysis of nationally representative data. *J Womens Health (Larchmt).* (2018) 27:196–202. doi: 10.1089/jwh.2016.6244
47. Seeman E, Bianchi G, Adami S, Kanis J, Khosla S, Orwoll E. Osteoporosis in men—consensus is premature. *Calcif Tissue Int.* (2004) 75:120–2. doi: 10.1007/s00223-004-4002-4
48. Orwoll DL, Chiles N, Jones M, Hochberg MC. Osteoporosis in men: update 2011. *Rheum Dis Clin North Am.* (2011) 37:401–14. doi: 10.1016/j.rdc.2011.08.004
49. Dy CJ, Lamont LE, Ton QV, Lane JM. Sex and Gender considerations in male patients with osteoporosis. *Clin Orthop Relat Res.* (2011) 469:1906–12. doi: 10.1007/s11999-011-1849-3
50. Orwoll DL, Chan J, Magaziner J. Hip fracture and its consequences: differences between men and women. *Orthop Clin N Am.* (2006) 37:611–22. doi: 10.1016/j.ocl.2006.08.003
51. Bilezikian JP. Osteoporosis in Men*. *J Clin Endocrinol Metabol.* (1999) 84:3431–4. doi: 10.1210/jcem.84.10.6060
52. Cosso R, Falchetti A. Vitamin K and bone metabolism: the myth and the truth. *Expert Rev Precis Med Drug Dev.* (2016) 1:301–17. doi: 10.1080/23808993.2016.1174061
53. Skalny AV, Aschner M, Tsatsakis A, Rocha JBT, Santamaria A, Spandidos DA, et al. Role of vitamins beyond vitamin D(3) in bone health and osteoporosis (review). *Int J Mol Med.* (2024) 53:5333. doi: 10.3892/ijmm.2023.5333
54. Raper N, Perloff B, Ingwersen L, Steinfeldt L, Anand J. An overview of USDA's dietary intake data system. *J Food Compos Anal.* (2004) 17:545–55. doi: 10.1016/j.jfca.2004.02.013
55. Rhodes DG, Murayi T, Clemens JC, Baer DJ, Sebastian RS, Moshfegh AJ. The USDA automated multiple-pass method accurately assesses population sodium intakes. *Am J Clin Nutr.* (2013) 97:958–64. doi: 10.3945/ajcn.112.044982
56. Rumpler WV, Kramer M, Rhodes DG, Moshfegh AJ, Paul DR. Identifying sources of reporting error using measured food intake. *Eur J Clin Nutr.* (2008) 62:544–52. doi: 10.1038/sj.ejcn.1602742
57. Blanton CA, Moshfegh AJ, Baer DJ, Kretsch MJ. The USDA automated multiple-pass method accurately estimates group total energy and nutrient intake 12. *J Nutr.* (2006) 136:2594–9. doi: 10.1093/jn/136.10.2594
58. Moshfegh AJ, Rhodes DG, Baer DJ, Murayi T, Clemens JC, Rumpler WV, et al. The US Department of Agriculture automated multiple-pass method reduces bias in the collection of energy intakes. *Am J Clin Nutr.* (2008) 88:324–32. doi: 10.1093/ajcn/88.2.324