Vitamin A and retinol intakes and the risk of fractures among participants of the Women's Health Initiative Observational Study[1–3]

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ABSTRACT

Background: Excessive intakes of vitamin A have been shown to have adverse skeletal effects in animals. High vitamin A intake may lead to an increased risk of fracture in humans.

Objective: The objective was to evaluate the relation between total vitamin A and retinol intakes and the risk of incident total and hip fracture in postmenopausal women.

Design: A total of 75,747 women from the Women's Health Initiative Observational Study participated. The risk of hip and total fractures was determined using Cox proportional hazards models according to different intakes of vitamin A and retinol.

Results: In the analysis adjusted for some covariates (age; protein, vitamin D, vitamin K, calcium, caffeine, and alcohol intakes; body mass index; hormone therapy use; smoking; metabolic equivalents hours per week; ethnicity; and region of clinical center), the association between vitamin A intake and the risk of fracture was not statistically significant. Analyses for retinol showed similar trends. When the interaction term was analyzed as categorical, the highest intake of retinol with vitamin D was significant ($P = 0.033$). Women with lower vitamin D intake ($\leq$11 μg/d) in the highest quintile of intake of both vitamin A (hazard ratio: 1.19; 95% CI: 1.04, 1.37; P for trend: 0.022) and retinol (hazard ratio: 1.15; 95% CI: 1.03, 1.29; P for trend: 0.056) had a modest increased risk of total fracture.

Conclusions: No association between vitamin A or retinol intake and the risk of hip or total fractures was observed in postmenopausal women. Only a modest increase in total fracture risk with high vitamin A and retinol intakes was observed in the low vitamin D–intake group. *Am J Clin Nutr* 2009;89:323–30.

INTRODUCTION

Excessive intakes of vitamin A have been shown to have adverse skeletal effects. Animal studies have revealed that retinoic acid suppresses osteoblastic activity, stimulates osteoclast formation, and antagonizes the ability of vitamin D to maintain normal serum calcium concentrations (1–6). These mechanisms are known contributors of increased bone resorption, which ultimately decreases bone mineral density and increases fracture probability (7). In humans, chronic vitamin A toxicity can cause hypercalcemia (8), impaired bone remodeling, and bone abnormalities (9, 10). In addition, high intake of synthetic retinoids has been associated with decreased bone mass (11, 12) and suppressed biochemical markers of bone turnover (13).

Much attention has focused on the potential deleterious impact of vitamin A intake on fracture risk (14–22); some studies have reported that higher dietary vitamin A intake is associated with higher fracture risk within the general population (14–16), and others reported no association (18, 19, 23). Two studies in women reported that high intakes of vitamin A were associated with an increased risk of hip fracture (14, 15). In a cohort study involving $\approx$72,000 postmenopausal nurses, those in the highest quintiles of vitamin A and retinol intakes were 1.5 and 1.9 times more likely to have a hip fracture, respectively, compared with those in the lowest quintiles of intake (14). Melhus et al (15) evaluated the association between vitamin A intake and fracture risk in a case-control study of Swedish women. A comparison of retinol intake and fracture risk revealed that women who reported retinol intake $\geq$1500 μg/d had twice the risk of experiencing a hip fracture compared with women who reported a dietary intake of $<$500 μg/d. In contrast, a population-based cohort study in 2016 Danish perimenopausal women found that a dietary retinol intake of 530 μg/d was not associated with detrimental effects on bone (18). A cohort of 34,703 postmenopausal women from the Iowa Women's Health Study showed no association between the risk of hip (or all) fractures and vitamin A or retinol intake from food and supplements or from food only (19).

In 2 prospective studies, biochemical markers of retinol intake were used to investigate the relation between vitamin A and fracture risk (17, 23). Conflicting results were found in these

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studies. One study reported a 64% increase in risk of any osteoporotic fracture for men in the top quintile of serum retinol relative to those in the middle quintile (17). The other study, involving British women >75 y, did not find any relation between serum retinoids and hip or total fracture (23).

A deleterious effect of vitamin A on bone may operate through its antagonistic relation with vitamin D. A high concentration of vitamin A intake is shown to increase the need for dietary vitamin D in chickens (24). In a study in humans, vitamin A intake corresponding to one serving of liver was shown to diminish the ability of vitamin D to increase intestinal calcium absorption (25).

To further investigate this issue in a large multiethnic population of women, we examined the relation between vitamin A exposure—assessed by dietary and supplement intakes of total vitamin A and retinol—and the risk of incident hip and total fracture in postmenopausal women participating in the Women's Health Initiative (WHI) Observational Study. The possible interactions between total vitamin A or retinol intake and vitamin D or calcium intake were also evaluated.

SUBJECTS AND METHODS

Study sample

The WHI Observational Study was established to explore the predictors and natural history of important causes of morbidity and mortality in postmenopausal women (26). It is a large, longitudinal study that enrolled 93,676 ethnically diverse women aged 50–79 y. The participants were enrolled at 40 centers throughout the United States between 1993 and 1998. Eligibility criteria for inclusion in the WHI were as follows: postmenopausal status, 50–79 y of age, unlikely to move or die ≤3 y, and not a current participant in any other clinical trials. The WHI cohort consists of non-Hispanic white, Hispanic, African American, American Indian, and Asian/Pacific Islander women. The study was reviewed and approved by the Human Subjects Review Committee at each participating institution. Participants provided signed informed consent.

At baseline enrollment, women completed screening and enrollment questionnaires through interview and self-report. Information on age, years since menopause, race and ethnicity, education, income, smoking, alcohol intake, use of hormone therapy, history of fracture, number of falls in last 12 mo, physical activity, and nutrient intakes were assessed from baseline questionnaires. By April 2005, 1.9% of the participants were lost to follow-up, 2.2% stopped follow-up, and 6.1% of the participants were deceased.

Fractures

Women received annual questionnaires in which they were asked to report all clinical fractures that had occurred in the past year. Fracture events were reported by WHI participants or by proxy respondents, which included family members, friends, health care professionals, and other informants. Proxy reports were obtained when tracing participants who had missed follow-up contacts or who had died. Approximately 79% of the fracture reports were from the participants themselves. Fracture site, date of fracture, and information on diagnosing institution were reported.

Requests for medical record confirmation were made for all hip fractures. Hip fractures were adjudicated by central review of radiology and other medical reports. Other fractures were counted on the basis of self-report. These included pelvis, spine or back, lower arm or wrist, upper arm or shoulder, upper leg (not hip), knee, lower leg or ankle, foot, tailbone, hand, elbow, and other. In the experience of the 3 WHI clinical centers that fully adjudicated all fractures, 78% of self-reported hip fractures and 71% of self-reported single-site fractures could be confirmed by medical records (27).

Dietary assessment

Dietary intake was assessed at baseline and at year 3 of follow-up with the WHI food-frequency questionnaire (FFQ), and only participants with FFQ data at both time points were included in the present study. The FFQ is based on instruments previously used in the Women's Health Trial Vanguard Study (28), the Women's Health Trial Full-Scale Study (29), the Working Well Study (30), and the Women's Health Trial Feasibility Study in Minority Populations (31). The instrument was designed by an ad hoc dietary assessment working group composed of WHI scientists to reflect regional and ethnic eating patterns in the United States (32).

The FFQ assessed the intake of 122 food items or food groups, with questions on usual frequency of intake (from "never or less than one per month" to "2+ times per day" for foods and "6+ times per day" for beverages) and on portion size (small, medium, and large compared with a stated medium size). The time reference for all questions was "in the past 3 months" (32). For quality-control purposes, all questions and 90% of the food groups (eg, fruits, vegetables, and breakfast foods) had to be completed. The FFQ nutrient database was derived from the University of Minnesota Nutrition Coding Center nutrient database (Nutrition Coordinating Center, Minneapolis, MN) (33). The measurement characteristics of the WHI FFQ were compared with short-term dietary recall and recording methods in a study by Patterson et al (32). The agreement of intakes of 30 nutrients estimated using the FFQ compared with corresponding estimates from a 4-d food record and four 24-h dietary recalls was evaluated. Means estimated by the FFQ were within 10% of the records or recalls. The reliability of the FFQ using intraclass correlation coefficients was high.

The usual intake of vitamin and mineral supplements was assessed by a computerized simplified inventory procedure (34). The participants brought their supplements to the clinic for an in-person interview. Trained nonnutritionists conducted the inventory at a computer station and directly entered the data about multiple vitamins and single supplements, including dose, frequency, and duration of use. The program consisted of a series of screens that prompted coders to enter information on the supplements, allowed them to enter dose in any unit on the label, and incorporated range checks for quality assurance. The procedure produced accurate estimates of micronutrient intakes from supplements in a separate validity study (34).

Exposure data were derived for total vitamin A and retinol from diet and supplements. All the nutrient intakes were calculated as the mean of the intakes at baseline and year 3 of follow-up. Dietary variables that may be potential confounders of the association between vitamin A and fractures were included in the analysis: energy, vitamin D, calcium, vitamin K, protein, alcohol, and caffeine.

Other covariates

Nondietary covariates at baseline included age, use of postmenopausal hormones (never, past, or current user), smoking status (never, past, or current smoker), body mass index (BMI; in kg/m^2, calculated at baseline), and metabolic equivalents (METs) per week. To control for sun exposure, region (Northeast, South, Midwest, West) and ethnicity (American Indian or Alaskan native, Asian or Pacific Islander, black or African American, Hispanic/Latino, white not of Hispanic origin, and other) were included in the analysis. Demographic and risk exposure data were obtained by self-report using standardized questionnaires. Physical measurements such as height and weight were taken by certified staff.

Statistical analysis

Only women who had dietary data from the 2 FFQs (baseline and year 3) were included in the analysis, and the average of the 2 measures was used. Descriptive analyses were used to compute means and measures of dispersion for dietary intakes and other covariates. One-factor analysis of variance was used to examine differences in the selected variables across quintiles. Person-time was accrued for each participant from the day of enrollment until the occurrence of any fracture, death, or the end of follow-up. The age- and multivariate-adjusted hazard ratios (HRs) for all fractures were computed for quintiles of total vitamin A and retinol referenced against the lowest quintile. Cox proportional hazards models to calculate multivariate HRs were used, adjusting simultaneously for the potential confounding variables; the assumptions for the analysis were evaluated in the model. The outcome variables were total fracture (ie, the first fracture regardless of site, which means that when one subject had 2 fractures, only the first was counted) and hip fracture (ie, just the hip was focused on and any other previous fractures were disregarded).

We previously decided to present the results stratifying by vitamin D intake and ethnic group; however, we still wanted to explore the possible interactions of total vitamin A and retinol with vitamin D and calcium. The interaction term was calculated by using the product of the categorical variables (5 quintiles of vitamin A or retinol, and 2 levels of vitamin D or calcium intakes above and below the mean) in the model. The confounding variables in the models were chosen from the model selection process and on the basis of relevant works by Lim et al (19) and Feskanich et al (14). To examine linear trends, the vitamin A and retinol exposure variables were entered into the models as continuous log-transformed variables. All the analyses were carried out by using Stata version 8.0 (StataCorp LP, College Station, TX).

RESULTS

From the initial sample of 93,676 women, only 75,747 had data for vitamin intakes for the baseline and year 3 periods. The mean age of the participants at baseline was 63.6 y. There were 10,405 incident total fractures and 588 hip fractures, the mean length of follow-up was 6.6 y, and the incidence of total fractures was 221/10,000 person-years. We excluded from the analysis women with previous fracture or a diagnosis of osteoporosis; however, excluding them did not change the results. Therefore, all 75,747 women were included in the final results.

The characteristics of the study population by quintiles of total vitamin A intake are shown in **Table 1**. The amounts of vitamin A, retinol, calcium, and vitamin D include intakes from food and supplements together. Women with higher vitamin A intake were more likely to be physically active and less likely to smoke ($P < 0.0001$). Those who consumed more vitamin A had higher energy, protein, calcium, vitamin D, vitamin K, alcohol, and caffeine intakes ($P < 0.01$). They also had higher mean intakes of retinol supplement, vitamin D supplement, and calcium supplement (data not shown). Total vitamin A intakes were lower among minority women, and >50% of the women in each minority group were in the first and second quintiles of total vitamin A intake.

The HRs of total fracture by quintiles of total vitamin A and retinol intakes are shown in **Table 2**. For the age-adjusted model, women in the fourth (HR: 1.09; 95% CI: 1.02, 1.16) and highest quintiles (HR: 1.09; 95% CI: 1.02, 1.16) of total vitamin A had a small and significant increase in risk compared with women in the lowest quintile. Similar results were obtained for the third (HR: 1.09; 95% CI: 1.03, 1.16), fourth (HR: 1.13; 95% CI: 1.06, 1.20), and highest quintiles (HR: 1.10; 95% CI: 1.03, 1.17) of retinol in relation to the lowest quintile (P for trend: <0.001).

After adjusting for selected covariates (age; energy, vitamin K, protein, alcohol, and caffeine intakes; smoking; BMI; hormone therapy use; total METs per week; ethnic group; and region), the HRs for fractures were significant in the fourth (HR: 1.08; 95% CI: 1.01, 1.16) and last quintiles (HR: 1.09; 95% CI: 1.01, 1.19) of total vitamin A intake (P for trend < 0.001) and in the third (HR: 1.08; 95% CI: 1.00, 1.15), fourth (HR: 1.11; 95% CI: 1.04, 1.18), and highest quintiles (HR: 1.08; 95% CI: 1.01, 1.16) of retinol intake (P for trend < 0.01). No association was found, however, between total vitamin A or retinol intake and risk of total fracture when vitamin D and calcium intakes were added as covariates to these multivariate analyses in the model. Stratified analyses by region (Northeast, South, Midwest, or West) and by hormone therapy use (never, past, or current) did not significantly change the association between total fractures and vitamin A or retinol intake within the strata (data not shown).

As part of our a priori hypotheses, we decided to analyze the association between total vitamin A or retinol intake and fracture, stratifying by vitamin D, calcium, and a combination of vitamin D and calcium intakes (**Table 3**). The interactions of vitamin A and retinol with calcium were significant ($P = 0.001$ in both analyses); however, the interactions were not significant with vitamin D. Only when the interaction term was analyzed as categorical was the highest intake of retinol with vitamin D significant ($P = 0.033$ for the subgroup analysis). The cutoffs for the stratification of vitamin D and calcium intakes were selected on the basis of the mean intake of each nutrient in the sample. Among the women in the lower vitamin D strata (intake ≤ 11 μg or 440 IU), there was a modest risk of fractures in the highest quintile of both total vitamin A (HR: 1.19, 95% CI: 1.04, 1.37; P for trend < 0.05) and retinol (HR: 1.15; 95% CI: 1.03, 1.29; P for trend: 0.056), compared with the lowest quintile. There were no significant risks in the groups with higher vitamin D intakes or lower and higher calcium intakes. The combination of lower vitamin D and calcium intakes resulted in an HR of 1.17 (95% CI: 1.01, 1.36; P for trend > 0.05) for total fractures among women in the highest compared with the lowest quintile of retinol. The associations between total vitamin A or retinol and total fractures among women with the lower intake of vitamin D (≤ 11 μg) stratified by ethnic group showed no statistically significant

TABLE 1
Characteristics of postmenopausal women ($n = 75,747$) by quintiles of vitamin A intake: Women's Health Initiative Observational Study[1]

	Quintiles of vitamin A intake (μg RE)[2]				
Characteristics	<5055	5055–5824	5825–6550	6551–7507	≥7508
Age (y)	63.7 ± 7.3[3]	63.8 ± 7.3	63.7 ± 7.3	63.6 ± 7.2	63.1 ± 7.2
BMI (kg/m^2)	27.1 ± 5.8	26.8 ± 5.5	26.7 ± 5.5	27.0 ± 5.6	27.6 ± 6.1
Physical activity (METs/wk)[4]	12.9 ± 14.1	13.8 ± 14.3	14.5 ± 14.3	14.7 ± 14.4	14.8 ± 14.8
Retinol intake (μg/d)[2,5]	412 ± 187	727 ± 284	983 ± 341	1227 ± 407	1968 ± 1266
Energy intake (kcal/d)[5]	1067 ± 253	1329 ± 312	1494 ± 349	1702 ± 389	2053 ± 635
Protein intake (g/d)[5]	46.2 ± 10.5	57.0 ± 12.9	63.8 ± 14.4	72.3 ± 16.0	86.6 ± 26.1
Calcium intake (mg/d)[2,5]	847 ± 429	1081 ± 607	1240 ± 498	1390 ± 462	1622 ± 547
Vitamin D intake (μg/d)[2,5]	5.6 ± 3.3	8.9 ± 4.2	11.5 ± 4.7	13.4 ± 4.6	15.4 ± 5.6
Vitamin K intake (μg/d)[5]	75.7 ± 9.4	85.3 ± 11.5	91.4 ± 12.9	99.0 ± 14.4	112 ± 23.4
Alcohol intake (g/d)[5]	4.1 ± 7.9	5.2 ± 9.2	5.9 ± 10.2	6.4 ± 10.9	6.8 ± 12.5
Caffeine intake (mg/d)[5]	131 ± 104	146 ± 107	154 ± 108	164 ± 112	174 ± 123
Current smoker [*n* (%)][6]	1013 (6.8)	905 (6.1)	748 (5.0)	713 (4.8)	739 (4.9)
Current HT user [*n* (%)][6]	6262 (41)	6837 (45)	7137 (47)	7383 (49)	7329 (48)
Ethnic group [*n* (%)][7]					
American Indian or Alaskan native	90 (32)	52 (19)	41 (15)	52 (19)	43 (15)
Asian or Pacific Islander	590 (28)	502 (23)	391 (18)	336 (16)	330 (15)
African American	1736 (35)	1005 (20)	796 (16)	662 (14)	732 (15)
Hispanic/Latino	754 (32)	516 (22)	385 (16)	334 (14)	365 (16)
White (not Hispanic)	11,715 (18)	12,876 (20)	13,362 (20)	13,590 (21)	13,493 (21)
Other	209 (26)	165 (21)	132 (17)	134 (17)	153 (19)

[1] Vitamin A, retinol, and other dietary variables were assessed at baseline and year 3; intakes were averaged using the 2 times. HT, hormone therapy; METs, metabolic equivalents; RE, retinol equivalent.

[2] Vitamin A, retinol, calcium, and vitamin D values include intake from food and supplements together.

[3] Mean ± SD (all such values).

[4] Differences in METs per week were found between quintile 1 and the rest of the quintiles and between quintile 2 and the rest of the quintiles, $P < 0.0001$ (one-factor ANOVA).

[5] Differences between columns were found for retinol, energy, protein, calcium, vitamin D, vitamin K, alcohol, and caffeine intakes, $P < 0.01$(one-factor ANOVA).

[6] For current smoker and current HT user, percentages are reported based on the total women in all the respectively smoking and HT user categories in each vitamin A quintile. Differences between columns were found for current smoker and current HT user, $P < 0.0001$(chi-square test).

[7] For ethnic group, percentages are reported based on the total women in each ethnic group.

relation of total fracture risk to vitamin A or retinol intake in any of the ethnic groups (data not shown).

The risk of hip fracture by quintile of total vitamin A and retinol in all the women of the study is shown in **Table 4**. Total vitamin A and retinol did not have a significant association with the risk of hip fracture in any of the age- or multivariate-adjusted models, and no dose-response relation was observed. Given the smaller number of hip fractures, stratified analysis by vitamin D and calcium intake was not conducted.

DISCUSSION

Conflicting results relating vitamin A and retinol intakes to fracture risk were observed in previous epidemiologic studies. The results in the present study showed a modest risk in total fractures associated with increased total vitamin A or retinol intakes; however, this association was observed only among women with low vitamin D intakes. In addition, no association between vitamin A intake and the risk of hip fracture was observed.

Excess vitamin A is known to have teratogenic effects on bone growth in mice (3). In growing animals, hypervitaminosis A can produce bone fractures (4, 5) and other skeletal anomalies (35). Patients undergoing long courses of treatment with retinoids have experienced progressive calcification of ligaments, modeling abnormalities of long bones, and osteoporosis (11, 36). Direct effects on bone osteoclasts and osteoblasts, such as increased bone resorption and decreased formation of vitamin A, have been shown in vitro (1, 2, 4, 6).

Vitamin A has been suggested to interfere with the action of vitamin D. In vitro studies have variously indicated antagonistic, additive, or synergistic interactions between vitamin A and D (37). In vivo studies have shown that a high concentration of vitamin A intake reduces the toxicity associated with hypervitaminosis D in rats (38) and turkey poults (35) and increases the need for dietary vitamin D in chickens (24). In a double-blind crossover clinical trial, Johansson and Melhus (25) showed that a large single daily dose of 15 mg retinyl palmitate (providing 8190 μg retinol) decreased the serum calcium response to a single dose of the activated form of vitamin D (2 μg 1,25-dihydroxyvitamin D_3) several hours after administration of both vitamins together. This study suggests a more complex mechanism for possible adverse effects of large amounts of retinol on bone health. Alternatively, excessive vitamin A may have toxic effects on bone mineral density that are independent of vitamin D status. In a study with rats (39), the administration of high doses of vitamin D did not prevent the appearance of bone fractures in rats that had hypervitaminosis A. Another study showed that the effects of retinoids on diminishing bone mass were not significantly greater in vitamin D–deficient rats than in vitamin D–replete rats (40).

TABLE 2
Hazard ratios of total fracture by quintiles of total vitamin A and retinol intakes among postmenopausal women in the Women's Health Initiative Observational Study[1]

	Quintiles of intakes					
	1	2	3	4	5	*P* for trend[2]
Vitamin A (μg RE/d)	<5055	5055–5824	5825–6550	6551–7507	≥7508	—
n	15,149	15,149	15,150	15,149	15,150	—
Cases	1993	2054	2102	2137	2119	—
Age-adjusted HR[3]	1.00	1.03 (0.97, 1.10)	1.07 (1.00, 1.14)	1.09 (1.02, 1.16)	1.09 (1.02, 1.16)	<0.001
Multivariate HR[4]	1.00	1.02 (0.96, 1.09)	1.06 (0.99, 1.13)	1.08 (1.01, 1.16)	1.09 (1.01, 1.19)	<0.001
Multivariate HR[5]	1.00	0.99 (0.92, 1.05)	1.00 (0.93, 1.07)	1.00 (0.92, 1.08)	0.98 (0.89, 1.08)	0.330
Retinol (μg/d)	<474	474–764	765–1092	1093–1425	≥1426	—
n	15,149	15,149	15,150	15,149	15,150	—
Cases	1977	2044	2110	2152	2122	—
Age-adjusted HR[3]	1.00	1.05 (0.99, 1.12)	1.09 (1.03, 1.16)	1.13 (1.06, 1.20)	1.10 (1.03, 1.17)	<0.001
Multivariate HR[4]	1.00	1.03 (0.96, 1.11)	1.08 (1.00, 1.15)	1.11 (1.04, 1.18)	1.08 (1.01, 1.16)	0.002
Multivariate HR[5]	1.00	1.01 (0.94, 1.08)	1.03 (0.96, 1.11)	1.04 (0.96, 1.13)	1.00 (0.92, 1.10)	0.800

[1] A total of 75,747 women contributed 471,062 person-years to this analysis; the total fracture count was 10,405. 95% CIs in parentheses. HR, hazard ratio; RE, retinol equivalent.
[2] Test for trend for linear increase in nutrient intake.
[3] Risk estimates were adjusted for age.
[4] Risk estimates were adjusted for age; energy, vitamin K, protein, alcohol, and caffeine intakes; smoking; BMI; HT use; total METs per week; ethnic group; and region.
[5] Risk estimates were adjusted for the variables listed in footnote 4 plus vitamin D and calcium.

There are only 2 prospective epidemiologic studies of vitamin A and retinol intakes (measured by dietary methodologies) and fracture risk in postmenopausal women (14, 19). In the Nurses' Health Study (14), the risk of hip fracture was 1.5 and 1.9 times greater in the highest quintile of vitamin A and retinol intakes, respectively, compared with the lowest quintile. In concordance with our study, the results from the Iowa Women's Health Study (19) of 34,703 women showed no association between vitamin A or retinol intake from food and supplements and the risk of hip or total fractures after adjusting for selected covariates such as age, nutrient intakes, BMI, cigarette smoking, medication use, and some diseases. The Nurses' Health Study was a large study ($n = 72{,}337$) that included a broader range of ages (34–77 y), although the racial composition of the sample was mostly white and from a specific occupation. The total average of vitamin D intake (from food and supplements) of the women from the Nurses' Health Study, although not expressly mentioned, is 2.5–4 μg lower than the vitamin D intake in our study and the Iowa Women's Health Study, and this may explain the risk of hip fractures related to vitamin A intake found in a population with low intakes of vitamin D.

Supplements contribute significantly to vitamin A intake in the United States. The mean intake of vitamin A from supplements in a sample of adult women in the Third National Health and Nutritional Examination Survey was 1338 μg/d. In our sample, the mean intake of vitamin A from supplements was 1075 μg/d at baseline and 1149 μg/d at year 3 follow-up. Many oily and supplemented foods contain vitamins A and D. The Recommended Dietary Allowance for vitamin A is 700–900 μg/d for men and women, with a tolerable upper intake of 3000 μg/d (41). The mean intake of total vitamin A in this study was 6400 μg/d, which is greater than the upper intake recommended. The issue is whether the effect of vitamin A on bone health occurs at the usual levels of retinol and vitamin D intakes experienced by most persons.

In the United States, milk and ready-to-eat cereals serve as the predominant food sources of vitamin D. Milk, however, is not uniformly consumed in the United States, and the amount of vitamin D added to milk may not be adequate to increase circulating 25-hydroxyvitamin D concentrations. In addition, only a few eligible milk products are fortified with vitamin D, such as a few brands of yogurt (42). Furthermore, the racial-ethnic groups at greatest risk of vitamin D insufficiency consume less milk and ready-to-eat cereals than do their white counterparts (43).

The mean intake of vitamin D in this study was 11 μg/d, which is a little higher than the current US recommendation for women aged 51–70 y (400 IU, equivalent to 10 μg/d) and lower than the recommendation for women aged ≥70 y (600 IU, equivalent to 15 μg/d) (44). The calcium requirement in older women is 1200 mg/d, which is similar to the mean intake of calcium found in our study (1236 mg/d). The findings in this study could therefore have implications for reducing the risk of osteoporotic fracture and for optimizing nonskeletal tissue function on the basis of dietary and supplemental intakes of vitamin A, vitamin D, and calcium.

One limitation to our study is that we were unable to distinguish between traumatic and spontaneous fractures, understanding that some fractures are more related to osteoporosis than others (45). The low number of hip fractures in this study may affect the detection of any association between hip fractures and vitamin A intake, which is an issue for future research. It should be mentioned that vitamin D intake is not the best indicator of serum vitamin D status, which also depends on solar radiation exposure, genetics, and other variables. We did not adjust for any medication use, and the failure to exclude women who were taking antiresorptive medications other than estrogen may affect the results. The inability to control for disease status, due to the lack of data when the analysis was done, is a further limitation. Although the study was conducted with a multiethnic cohort, the results may not be generalizable to all other ethnic groups

TABLE 3
Hazard ratios of total fracture by vitamin D and calcium intakes among postmenopausal women in the Women's Health Initiative Observational Study[1]

	Vitamin A			Retinol		
Strata	*n*	Mean vitamin A[2]	Multivariate HR (95% CI)[3]	*n*	Mean retinol[2]	Multivariate HR (95% CI)[3]
		μg RE/d			*μg/d*	
Lower vitamin D intake (≤11 μg/d)			*P* for trend: 0.022			*P* for trend: 0.056
Quintile 1	14,199	4445	1.00	14,770	348	1.00
Quintile 2	10,906	5430	1.02 (0.94, 1.10)	13,424	609	1.02 (0.95, 1.10)
Quintile 3	7575	6162	1.10 (1.00, 1.20)	7484	894	1.05 (0.97, 1.15)
Quintile 4	4773	6944	1.11 (0.99, 1.24)	2321	1219	1.09 (0.96, 1.23)
Quintile 5	2966	8902	1.19 (1.04, 1.37)	2420	2488	1.15 (1.03, 1.29)
Higher vitamin D intake (>11 μg/d)			*P* for trend: 0.678			*P* for trend: 0.521
Quintile 1	950	4710	1.00	379	370	1.00
Quintile 2	4243	5507	0.99 (0.81, 1.19)	1725	664	1.07 (0.79, 1.44)
Quintile 3	7575	6205	0.93 (0.78, 1.12)	7666	967	1.00 (0.75, 1.32)
Quintile 4	10,376	7007	0.93 (0.77, 1.12)	12,828	1246	1.00 (0.75, 1.31)
Quintile 5	12,184	8957	0.87 (0.72, 1.06)	12,730	2123	0.95 (0.72, 1.25)
Lower calcium intake (≤1236 mg/d)			*P* for trend: 0.446			*P* for trend: 0.490
Quintile 1	12,954	4442	1.00	12,796	343	1.00
Quintile 2	10,959	5441	1.01 (0.94, 1.09)	10,820	612	0.99 (0.92, 1.08)
Quintile 3	8708	6170	1.03 (0.94, 1.12)	7923	930	1.05 (0.97, 1.14)
Quintile 4	6389	6951	1.06 (0.96, 1.18)	5975	1231	1.06 (0.97, 1.16)
Quintile 5	3270	8727	1.02 (0.90, 1.16)	4766	2196	1.00 (0.91, 1.10)
Higher calcium intake (>1236 mg/d)			*P* for trend: 0.080			*P* for trend: 0.207
Quintile 1	2195	4577	1.00	2353	374	1.00
Quintile 2	4190	5481	1.04 (0.91, 1.20)	4329	622	1.15 (1.01, 1.32)
Quintile 3	6442	6201	1.07 (0.94, 1.22)	7227	932	1.10 (0.96, 1.25)
Quintile 4	8760	7014	1.04 (0.91, 1.19)	9174	1248	1.13 (0.99, 1.29)
Quintile 5	11,880	8982	1.03 (0.89, 1.18)	10,384	2175	1.11 (0.96, 1.25)
Lower vitamin D and calcium intakes			*P* for trend: 0.313			*P* for trend: 0.258
Quintile 1	12,393	4430	1.00	12,659	343	1.00
Quintile 2	8532	5425	1.00 (0.92, 1.10)	10,044	607	0.98 (0.90, 1.07)
Quintile 3	5253	6153	1.02 (0.91, 1.14)	4515	896	1.01 (0.91, 1.12)
Quintile 4	2803	6918	1.06 (0.91, 1.23)	1474	1216	1.06 (0.91, 1.23)
Quintile 5	1095	8886	1.18 (0.98, 1.41)	1384	2498	1.17 (1.01, 1.36)
Higher vitamin D and calcium intakes			*P* for trend: 0.393			*P* for trend: 0.671
Quintile 1	389	4707	1.00	242	380	1.00
Quintile 2	1816	5521	1.20 (0.82, 1.48)	949	654	1.16 (0.80, 1.69)
Quintile 3	4120	6212	1.01 (0.76, 1.34)	4258	961	1.02 (0.72, 1.44)
Quintile 4	6790	7024	1.00 (0.76, 1.33)	8327	1251	1.05 (0.74, 1.48)
Quintile 5	10,009	9025	0.95 (0.71, 1.27)	9348	2141	1.02 (0.72, 1.43)

[1] The cutoffs for the vitamin D and calcium stratification were selected based on the mean of each nutrient in the study population. HR, hazard ratio; RE, retinol equivalent.

[2] The interactions of vitamin A and retinol with calcium were significant ($P = 0.001$ in both analyses); however, the interactions were not significant with vitamin D. Only when the interaction term was analyzed as categorical was the highest intake of retinol with vitamin D significant ($P = 0.033$ for the subgroup analysis).

[3] Risk estimates were adjusted for age; energy, vitamin K, protein, alcohol, and caffeine intakes; smoking; BMI; HR therapy use; total METs per week; ethnic group; and region.

because the sample size of some of them was small and the groups did not have the power to observe a difference.

The strengths of this study are the high follow-up rates and the large number of participants, which allowed an adequate number of relatively rare events to be captured. The use of an average of 2 FFQs to determine the intakes of total vitamin A, retinol, and other nutrients is a further advantage because it provided a more accurate estimate of intakes, avoiding some of the random error associated with using only one dietary measurement. Although a number of epidemiololgic studies examined the association between vitamin A and fracture risk, this study is the third longitudinal study to explore the issue in postmenopausal women. Because of its large sample size, this study had the ability to explore interactions between vitamin A intake and other nutrients (specifically vitamin D and calcium) on fracture risk.

In conclusion, this study did not find an association between total vitamin A or retinol intake and the risk of hip or total fractures. Only a modest increase in total fracture incidence with high total vitamin A or retinol intake was observed in the population of postmenopausal women who had low vitamin D intakes. In osteoporosis prevention, it is important to take into account the dietary and supplemental combined intakes of vitamins A and D among postmenopausal women. More studies using better evaluations of the vitamin A and D status are necessary.

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TABLE 4
Hazard ratios of hip fracture by quintiles of total vitamin A and retinol intakes among postmenopausal women in the Women's Health Initiative Observational Study[1]

	Quintiles of intakes					
	1	2	3	4	5	*P* for trend[2]
Vitamin A (μg RE/d)	<5055	5055–5824	5825–6550	6551–7507	≥7508	—
n	15,149	15,149	15,150	15,149	15,150	—
Cases	122	121	113	113	119	—
Age-adjusted HR[3]	1.00	0.99 (0.77, 1.27)	0.94 (0.73, 1.22)	0.96 (0.74, 1.23)	1.06 (0.83, 1.37)	0.612
Multivariate HR[4]	1.00	1.01 (0.78, 1.32)	0.99 (0.75, 1.31)	1.03 (0.76, 1.38)	1.24 (0.88, 1.73)	0.200
Multivariate HR[5]	1.00	0.99 (0.75, 1.30)	0.94 (0.69, 1.28)	0.96 (0.68, 1.35)	1.14 (0.76, 1.71)	0.445
Retinol (μg/d)	<474	474–764	765–1092	1093–1425	≥1426	—
n	15,149	15,149	15,150	15,149	15,150	—
Cases	112	129	94	124	129	—
Age-adjusted HR[3]	1.00	1.22 (0.95, 1.57)	0.87 (0.66, 1.15)	1.13 (0.87, 1.46)	1.21 (0.94, 1.55)	0.373
Multivariate HR[4]	1.00	1.23 (0.94, 1.60)	0.89 (0.67, 1.19)	1.10 (0.84, 1.45)	1.25 (0.95, 1.64)	0.415
Multivariate HR[5]	1.00	1.19 (0.91, 1.57)	0.84 (0.61, 1.14)	1.00 (0.73, 1.39)	1.13 (0.81, 1.59)	0.925

[1] A total of 75,747 women contributed 500,888 person-years to this analysis; the hip fracture count was 588. 95% CIs in parentheses. HR, hazard ratio; RE, retinol equivalent.

[2] Test for trend for linear increase in nutrient intake.

[3] Risk estimates were adjusted for age.

[4] Risk estimates were adjusted for age; energy, vitamin K, protein, alcohol, and caffeine intakes; smoking; BMI; HR therapy use; total METs per week; ethnic group; and region.

[5] Risk estimates were adjusted for the variables listed in footnote 4 plus vitamin D and calcium.

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