Dietary patterns and hip fracture in the Adventist Health Study 2: combined vitamin D and calcium supplementation mitigate increased hip fracture risk among vegans

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ABSTRACT

Background: Concerns regarding the adequacy of vegetarian diets with respect to fracture risk continue.

Objectives: We aimed to explore the influence of 5 previously defined dietary patterns on hip fracture risk and whether this association is modified by concomitant calcium and vitamin D supplementation.

Methods: The Adventist Health Study 2 is a prospective cohort study in which participants were enrolled during 2002–2007; proportional hazards regression analyses were used to estimate fracture risk. Participants reside throughout the United States and Canada. A total of 34,542 non-Hispanic white peri- and postmenopausal women and men 45 y and older responded to the biennial hospital history form and were followed for a median of 8.4 y.

Results: The study identified 679 incident hip fractures during 249,186 person-years of follow-up. Fracture risk varied according to dietary pattern, with a clear effect modification by concurrent supplementation with both vitamin D and calcium. In multivariable models, including adjustment for calcium and vitamin D supplementation, female vegans had 55% higher risk of hip fracture (HR: 1.55; 95% CI: 1.06, 2.26) than nonvegetarians (NVEGs), whereas there was no association between diet pattern and hip fracture risk in men. When further stratifying females on supplement use with both vitamin D and calcium, vegans taking both supplements were at no greater risk of hip fracture than the subjects with other dietary patterns including the NVEGs.

Conclusions: Without combined supplementation of both vitamin D and calcium, female vegans are at high risk of hip fracture. However, with supplementation the excessive risk associated with vegans disappeared. Further research is needed to confirm the adequacy of a vegan diet supplemented with calcium and vitamin D with respect to risk of fracture. *Am J Clin Nutr* 2021;114:488–495.

Keywords: diet pattern, vegan, hip fracture, dietary nutrients, Adventist Health Study

Introduction

Dietary patterns with high consumption of fruits and vegetables have been associated with better bone health outcomes, such as higher bone mineral density (BMD) (1) and reduced fracture risk (2–5). There is also a growing body of evidence about the possible health benefits of vegetarian diets, because they have been shown to reduce the risk of many chronic diseases such as diabetes (6), cardiovascular diseases (7, 8), and cancers (9, 10).

However, there are lingering concerns about the adequacy of vegetarian diets for bone health. In particular, the vegan diet has been criticized (11–15). Because of the lack of dairy consumption among vegans, concern about osteoporosis and risk of fracture has long been expressed in the literature (16). In a relatively recent review, Tucker (12) postulates that vegetarians as well as vegans are at increased risk of fracture in light of characteristically low dietary intakes of calcium, vitamin D, zinc, n–3 PUFAs, and protein, all dietary nutrients which have been shown to be important and positively associated with BMD. Some of these nutrients are either found largely or more easily bioavailable in animal protein sources (12). Not surprisingly, lower BMD has been more consistently observed among vegans than among subjects with other dietary patterns (14, 17–19). A 2009 Bayesian meta-analysis reported a 4% and 6% lower BMD among vegetarians and vegans, respectively, than among nonvegetarians (18). However, most of the studies reviewed in this analysis were cross-sectional.

Few prospective studies have examined the effects of vegetarian diets on risk of fractures. The Adventist Health Study (AHS)-1 (20) and -2 (5) have reported that consumption of foods high

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Abbreviations used: AHS-2, Adventist Health Study 2; BMD, bone mineral density; HT, hormone therapy; LOV, lacto-ovo-vegetarian; NVEG, nonvegetarian; PYRS, person-years.

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in plant protein decreased the risk of forearm and hip fracture, respectively, among vegetarians. On the other hand, the Oxford study (15) as well as the AHS-2 (5) have both found that the vegan diet, compared with other diet patterns, is associated with higher incidence of hip fractures. Although vegetarian diets are increasingly recognized as beneficial in reducing the risk of many chronic diseases including cancer (21) and heart disease (9), the efficacy of plant-based diets for bone health continues to be questioned.

The AHS-2 is a large American cohort, of whom nearly half are vegetarians including ∼8% vegans, and it is therefore well suited to study the risk of fractures among these dietary groups. The purposes of this study were *1*) to examine the association of hip fracture with 5 previously described dietary patterns (22) in non-Hispanic white women and men 45 y of age and older, and *2*) to determine if this association is modified by calcium and vitamin D supplementation.

Methods

The AHS-2, a large National Cancer Institute–funded cohort study to examine relations between lifestyle and health outcomes, consists of ∼96,000 members of the Seventh-day Adventist church in North America (i.e., the United States and Canada) who were recruited between 2002 and 2007 with ∼27% self-identifying as black. The study population is limited to non-Hispanic white peri- and postmenopausal women and men 45 y and older who completed ≥1 follow-up questionnaire. Owing to lower incidence of osteoporosis, lower risk of fracture, and lower serum vitamin D concentrations among blacks (23), they, and a smaller group, mostly Hispanics and Asians (8.5% of the AHS-2 cohort), were excluded (**Supplemental Figure 1**). Those with physician-diagnosed osteoporosis or any fracture recorded on the baseline questionnaire were also excluded, yielding a cohort of 34,542 (18,732 women and 15,810 men). The study was approved by the Loma Linda University Institutional Review Board.

At enrollment, participants completed a comprehensive lifestyle survey including a validated FFQ. To calibrate the questionnaire, >1100 randomly selected participants completed several 24-h recalls of diet and 7-d recalls of physical activity (24). Biological samples were also collected for laboratory analysis and validation of the dietary data. A more detailed profile of the AHS-2 cohort has been published elsewhere (25). Biennially, participants were mailed follow-up questionnaires including the following item: “Have you had any fractures (broken bones) of the wrist or hip after 2001? Include only those that came from a fall or minor accident.” Answer options were 2-y time categories such as 2002–2003 and 2004–2005. To date, occurrence of hip fractures has been identified in 3 follow-up questionnaires, the most recent one being in 2015. The midpoint of the selected time interval for hip fracture was used as the time of censoring for cases, whereas those without a reported hip fracture were censored at the time of return of the last biennial questionnaire.

Based on the responses to the FFQ, 5 dietary patterns [vegan, lacto-ovo-vegetarian (LOV), pesco-vegetarian, semivegetarian, and nonvegetarian (NVEG)] have been defined along a continuum of avoidance of various types of animal food sources in the diet. Vegans, with rare exception (<1 time/mo), consume only a plant-based diet, whereas LOVs include dairy and eggs in their diet. In addition to dairy and eggs, pesco-vegetarians add fish to their diet. Semivegetarians are defined by a very low frequency of fish and nonfish meat consumption (≤1 times/wk). The NVEGs, comprising 42% of the cohort, consume fish and meat combined >1 time/wk. Precise definitions for the diet patterns have been previously described (26).

Statistics

Nutrient intakes, using the Nutrition Data System for Research database (24), and relevant covariates known to be associated with bone health were compared across the 5-diet-pattern continuum using chi-square tests and 1-factor ANOVA with Scheffe post hoc comparisons for categorical and quantitative variables, respectively. Candidate covariates included energy, total calcium, total vitamin D, potassium, height, weight, education, self-reported health, physical activity, sun-reactive skin type (light/moderate compared with dark tanning), daylight exposure time (</≥1 h), menopausal status (peri- or postmenopausal), hormone therapy (HT), alcohol status, smoking status, prevalent cancer, and number of comorbidities (0, 1, or >1). These self-reported comorbidities included a total of 13 grouped into cardiovascular (angina pectoris, myocardial infarction, stroke, transient ischemic attack, congestive heart failure), respiratory (asthma, chronic bronchitis, emphysema), neurological (Parkinson disease), and musculoskeletal (rheumatoid arthritis, degenerative arthritis, degenerative disc disease/sciatica, fibromyalgia). Including this comorbidity variable or only musculoskeletal comorbidities or only rheumatoid arthritis did not change the main effect, and these were therefore not included in the final model. Student’s *t* test was used to compare nutrients by sex. Differences between cases and noncases were examined with Student’s *t* test for quantitative variables and chi-square tests for categorical variables.

Cox proportional hazards models, with attained age as the time variable, were used to analyze the effects of the 5 dietary patterns on risk of hip fracture. NVEG was used as the reference group. All nutrient variables in the multivariable models were energy adjusted using the residual method (27) and log transformed. The proportional hazards assumption was verified for sex and other categorical covariates using Schoenfeld residuals. Multivariable analyses were performed on men and women separately and together. Effect modification by sex was tested with an interaction term in the final model and was significant. Because both calcium and vitamin D intakes were lowest among vegans compared with other diet patterns, effect modification by supplementation with calcium and vitamin D separately and together were also tested in models for the entire study population and for women alone. All supplement effect modifications tested were significant among women. Subsequently, the effects on hip fracture risk of consuming no supplements, calcium only, or both by diet pattern were modeled separately. There were only 373 women taking vitamin D supplements alone and among these there were only 2 hip fractures. Therefore, we were not able to assess risk on hip fracture among this group separately.

All models for men and women combined controlled for the same covariates. In addition, models for women controlled for menopausal status and HT. To develop the final models, multiple imputation was used to fill both missing dietary data from the FFQ, which was typically 3%–10% per food frequency item, and

TABLE 1 Nutrient intake and lifestyle factors by dietary pattern for non-Hispanic white women and men aged 45 y and older[1]

	Vegans (n = 2832, hip fracture cases = 64)	Lacto-ovo-vegetarians (n = 12,008, hip fracture cases = 270)	Pesco-vegetarians (n = 2904, hip fracture cases = 70)	Semivegetarians (n = 2142, hip fracture cases = 42)	Nonvegetarians (n = 14,656, hip fracture cases = 233)	P
Age	62.8 ± 11.1	63.6 ± 11.4	65.3 ± 11.4	64.0 ± 11.3	62.5 ± 10.7	<0.0001[2]
Female	52.7	53.7	55.4	56.8	54.5	0.002[2]
Education (Bachelor's or higher)	32.1	39.2	30.8	28.0	23.3	<0.0001[2]
Hormone use (current)	7.8	18.2	19.3	21.1	21.8	<0.0001[2]
Physical activity (walking >5 miles/wk)	40.3	32.0	30.7	23.8	22.5	<0.0001[2]
Alcohol consumption (ever)	27.9	20.5	34.5	32.6	49.4	<0.0001[2]
Smoking (ever)	13.1	9.8	17.0	16.9	23.6	<0.0001[2]
Sunlight exposure (<1 h/d)	26.1	30.4	27.8	28.8	24.8	<0.0001[2]
Skin type (light tanning vs. dark tanning)	82.6	83.2	83.2	82.5	80.5	<0.0001[2]
Using both vitamin D and calcium supplements	32.3	46.9	51.5	49.1	49.7	<0.0001[2]
Comorbidities[3]						
1	22.9	23.9	24.8	26.2	26.8	<0.0001[2]
>1	8.7	13.1	15.7	18.0	18.4	
Prevalent cancer (yes)	9.2	9.7	10.9	9.5	10.6	
Energy, kcal	1850 ± 678	1887 ± 689	1956 ± 724	1764 ± 695[4]	1942 ± 752	<0.0001[5]
Total protein, g/d	67.6 ± 27.9	68.9 ± 28.2	72.5 ± 29.5[4]	63.9 ± 26.9[4]	74.8 ± 30.3[4]	<0.0001[5]
Animal protein, g/d	2.48 ± 2.1[4]	11.5 ± 10.3[4]	15.7 ± 11.3	15.5 ± 10.9	31.1 ± 18.1[4]	<0.0001[5]
Plant protein, g/d	65.1 ± 26.9[4]	57.4 ± 25.4	56.8 ± 25.9	48.4 ± 23.1[4]	43.6 ± 22.3[4]	<0.0001[5]
Dairy protein, g/d	0.003 ± 0.04[4]	6.8 ± 8.7[4]	7.7 ± 9.0[4]	8.8 ± 9.3[4]	11.6 ± 9.9[4]	<0.0001[5]
Nondairy animal protein, g/d	2.5 ± 2.1[4]	4.7 ± 4.4[4]	8.0 ± 5.4[4]	6.7 ± 4.8[4]	19.5 ± 13.3[4]	<0.0001[5]
Soy protein, g/d	16.5 ± 13.9	16.7 ± 13.7	16.1 ± 14.2	12.8 ± 11.5[4]	9.1 ± 1.4[4]	<0.0001[5]
Nonsoy plant protein, g/d	48.7 ± 21.1[4]	40.7 ± 18.4	40.7 ± 18.8	35.6 ± 17.4	34.6 ± 18.7	<0.0001[5]
Animal:plant protein ratio	0.04 ± 0.03[4]	0.24 ± 0.30[4]	0.33 ± 0.30[4]	0.39 ± 0.49[4]	0.90 ± 0.78[4]	<0.0001[5]
Total protein, g/kg body weight	1.00 ± 0.44	0.94 ± 0.41	1.00 ± 0.44	0.84 ± 0.39[4]	0.93 ± 0.41	<0.0001[5]
Dietary calcium, mg/d	788 ± 348[4]	883 ± 421[4]	937 ± 438	852 ± 426[4]	920 ± 460	<0.0001[5]
Calcium supplements, mg/d	287 ± 446[4]	386 ± 476	431 ± 497	398 ± 484	405 ± 493	<0.0001[5]
Total calcium, mg/d	1076 ± 570[4]	1269 ± 641	1368 ± 671[4]	1250 ± 652	1325 ± 681[4]	<0.0001[5]
Magnesium, mg/d	607 ± 264[4]	538 ± 254[4]	579 ± 282[4]	491 ± 250	493 ± 251	<0.0001[5]
Phosphorus, mg/d	1248 ± 480	1266 ± 499	1344 ± 534	1204 ± 503[4]	1339 ± 542	<0.0001[5]
Potassium, mg/d	3824 ± 1553[4]	3449 ± 1392[4]	3693 ± 1511[4]	3148 ± 1378[4]	3322 ± 1394[4]	<0.0001[5]
Sodium, mg/d	3304 ± 1930	3532 ± 1941	3381 ± 1874	3211 ± 1848	3592 ± 2056	<0.0001[5]
Dietary vitamin D, μg/d	2.4 ± 2.6[4]	3.3 ± 3.2	4.3 ± 3.4[4]	3.5 ± 3.0	4.9 ± 3.6[4]	<0.0001[5]
Vitamin D supplements, μg/d	4.9 ± 24.5[4]	6.3 ± 18.7	7.6 ± 24.7	6.8 ± 20.4	7.2 ± 22.7	<0.0001[5]
Total vitamin D intake, μg/d	7.3 ± 25.0[4]	9.6 ± 19.1	11.9 ± 25.0	10.3 ± 20.5	12.1 ± 23.0	<0.0001[5]

[1] n = 34,542. Values are means ± SDs or percentages.
[2] Chi-square test.
[3] Angina pectoris, myocardial infarction, stroke, transient ischemic attack, congestive heart failure, asthma, Parkinson disease, rheumatoid arthritis, degenerative arthritis, degenerative disc disease/sciatica, or fibromyalgia.
[4] Different from all other groups at $P < 0.05$ (1-factor ANOVA Scheffé post hoc comparisons).
[5] One-factor ANOVA.

missing nondietary data (28). This imputation was guided by a random subsample of data originally missing in the questionnaire and subsequently completed in a phone interview. Multivariable HRs and CIs were calculated using 5 imputed data sets; the 5 sets of β-coefficients and their estimated variances were used to calculate composite point estimates and variances (28). All analyses were performed with SAS version 9.4 (SAS Institute, Inc.) or the R computer language.

Results

LOVs and NVEGs comprised 77% of the study population (**Table 1**). There were notable differences in lifestyle factors among diet patterns. Vegans reported the lowest use of HT and highest frequency of walking ≥5 miles/wk. LOVs were more likely to have a graduate degree and least likely to have ever smoked. Vegans and LOVs generally had lower numbers of comorbidities than the other 3 diet patterns. NVEGs were least likely to have a graduate degree and most likely to ever have smoked or used alcohol. The greatest differences in nutrient intake occurred between subjects on vegan and NVEG diets (**Supplemental Table 1**). Vegans had the highest intakes of plant protein, magnesium, and potassium and the lowest intakes of animal protein, calcium, and vitamin D, whereas NVEGs had the highest intakes of total protein, animal protein, and dietary and total vitamin D and lowest intake of plant protein. Furthermore, NVEGs consumed twice the intake of animal protein that the semi- and pesco-vegetarians did. Among vegans, 32% supplemented with both vitamin D and calcium compared with ∼50% in the other dietary groups. Interestingly, magnesium intake was also consistently (22%–29%) higher across diet patterns among those who consumed both calcium and vitamin D than among those taking neither or only 1 of the supplements (data not shown). In addition,

TABLE 2 Nutrient intake for non-Hispanic white women and men aged 45 y and older[1]

Nutrient	Women (n = 18,732, hip fracture cases = 419)	Men (n = 15,810, hip fracture cases = 216)	P^2
Energy, kcal	1830 ± 698	1995 ± 736	<0.0001
Total protein, g/d	68.8 ± 28.5	74.2 ± 30.0	<0.0001
Animal protein, g/d	19.5 ± 16.9	19.9 ± 17.8	<0.0001
Plant protein, g/d	49.3 ± 24.3	54.3 ± 26.1	<0.0001
Dairy protein, g/d	8.6 ± 9.6	8.3 ± 9.5	0.0004
Nondairy animal protein, g/d	10.9 ± 11.1	11.7 ± 12.5	<0.0001
Soy protein, g/d	12.7 ± 12.9	13.7 ± 13.6	<0.0001
Nonsoy plant protein, g/d	36.6 ± 17.5	40.6 ± 19.2	<0.0001
Total protein, g/kg body weight	0.98 ± 0.44	0.90 ± 0.39	<0.0001
Dietary calcium, mg/d	890 ± 437	897 ± 435	0.55
Calcium supplements, mg/d	505 ± 516	254 ± 404	<0.0001
Total calcium, mg/d	1396 ± 1386	1152 ± 1142	<0.0001
Magnesium, mg/d	527 ± 261	523 ± 255	0.09
Phosphorus, mg/d	1263 ± 510	1340 ± 532	<0.0001
Potassium, mg/d	3372 ± 1415	3494 ± 1435	<0.0001
Sodium, mg/d	3502 ± 2010	3511 ± 1948	<0.0001
Dietary vitamin D, μg/d	3.9 ± 3.4	4.1 ± 3.5	<0.0001
Vitamin D supplements, μg/d	7.5 ± 23.3	5.8 ± 19.4	<0.0001
Total vitamin D, μg/d	11.4 ± 23.7	9.9 ± 19.8	<0.0001

[1] n = 34,542. Values are means ± SDs unless otherwise indicated.
[2] Student t tests.

the nonsupplemented vegans had 11.2% lower dietary vitamin D intake than the supplemented vegans and 31%–53% lower dietary vitamin D intake than those in the other dietary groups (data not shown). Nutrient intake for men and women was relatively similar (**Table 2**). However, as expected, men consumed more total protein (g/d) than women, but total protein adjusted for body weight ($g \cdot kg^{-1} \cdot d^{-1}$) was lower for men than for women: 0.90 and 0.98, respectively. Also, as expected, plant protein consumption, especially nonsoy, was considerably higher than animal protein consumption in this cohort. Most notably, total calcium and total vitamin D intakes were higher in women, largely due to higher frequency of supplementation.

There were 419 hip fractures in women [3.09/1000 person-years (PYRS)] and 260 in men (2.29/1000 PYRS) during a median 8.4 y of follow-up for a total of 249,186 PYRS. **Table 3** shows differences between cases and noncases, stratified on sex. The distribution of diet pattern by sex was remarkably similar. Being older, weighing less, and having >1 comorbidity were associated with hip fracture in both sexes. In addition, prevalent cancer was associated with hip fracture in men.

In pooled analyses of men and women, there was a nonsignificant increasing trend in fracture risk with increasingly plant-based diet patterns (**Table 4**). However, the effect of diet pattern was modified by sex (P = 0.05), indicating the effect was largely driven by women.

Men

No association was found between diet pattern and hip fracture risk in age-adjusted analyses. Multivariable analysis and stratification on supplementation with vitamin D and/or calcium did not change these findings.

Women

There was a significant association of diet pattern with hip fracture, with a higher proportion of cases among those consuming a plant-based diet. The incidence of hip fracture per 1000 PYRS was 3.9 and 2.4 for vegans and NVEGs, respectively.

Age-adjusted models showed increasing risk of hip fracture across the diet continuum from NVEGs to vegans (P-trend = 0.03) (Table 4), with vegans having a 53% higher age-adjusted risk of fracture than NVEGs (HR: 1.53; 95% CI: 1.07, 2.17). Multivariable analyses did not change the findings substantially. However, interactions between diet pattern and calcium or vitamin D supplement intake alone or together in multivariable models were each significant. **Table 5** shows the multivariable association between diet pattern and hip fracture in the various subgroups of those taking no supplement, only a calcium supplement, or both supplements. Vegan women who consumed neither supplement had almost 3 times the risk of hip fracture relative to NVEG women (HR: 2.99; 95% CI: 1.54, 5.82; P-trend = 0.006). In contrast, among those with calcium and vitamin D supplementation combined, no increase in risk of hip fracture was found across dietary patterns (P-trend = 0.78). Among those who only supplemented with calcium, there was a nonsignificant increased risk for all vegetarian dietary patterns, with pesco-vegetarians and vegans having the highest HRs of 1.88 and 1.62, respectively, but no significant trend was found across the diet categories (P-trend = 0.36).

Discussion

A recent meta-analysis of fracture outcomes in a small number of cohort studies concluded that vegans had higher fracture rates than omnivores (29), consistent with our findings. Recently, the EPIC (European Prospective Investigation into Cancer and

TABLE 3 Baseline characteristics of cases and noncases by sex[1]

	Women			Men		
	Cases ($n = 419$)	Noncases ($n = 18{,}313$)	*P*	Cases ($n = 260$)	Noncases ($n = 15{,}550$)	*P*
Dietary pattern			0.0003[2]			0.54[2]
Vegan	42 (10.0)	1423 (7.8)		22 (8.5)	1345 (8.6)	
Lacto-ovo-vegetarian	166 (39.6)	6281 (34.3)		104 (40.0)	5457 (35.1)	
Pesco-vegetarian	48 (11.5)	1562 (8.5)		22 (8.5)	1272 (8.2)	
Semivegetarian	28 (6.7)	1189 (6.5)		14 (5.4)	911 (5.9)	
Nonvegetarian	135 (32.2)	7858 (42.9)		98 (37.7)	6565 (42.2)	
Age, y	73.2 ± 10.7	62.8 ± 10.7	<0.0001[3]	70.9 ± 10.7	63.3 ± 11.5	<0.0001[3]
Height, cm	163 ± 6.7	163 ± 6.7	0.16[3]	1.78 ± 8.2	1.78 ± 7.2	0.99[3]
Weight, kg	73.1 ± 17.1	69.1 ± 15.8	<0.0001[3]	85.1 ± 15.7	82.5 ± 16.3	<0.0001[3]
Education			0.08[2]			0.48[2]
Some college or less	308 (73.5)	12,729 (69.5)		139 (53.5)	7967 (51.2)	
Bachelor's or higher	111 (26.5)	5584 (30.5)		121 (46.5)	7583 (48.8)	
Health self-report			0.0007[2]			0.37[2]
Fair/poor	79 (19.5)	2445 (13.6)		35 (13.8)	1814 (12.0)	
Good/excellent	327 (80.5)	15,508 (86.4)		219 (86.2)	13370 (88.0)	
Using both vitamin D and calcium supplement			0.11[2]			0.29[2]
Yes	233 (55.6)	9468 (51.7)		118 (45.4)	6548 (42.1)	
No	186 (44.4)	8845 (48.3)		142 (54.6)	9002 (57.9)	
Hormone use			0.57[2]			
Never/past	343 (81.9)	14,790 (80.8)				
Current	76 (18.1)	3523 (19.2)				
Alcohol			<0.0001[2]			0.0008[2]
Never	332 (79.2)	11,769 (64.3)		168 (64.6)	8424 (54.2)	
Ever	87 (20.8)	6544 (35.7)		92 (35.4)	7126 (45.8)	
Smoke			<0.0001[2]			0.26[2]
Never	391 (93.2)	15,152 (82.7)		195 (75.0)	11,175 (71.9)	
Ever	28 (6.7)	3161 (17.3)		65 (25.0)	4375 (28.1)	
Physical activity, miles/wk			0.0003[2]			0.20[2]
≤5	335 (80.0)	13,160 (71.9)		187 (71.9)	10,605 (68.2)	
>5	84 (20.2)	5153 (28.1)		73 (28.1)	4945 (31.8)	
Comorbidities[4]			0.0002[2]			<0.0001[2]
None	207 (49.4)	10,873 (59.4)		143 (55.0)	10,400 (66.9)	
1	127 (30.3)	4611 (25.2)		71 (27.3)	3429 (22.1)	
>1	85 (20.3)	2829 (15.5)		46 (17.7)	1721 (11.1)	
Prevalent cancer			0.36[2]			0.009[2]
No	371 (88.5)	16,499 (89.9)		224 (86.2)	14,135 (90.9)	
Yes	48 (11.5)	1847 (10.1)		36 (13.8)	1415 (9.1)	
Sunlight exposure, h/d			0.01[2]			0.31[2]
≤1	137 (32.7)	4985 (27.2)		33 (12.7)	2325 (15.0)	
>1	282 (67.3)	13,328 (72.8)		227 (87.3)	13,225 (85.0)	
Calcium supplement, mg/d			0.08[2]			0.18[2]
None	117 (27.9)	6073 (33.2)		117 (45.0)	7900 (50.8)	
≤800	159 (38.0)	6519 (35.6)		106 (40.8)	5691 (36.6)	
>800	143 (34.1)	5721 (31.2)		37 (14.2)	1959 (12.6)	
Vitamin D supplement			0.34[2]			0.54[2]
No	184 (43.9)	8474 (46.3)		139 (53.5)	8607 (55.4)	
Yes	235 (56.1)	9839 (53.7)		121 (46.5)	6943 (44.6)	

[1] $n = 34{,}542$. Values are mean ± SD or n (%) unless otherwise indicated.
[2] Chi-square test.
[3] Two-sample t test.
[4] Angina pectoris, myocardial infarction, stroke, transient ischemic attack, congestive heart failure, chronic bronchitis, emphysema, asthma, Parkinson disease, rheumatoid arthritis, degenerative arthritis, degenerative disc disease/sciatica, or fibromyalgia.

Nutrition)-Oxford cohort study (15) reported that the risk of hip fracture among 4 dietary patterns was highest among vegans (HR: 2.32) and concluded that the higher risk was due in part to low calcium intake. In the same cohort, vegans and vegetarians had lower serum concentrations of 25-hydroxyvitamin D than meat and fish eaters (30). In the current study, mean dosage of each supplement differed little by pattern: ∼660 mg Ca/d and ∼13.5 μg vitamin D/d. However, the proportion of vegans using both supplements (32%) was significantly lower than for the other patterns (∼50%). When comparing dietary intakes among

TABLE 4 Age- and multivariable-adjusted HR models of associations of diet pattern and risk of hip fracture in non-Hispanic white women and men aged 45 y and older, separately and combined, who were participants in the Adventist Health Study 2, USA, 2002–2015[1]

	Women (n = 18,712, hip fracture cases = 419)		Men (n = 15,798, hip fracture cases = 260)		All (n = 34,510, hip fracture cases = 679)	
	n (Cases)	HR (95% CI)	*n* (Cases)	HR (95% CI)	*n* (Cases)	HR (95% CI)
Age-adjusted		*P*-trend = 0.03		*P*-trend = 0.84		*P*-trend = 0.09
Nonvegetarian	6565 (135)	Ref.	7858 (98)	Ref.	14,656 (233)	Ref.
Semivegetarian	911 (28)	0.99 (0.64, 1.52)	1189 (14)	0.79 (0.42, 1.47)	2142 (42)	0.92 (0.64, 1.33)
Pesco-vegetarian	1272 (48)	1.21 (0.83, 1.76)	1562 (22)	0.77 (0.48, 1.25)	2904 (70)	1.01 (0.75, 1.36)
Lacto-ovo-vegetarian	5457 (166)	1.18 (0.93, 1.49)	6281 (104)	1.06 (0.80, 1.41)	12,008 (270)	1.13 (0.94, 1.35)
Vegan	1345 (42)	1.53 (1.07, 2.17)	1423 (22)	0.93 (0.58, 1.49)	2832 (64)	1.22 (0.92, 1.62)
Multivariable		*P*-trend = 0.05		*P*-trend = 0.57		*P*-trend = 0.06
Nonvegetarian	6565 (135)	Ref.	7858 (98)	Ref.	14,656 (233)	Ref.
Semivegetarian	911 (28)	0.99 (0.64, 1.53)	1189 (14)	0.79 (0.42, 1.48)	2142 (42)	0.92 (0.64, 1.33)
Pesco-vegetarian	1272 (48)	1.20 (0.81, 1.78)	1562 (22)	0.81 (0.50, 1.32)	2904 (70)	1.03 (0.76, 1.41)
Lacto-ovo-vegetarian	5457 (166)	1.17 (0.91, 1.50)	6281 (104)	1.11 (0.81, 1.51)	12,008 (270)	1.16 (0.95, 1.40)
Vegan	1345 (42)	1.55 (1.06, 2.26)	1423 (22)	1.01 (0.61, 1.68)	2832 (64)	1.31 (0.97, 1.78)

[1]All models adjusted for age, height, weight, energy, calcium, potassium, vitamin D, alcohol intake, outdoor exposure, physical activity, education, alcohol, and smoking. Model for women in addition adjusted for menopausal status and hormone therapy. Model for all in addition adjusted for sex.

women, a vegan pattern was associated with significantly lower intakes of calcium and vitamin D and with an increased risk of hip fracture compared with an NVEG diet. However, the vegan diet, when supplemented with both calcium and vitamin D, was associated with the same risk as or a lower risk of fracture than NVEG or the other diet categories. Our results therefore suggest that both vitamin D and calcium are independently important and necessary for an optimal vegan diet.

Only women showed an increasing risk of hip fracture across the diet patterns. Several factors may play a role in the observed sex difference. Power to detect the same effect in men may be low owing to the combined effects of there having been fewer men in the study and an inherently lower risk of hip fracture, because men account for only 30% of hip fractures (31). However, CIs for men and women are about the same (Table 4), making this an unlikely explanation for the sex differences in hip fracture risk by diet. Statistics also show that women fall more often and sustain an injury in a higher percentage of falls than men (31). The lower risk of fracture in men has been attributed to anatomic and hormonal advantages. In early adulthood, men have higher BMD and larger bones for a given height and weight than women (32). With aging, greater loss in bone density and greater increases in cortical bone porosity have been observed in women (33, 34). Furthermore, the impact of declining testosterone in males has minimal impact on bone loss compared with declining female hormones (31). It is also possible that men in this cohort experience greater bone health advantage from a diet with adequate fruits and vegetables, as shown for the Mediterranean diet in several European cohort studies (2, 35–37).

Lack of supplementation with both calcium and vitamin D among vegan women was associated with lower use of hormone replacement and lower dietary vitamin D and magnesium. HT is shown to be protective against hip fracture (38). The lower nutrient intake among nonsupplemented vegans might suggest a poorer quality of diet, such as the proverbial "Western diet" (39) or a more inflammatory (40) diet, both associated with increased risk of hip fracture. This is unlikely, because an earlier report on the dietary patterns of the parent AHS-2 cohort (41) found that vegans had the highest intakes of fiber, vitamin C, folate, β-carotene, vitamin E, and magnesium which are strongly anti-inflammatory (42), and they also had the lowest intakes of inflammatory saturated and *trans* fats. Furthermore, intake of sugar was shown to be no greater in vegans in the parent AHS-2 cohort (41) than in other diet groups. Although magnesium intake

TABLE 5 Multivariable-adjusted HR models of associations of diet pattern and risk of hip fracture for non-Hispanic white women by supplement use in the Adventist Health Study 2, USA, 2002–2015[1]

	Consumed no supplements (n = 5817, hip fracture cases = 115) (*P*-trend = 0.006)		Consumed calcium supplements only (n = 2841, hip fracture cases = 69) (*P*-trend = 0.36)		Consumed both supplements (n = 9701, hip fracture cases = 233) (*P*-trend = 0.78)	
	n (Cases)	HR (95% CI)	*n* (Cases)	HR (95% CI)	*n* (Cases)	HR (95% CI)
Nonvegetarian	2316 (25)	Ref.	1200 (20)	Ref.	4314 (10)	Ref.
Semivegetarian	363 (7)	1.38 (0.57, 3.32)	174 (4)	1.31 (0.39, 4.43)	655 (93)	0.83 (0.46, 1.48)
Pesco-vegetarian	443 (12)	1.45 (0.63, 3.38)	236 (11)	1.88 (0.77, 4.57)	901 (24)	0.99 (0.60, 1.61)
Lacto-ovo-vegetarian	1983 (47)	1.56 (0.91, 2.66)	997 (26)	1.23 (0.65, 2.32)	3336 (17)	1.08 (0.78, 1.48)
Vegan	712 (24)	2.99 (1.54, 5.82)	234 (8)	1.62 (0.67, 3.93)	495 (89)	0.84 (0.42, 1.66)

[1]All models adjusted for age, menopausal status, hormone therapy, height, weight, energy, potassium, outdoor exposure, physical activity, education, alcohol, smoking, and calcium and vitamin D (total intake if not consuming the supplement, otherwise only dietary intake).

was lower among nonsupplemented than among supplemented vegans, it was still higher than in all other dietary groups. On the other hand, the 27%–51% lower dietary vitamin D intake among vegans than among the other diet groups could be an explanation for the 3-fold increase in risk of hip fracture.

The low dietary intake of both calcium and vitamin D in this large population of vegans reinforces the concern regarding the adequacy of a vegan diet for bone health. Supplementation with both nutrients was associated with a strong risk reduction in vegans, suggesting that strict adherence to a vegan diet may necessitate supplementation with both calcium and vitamin D. Currently the supplemental use of both nutrients for the purpose of fracture prevention is intensely debated (43). Conclusions of a number of meta-analyses of randomized clinical trials of calcium and vitamin D supplementation are challenging the routine practice of supplementation with calcium and/or vitamin D in healthy community-dwelling adults over the age of 50 y without demonstrated vitamin D insufficiency (44–46). Others have expressed caution against premature conclusions, citing study design concerns (47). Furthermore, a recent systematic review and meta-analysis of both observational studies and randomized clinical trials (48) concluded that using both supplements together is a promising strategy to reduce the risk of fracture among those at elevated risk.

Because vegans in this study have the lowest number of comorbidities among the diet patterns, this would qualify them as healthy community-dwelling adults. Nevertheless, the very dietary choices that appear to be associated with low comorbidities also appear to contribute to higher risk of hip fracture. Thus, our findings support the importance of an adequate intake of calcium and vitamin D to prevent hip fracture in women consuming a vegan diet.

The size of the overall cohort, the largest known longitudinal study of vegans and vegetarians, use of a validated FFQ (49), guided imputation for missing data, and length of follow-up are strengths of this study. Nonetheless, there was low power to detect a significant effect of consuming only calcium or vitamin D alone among vegans. Also, in spite of finding no effect of time spent outdoors or skin type in our models, lack of adjustment for amount of body exposure to sunlight, an important determinant of serum vitamin D, is also a limitation that may confound the impact of vitamin D supplementation on fracture risk (50). The lack of repeat dietary surveys to adjust for changes in diet over the 8- to 13-y follow-up period is a weakness of the study, although unpublished findings show that change of their basic dietary pattern is quite uncommon among subjects in the AHS-2. The importance of adequate dietary protein intake in relation to hip fracture risk among vegans has been observed in the recent study by Tong et al. (15). In unpublished data, low protein intake was a risk factor for vegans compared with NVEGs only among those consuming less than the median intake for our cohort. Accuracy of self-reported hip fracture, although another source of error, has nevertheless been reported as relatively high (51). However, some hip fractures as a cause of death could have been missed, because data from death certificates were not obtained. Inclusion of individuals with prevalent cancer who may have been on medications for cancer could have altered the effects of diet on fracture risk. However, controlling for prevalent cancer in the final model among men did not change the estimates of primary effects. Finally, some have reported a slight increase in fracture risk among healthy subjects taking supplements of vitamin D and calcium (52). We cannot exclude a possible attenuation of our findings in the final stratified analysis caused by a slight increase in hip fracture risk among our reference group, the supplemented NVEGs. Lastly, results may only be generalizable to whites, because nonwhites were excluded from this study.

In conclusion, the purpose of this study was to examine the association between hip fracture and 5 dietary patterns. Among white women, a vegan diet was associated with significantly higher risk of hip fracture. However, a vegan diet supplemented with both vitamin D and calcium yielded no greater risk of hip fracture than the NVEG diet. Further research is needed to confirm the adequacy of a supplemented vegan diet with respect to risk of osteoporosis and fracture in comparison with supplemented NVEGs.

The authors' responsibilities were as follows—DLT, RK, WLB, and SFK: collaborated in the conception of this paper; DLT: conducted the statistical analyses and wrote the paper; RK: assisted in interpretation of the findings and the refining of manuscript drafts; WLB and SFK: provided overall guidance and statistical consultation; SFK: had primary responsibility for the final content; GEF: as the Principal Investigator of the AHS-2, contributed statistical advice and provided consultation on the final draft; and all authors: read and approved the final manuscript. The authors report no conflicts of interest.

Data availability

Data described in the article, codebook, and analytic code will be made available upon request pending application and approval.

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