Published in final edited form as:

Osteoporos Int. 2009 November ; 20(11): 1853–1861. doi:10.1007/s00198-009-0897-y.

Protective effect of total and supplemental vitamin C intake on the risk of hip fracture - A 17-year follow-up from the Framingham Osteoporosis Study

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Abstract

Introduction—Dietary antioxidants such as vitamin C may play a role in bone health. We evaluated associations of vitamin C intake (total, dietary and supplemental) with incident hip fracture and non-vertebral osteoporotic fracture, over a 15 to 17-y follow-up, in the Framingham Osteoporosis Study.

Methods—366 men and 592 women (mean age 75 yr $\pm$ 5) completed a food frequency questionnaire (FFQ) in 1988–89 and were followed for non-vertebral fracture until 2003 and hip fracture until 2005. Tertiles of vitamin C intake were created from estimates obtained using the Willett FFQ, after adjusting for total energy (residual method). Hazard Ratios were estimated using Cox-proportional hazards regression, adjusting for covariates.

Results—Over follow-up 100 hip fractures occurred. Subjects in the highest tertile of total vitamin C intake had significantly fewer hip fractures (P trend=0.04) and non-vertebral fractures (P trend=0.05) compared to subjects in the lowest tertile of intake. Subjects in the highest category of supplemental vitamin C intake had significantly fewer hip fractures (P trend=0.02) and non-vertebral fractures (P trend=0.07) compared to non-supplement users. Dietary vitamin C intake was not associated with fracture risk (all $P>0.22$).

Conclusion—These results suggest a possible protective effect of vitamin C on bone health in older adults.

Keywords

ageing; bone; fracture; nutrition; population studies; vitamin C

Introduction

More than 1.5 million Americans experience osteoporotic fractures each year (1) with annual cost of nearly \$14 billion to the US healthcare system (2). Among 50-year old Caucasian women, the lifetime risk of hip, spine, or forearm fracture is approximately 40% (3). Of these fractures, hip fractures are the most serious, as they almost always result in hospitalization, lead to permanent disability in about 50% of the cases, and are fatal in approximately 20% of the cases (4).

Studies have consistently shown that higher fruit and vegetable intake has positive effects on bone mineral status (5–10). There is evidence that reactive oxygen intermediates may be involved in the bone-resorptive process (11–14) and that dietary antioxidants such as vitamin C, are capable of decreasing this oxidative stress (15). In addition, bone matrix contains over 90% of protein as collagen (16) and vitamin C is an essential cofactor for collagen formation and synthesis of hydroxyproline and hydroxylysine (17), therefore, vitamin C may help in strengthening bone and preventing fractures.

Experimentally-induced deficiency of vitamin C in animals leads to impaired bone mass, cartilage and connective tissue (18,19). However, few observational studies have examined the association of vitamin C and risk of hip fracture (20,21). One study (20) reported an OR of 3.0 for hip fracture among current smokers with a low intake of vitamin C (20). Another study reported a threshold effect for vitamin C intake among elderly men and women who were former or current smokers (21). A previous study by our group in the Framingham Osteoporosis Study reported protective effect of vitamin C against 4-year bone loss in older men (22). Therefore, we hypothesized that higher intake of total, supplemental and dietary vitamin C will be associated with a reduced risk of hip fracture as well as non-vertebral osteoporotic fracture in the Framingham Osteoporosis Study.

Methods

Participants

The Framingham Study began in 1948 to examine risk factors for heart disease. The original subjects (5209 men and women, aged 28–62 yr) were selected as a population-based sample of two-thirds of the households in Framingham, Massachusetts and have been examined biennially for more than 50 yr (23). In 1988–89, 1402 surviving subjects from the original cohort participated in the Framingham Osteoporosis Study. We excluded 426 subjects with missing or incomplete food frequency questionnaires (FFQ) (based on the criteria of >12 food items left blank) or with energy intakes <2.51 or >16.74 MJ (<600 or >4000 kcal/d) at the 20th exam. Of 976 subjects with complete FFQ and fracture information, we excluded 30 subjects with prior hip fracture (Figure 1). We further excluded 17 participants with missing covariate information on body mass index (BMI), multivitamin use or current estrogen use. The final analytic sample (n=929) was followed for incident hip fracture from the date when they completed the FFQ to the end of 2005. For analyses of non-vertebral osteoporotic fractures, 11 additional subjects with prior non-vertebral fracture and 17 with missing covariate information were excluded for a final analytic sample of 918. Subjects were followed for incident non-vertebral osteoporotic fracture from the date when they completed the FFQ to the end of 2003. All participants provided informed consent for their participation. The Institutional Review Board for Human Research at Boston University, Hebrew Rehabilitation Center, and Tufts University approved this study.

Assessment of dietary intake

Usual dietary intake was assessed in 1988–89 with a semi-quantitative, 126-item Willett FFQ (24,25). Questionnaires were mailed to the study participants prior to their scheduled clinic visit. They were asked to complete them, based on their intake over the previous year, and to bring them to the clinic examination, where they were reviewed with participants by clinic staff. This FFQ has been validated for many nutrients and in several populations against multiple diet records and blood measures (26,27). Intake of vitamin C (mg/d), total calcium (mg/d), vitamin D (IU/d), caffeine (mg/d), alcohol (g/d), potassium (mg/d), and total energy (MJ) were assessed using the food list section of the FFQ. Based on their alcohol intake, subjects were categorized as non drinker, moderate drinker: <13.2 g of alcohol/d for women and <26.4 g of alcohol/d for men and heavy drinker: ≥13.2 g of alcohol/d for women and ≥26.4 g of alcohol/d for men, based on the cut-offs recommended by dietary guidelines for Americans (28). Intake of multivitamin supplements, as recorded on the supplement section of the FFQ, was coded as a yes-no variable. Total vitamin C included the full reported amount from diet plus supplements. Given the highly irregular distribution of supplement intake alone, it was entered as a categorical variable when used as a covariate in the same model with dietary vitamin C: group 1: non-supplement users, group 2: supplement intake <75 mg/d, group 3: supplement intake ≥75 mg/d. This cutoff point was selected to indicate use consistent with taking a regular multivitamin, versus vitamin C supplements at higher doses (29).

Assessment of fracture

As reported previously (30), all records of hospitalizations and deaths for the study participants were systematically reviewed for occurrence of hip fracture. Beginning in 1983 (18th biennial examination in the Framingham Study), hip fractures and other non-spine fractures were reported by interview at each biennial examination or by telephone interview for participants unable to attend an examination. Reported hip fractures were confirmed by review medical records and radiographic and operative reports. Incident hip fracture was defined as a first-time fracture of the proximal femur. Self-reported non-vertebral fractures were ascertained at biennial examinations. Since the literature reports that the percent of false-positives is low for self-reported fractures at the hip, shoulder, wrist, elbow, ankle, and pelvis (31), we categorized the group of non-vertebral fractures as having any of the following: self reported first-time adult fracture of the shoulder, wrist, elbow, ankle and pelvis or a confirmed first-time hip fracture.

Potential confounding factors

Previous studies on this cohort have reported several risk factors for osteoporosis. These include age, female sex (32), lower BMI (33), current smoking (34), higher caffeine intake (35), higher alcohol intake (36), low physical activity (37), and low intake of calcium and vitamin D (38) and a protective effect of current estrogen use in women (32). BMI (kg/m²), a known risk factor for osteoporosis, was calculated in the Framingham Study from measurements of height at exam 1 (1948–1949), taken without shoes, in inches, and measurements of weight taken at the 20th examination in pounds (converted to kg) with a standardized balance-beam scale. As BMI is a measure of relative weight, designed to be independent of height, we included both BMI and height at exam 1 in our equations to adjust for ponderosity and body stature, which may be related to dietary intake and fracture (8).

Smoking status was assessed via questionnaire in 1988–89 as current cigarette smoker (smoked regularly in the past year), former smoker or never smoked. Physical activity was measured with the Framingham physical activity index, as an estimated measure of energy expenditure calculated from questions about number of hours spent in heavy, moderate, light, or sedentary activity and number of hours spent sleeping during a typical day (8). The physical activity index at the 1986–87 exam (exam 19) was used for the subjects who had a missing physical

activity index at the 1988–89 exam (exam 20). For estrogen, women were divided into two groups: those currently using estrogen or who had been using continuously for >1 yr and those who had never used estrogen, had only used it previously or, although currently using, had used it for <1 yr, as there is evidence that past or short term use does not sustain bone benefits (39). A previous study by our group supported the hypothesis that alkaline producing dietary components such as potassium, present in fruit and vegetables, play a beneficial role in bone health (9). Therefore final models were adjusted for estimated potassium intake from the FFQ and baseline BMD at the femoral neck, to examine if the association of vitamin C intake with fracture was independent of these variables. BMD was measured in the original cohort in 1988–89 at the femoral neck in g/cm² using a Lunar DP2 dual photon absorptiometer.

Statistical analysis

We tested for interactions for vitamin C intake with sex and smoking (never/former/current smoking) because a previous study identified a significant interaction of vitamin C with smoking, in the analyses of hip fracture (20). Total and dietary vitamin C intakes were adjusted for total energy intake using the residual method (25). Logarithmic transformation was applied to total vitamin C while square root transformation was applied to dietary vitamin C to achieve normality, before creating residuals. Vitamin C intakes were adjusted for total energy intake using the residual method because this method is preferred when the dietary variables are categorized for analysis (40). Dietary vitamin C intakes were regressed on total energy; residuals from the regression line were saved and then added to a constant to return to the original scale. The constant equals the predicted nutrient intake for the mean energy intake of the study population. Potassium intakes were adjusted for total energy intake by including energy intake in the multivariate equation. Hazard ratios (HRs) and 95% CI were estimated for men and women (combined and separately) for continuous as well as tertile categories of total and dietary vitamin C intake, and categories of supplemental vitamin C intakes using Cox proportional hazards regression. After adjusting for potential confounders and covariates, results from continuous analyses and categorical analyses revealed similar patterns. Therefore only the categorical analysis results are presented, as they are easily interpretable. HRs were used to estimate the relative increase in the risk of hip fracture as well as non-vertebral fracture for each of the two higher categories as compared with the lowest category (referent); we also tested for linear trend across the categories.

Multivariate models were adjusted for sex, age, BMI, height at exam 1, total energy intake, physical activity index, alcohol intake, smoking and intake of total calcium, total vitamin D, caffeine, multivitamin use and current estrogen use (in women alone). HRs for supplemental and dietary vitamin C were estimated from the same model, adjusting for each other. For analyses on the combined sample of men and women, we created a grouping variable to adjust for sex and current estrogen use simultaneously (referent group 1: men, group 2: never or former estrogen using women and group 3: current estrogen using women). With age, sex, BMI and height in the models, we performed backward stepwise regression such that any additional covariate that changed the β -coefficient of the primary exposure by more than 10% was included in the parsimonious model. Based on this method, smoking status, total calcium and vitamin D intake, and caffeine intake were excluded from the parsimonious models for total, and for supplemental and dietary vitamin C intake. Additionally, physical activity index was excluded from the parsimonious model for total vitamin C intake. Final models were adjusted for potassium intake (mg/d) and baseline femoral neck BMD. We also examined the final models using two categories for total and dietary vitamin C (category 1: vitamin C intake < Recommended Dietary Allowance (RDA) for vitamin C i.e. 90 mg/d in men and 75 mg/d in women and category 2: vitamin C intake $\geq$ RDA for vitamin C) instead of the tertile categories.

All analyses were performed using SAS statistical software (SAS Institute Inc. SAS user's guide, version 9.1 Cary, NC: SAS Institute Inc, 2001). A nominal two-sided *P*-value of <0.05 was considered statistically significant for all the analyses.

Results

Subject characteristics

Women represented two thirds (61%) of the study sample. The mean age of men and women was ~75 y, and mean BMI was 25.4 (Table 1). Approximately one third of the subjects reported education beyond high school. More than half of the subjects reported alcohol use and ever having smoked cigarettes. The majority of the women (95%) reported no current estrogen use. Approximately one fourth of the subjects reported multivitamin supplement use, and one third reported vitamin C supplement use. The mean intake of calcium was 803 mg/d while that of total vitamin C was 244 mg/d.

Crude incidence rates

In the 17 yr of follow-up, 100 hip fractures (20 in men and 80 in women) were reported among 976 participants. In the combined sample of men and women, incidence rates for hip fracture were (69/7096) 9.7 per 1000 person-yr for the lowest tertile of supplemental vitamin C intake, (16/1172) 13.7 per 1000 person-yr for the second tertile and (15/1978) 7.6 per 1000 person-yr for the highest tertile of supplemental vitamin C intake. In the 15-yr of follow-up, 180 non-vertebral osteoporotic fractures (25 in men and 155 in women) were reported among 946 men and women. In the combined sample, incidence rates for non-vertebral fracture were (120/6903) 17.3 per 1000 person-yr for the lowest tertile of supplemental vitamin C intake, (25/1102) 22.7 per 1000 person-yr for the second tertile and (30/1881) 15.9 per 1000 person-yr for the highest tertile of supplemental vitamin C intake.

Interaction with sex and smoking status

In the analyses for hip fracture and for non-vertebral fracture, no significant interactions were seen with sex or smoking status (*P* values ranged from 0.08 to 0.91). Similar trends in the associations were observed for men and women. Therefore, results are presented for the combined sample of men and women.

Total vitamin C intake and the risk of fracture

Among men and women in this study, subjects in the highest tertile of total vitamin C intake (median: 313 mg/d) had a significantly lower risk of hip fracture as compared to subjects in the lowest tertile of intake (median: 94 mg/d) (HR T3: 0.56, 95% CI: 0.31–0.98, *P*=0.04, HR T2: 0.73, 95% CI: 0.44–1.20, *P*=0.21, *P* for trend = 0.04, Global test *P* value=0.0001) (Figure 2). Similarly, subjects in the highest tertile of total vitamin C intake (median: 308 mg/d) had lower risk of non-vertebral osteoporotic fracture as compared to subjects in the lowest tertile of intake (median: 95 mg/d) (HR T3: 0.66, 95% CI: 0.43–1.01, *P*= 0.06, HR T2: 0.93, 95% CI: 0.65–1.36, *P*= 0.73, *P* for trend = 0.05, Global test *P* value<0.0001) (Figure 2).

Supplemental vitamin C intake and risk of fracture

Subjects in the highest category of supplemental vitamin C intake (median: 260 mg/d) had significantly lower risk of hip fracture as compared to non-supplement users (HR T3: 0.31, 95% CI: 0.13–0.73, *P*=0.007, HR T2: 0.50, 95% CI: 0.20–1.24, *P*=0.13, *P* for trend = 0.02, Global test *P* value<0.0001) (Figure 3). Similarly, subjects in the highest category of supplemental vitamin C intake (median: 260 mg/d) tended to have lower risk of non-vertebral osteoporotic fracture as compared to non-supplement users, but this only approached

significance (HR T3: 0.58, 95% CI: 0.30–1.11, $P=0.10$, HR T2: 0.80, 95% CI: 0.38–1.71, $P=0.57$, P for trend = 0.07, Global test P value<0.0001) (Figure 3).

Dietary vitamin C intake and risk of fracture

A protective trend in association was observed for dietary vitamin C and risk of hip fracture as well as non-vertebral osteoporotic fracture, but these associations were not statistically significant ($P=0.22$ for HR T3 and 0.44 for HR T2, Global test P value<0.0001) (data not shown). The median intake of dietary vitamin C for the hip fracture analysis was 86 mg/d for tertile 1, 133 mg/d for tertile 2 and 208 mg/d for tertile 3.

Final adjustment for potassium intake and baseline BMD

After adjustment for potassium intake, the associations (HR) did not change except for the HR for total vitamin C with hip fracture (HR T3: 0.56, T2: 0.73, P trend=0.06, Global test P value=0.0002), which became marginally significant and the HR for total vitamin C with non-vertebral fracture (HR T3: 0.74, T2: 1.03, P trend=0.19, Global test P value<0.0001), which lost statistical significance. The associations remained unchanged after adjustment for baseline BMD at femoral neck (Table 2).

When we reanalyzed the data by creating two categories for total and dietary vitamin C (category 1: vitamin C intake < Recommended Dietary Allowance (RDA) i.e. 90 mg/d in men and 75 mg/d in women and category 2: vitamin C intake $\geq$ RDA for vitamin C). We observed that subjects with total vitamin C intakes $\geq$ RDA for vitamin C had fewer hip fractures as compared to subjects with total vitamin C intakes < RDA for vitamin C. However, the associations did not reach significance ($P=0.61$). Similar results were also observed for dietary vitamin C intakes ($P=0.40$). Furthermore, we did not observe any significant associations for non-vertebral osteoporotic fractures ($P=0.59$ for total vitamin C and 0.76 for dietary vitamin C intake).

Discussion

This study examined prospective associations between vitamin C intake and the risk of hip fracture as well as non-vertebral osteoporotic fracture in elderly men and women over a relatively long follow up period. We found protective associations for higher levels of total and supplemental vitamin C with hip fracture and non-vertebral osteoporotic fracture over 17-yr of follow-up. These results are consistent with the hypothesis of the study. However, no statistically significant associations were observed with dietary vitamin C intake in the fully adjusted model. Furthermore, some associations were attenuated after adjustment for potassium intake, a marker of fruit and vegetable intake.

Association of vitamin C with fracture

Several observational studies have examined vitamin C in relation to bone health. Maggio et al., reported that a group of elderly osteoporotic women had consistently lower levels of all natural antioxidants tested (including vitamin C) than controls (41). In the NHANES III in 1988–94 ($n=13,080$ adults age 20–90 y), serum ascorbic acid was associated with lower risk of self-reported fracture in postmenopausal women who had ever smoked and had a history of estrogen therapy (OR: 0.51, 95% CI: 0.36–0.70) (42). Among men, dietary ascorbic acid was associated in a non-linear fashion with self-reported fracture ($P=0.01$). A dietary ascorbic acid intake of approximately 200 mg/d was associated with the lowest prevalence of self-reported fracture. However, among men, at ascorbic acid intakes of <100 and >250 mg/d, the prevalence of self-reported fractures rose. The Swedish Mammography cohort ($n=66,651$ women) reported that the OR for hip fracture among current smokers with a low intake of vitamin E (median intake ≤ 6.2 mg/d) was 3.0 (95% CI: 1.6–5.4) and for vitamin C (median intake ≤ 67

mg/d), 3.0 (95% CI: 1.6–5.6). However, in current smokers with a low intake of both vitamin E and C, the OR increased to 4.9 (95% CI: 2.2–11.0) (20). In contrast, the Utah Study of Nutrition and Bone Health reported that vitamin C intake did not have a statistically significant graded association with hip fracture risk among men and women, aged ≥ 50 yr, who had ever smoked but instead their data showed a threshold effect. The protective association of total vitamin C was observed at the median intake of 159 mg/d. Further increase in the intake of total vitamin C did not provide additional benefit (21). Together these studies provide evidence of the association of vitamin C with fractures.

Interaction of vitamin C with other factors

Published reports have suggested that the association of vitamin C with bone is complex and may include interactions with several other factors such as sex, smoking status, vitamin E intake and current estrogen use. Unlike the above studies, we did not find any effect modification.

While little work has been published on vitamin C and fracture, a number of studies have reported on a dietary link to BMD. Previous research by our group demonstrated that fruit and vegetable specific nutrients such as potassium have a beneficial effect on BMD (6,9). A recent study by Lanham-New reviewed data from many studies that showed a positive link between potassium-rich, bicarbonate-rich foods (particularly fruit and vegetables) and indices of bone health (43). Therefore, the protective effect of dietary vitamin C intake on fracture could be confounded by potassium and other alkali forming components present in fruit and vegetables. In our study, adjustment for potassium intake only attenuated the protective association of total vitamin C with hip fracture and the association of total vitamin C with non-vertebral osteoporotic fracture, which lost statistical significance. Further, the use of vitamin C supplements but not dietary vitamin C intake was protective. A similar pattern of effect was also reported for vitamin D and bone health in a previous study. Together, these results suggest that it may be difficult to separate the protective effect of dietary vitamin C intake from other protective nutrients present in fruit and vegetables. Although it is possible to consume the amount of vitamin C shown in our study to be protective from food, lower vitamin C intake from dietary sources in our study sample, and the U.S. population in general, limited our ability to see results with fracture through diet alone. Although mean dietary intakes were above the current RDA for vitamin C, they fell well below the amount shown here to be protective. However, if current recommendations to consume 5–9 fruit and vegetable servings per day were followed, this consumption could provide the amount of vitamin C associated with lower fracture risk, while contributing other health protective nutrients. More research is needed to clarify the effect of high vitamin C intakes from diet alone.

It is important to note that the total and supplemental vitamin C appeared less effective against non-vertebral osteoporotic fractures than hip fractures. The reason for this is not clear; however reliance on self-report for these fractures may be one possible explanation. Although we limited our analyses to specific fracture sites that are considered to be more accurate, self-reported fractures may include misclassification and resultant attenuation of results. Additionally, we also observed that the crude incidence rates for hip fracture as well as for non-vertebral osteoporotic fracture were not linear however the adjusted hazard ratios did appear to indicate a linear trend.

Biologic mechanisms for vitamin C

Published studies have consistently reported that higher fruit and vegetable intake has positive effects on BMD (5–10). It is, therefore, possible that fruit and vegetable specific antioxidants may play a role (44). There is evidence that vitamin C may be protective of bone health, through their action on oxidative stress. Oxidative stress may increase bone resorption through activation of Nuclear Factor κ B protein (NF κ B), which is a crucial mediator of Tumor Necrosis

Factor- α (TNF- α) and osteoclastogenesis (45–47). Vitamin C is capable of reducing oxidative stress by scavenging singlet oxygen and peroxy radicals. Therefore, vitamin C may affect bone health by inhibiting bone resorption. In a previous study by our group in the same cohort (22), null associations were observed for vitamin C intake and BMD among women. However, in men, higher total vitamin C intake was associated with less femoral neck and trochanter-BMD loss with low calcium (all P -trend ≤ 0.03), or vitamin E intakes (all P -trend = 0.03). Furthermore, higher dietary vitamin C intake (median intake of 196 mg/d) tended to be associated with lower femoral neck-BMD loss (P -trend = 0.09). These associations were attenuated but retained borderline significance (P -trend < 0.1) after adjusting for potassium intake (a marker of fruit and vegetable intake), suggesting that vitamin C effects may not be separated from other protective factors in fruit and vegetables. However, in this study, after adjustment for baseline femoral neck BMD, the observed associations did not change, suggesting that the protective effect of total and supplemental vitamin C on hip fracture may not be mediated through effects on BMD alone. Alternative mechanisms to explain our findings may include effects on bone quality either through effects on collagen or non-bone effects on the risk of falls. Bone matrix contains over 90% of protein as collagen (16) and vitamin C is an essential cofactor for collagen formation and synthesis of hydroxyproline and hydroxylysine (17). Supporting these mechanisms, two animal studies have reported that vitamin C accelerates fracture healing in rats (48,49). Another *in vitro* study (50) reported that the extent and nature of collagen cross-linking contribute to the mechanical properties of fetal bovine cortical bone independently of BMD. Taken together, these findings suggest that vitamin C may play a multi-factorial role in protecting bone health.

The current study is unique in that it used data from a population-based cohort that included both older men and women. Furthermore, the prospective design of this study, with over 15 to 17-yr of follow-up of subjects, helps in minimizing recall biases and misclassification. However, this study has some limitations. Non-vertebral osteoporotic fractures were self-reported in our study and may have resulted in misclassification. To minimize this possibility, we used only those self-reported fractures at specific bone sites that have been shown to have low percentages of false-positives (31); additionally we used confirmed hip fracture as a part of non-vertebral fracture. Another limitation of this study was that we examined only the dietary intakes but not serum measures of vitamin C. The complete dietary data were available only at the baseline and therefore, we were unable to adjust for possible secular changes in diet during the follow-up period. However, we examined the correlations of total, supplemental and dietary vitamin C intakes over 4-yr of follow-up (at exam 20 and exam 22) for the smaller subset with repeated dietary assessments and observed good correlations of 0.7 for total and supplemental vitamin C and a reasonable correlation of 0.4 for dietary vitamin C intake measurements over the 4-y time frame. In any observational study, residual confounding may occur, despite control for several potential confounders.

In summary, we observed a protective effect against fracture with total and supplemental vitamin C in this population of elderly Caucasian men and women. More studies are needed to examine these associations in other populations. Future studies should also consider the possible need to increase the dietary recommended intakes (DRI) for vitamin C, based on accumulating evidence of protective effects on bone and against other chronic diseases.

Acknowledgments

Funding sources: This study was supported by the United States Department of Agriculture, Agriculture Research Services agreement number 58-1950-7-707; Framingham Osteoporosis grant number R01 AR/AG 41398 and the NHLBI's Framingham study contract grant number N01-HC-25195.

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Fig. 1.

Flowchart showing total number of subjects enrolled in the Framingham Heart Study and the final number of subjects included in the analyses

^a Framingham Heart Study

^b Food Frequency Questionnaire

a. HIP FRACTURE

b. NON-VERTEBRAL OSTEOPOROTIC FRACTURE

Fig. 2.

Inverse association of total vitamin C intake and risk of (a): Hip fracture and (b): Non-vertebral osteoporotic fracture in the elderly men and women of the Framingham Osteoporosis Study a

Squares represent HR for hip fracture and non-vertebral osteoporotic fracture
Lines represent 95% CI

HR is significantly different from HR of tertile 1: * $P < 0.05$

P for trend=0.04 for hip fracture and 0.05 for non-vertebral osteoporotic fracture

^a Full models were adjusted for sex and estrogen use (group 1: men, group 2: never or former estrogen users, group 3: current estrogen users), age at exam 20 (yr), BMI (kg/m^2), height at exam 1 (m), total energy intake (MJ), and multivitamin use (yes/no)

a. HIP FRACTURE

b. NON-VERTEBRAL OSTEOPOROTIC FRACTURE

Fig. 3.

Inverse association of vitamin C intake from supplements a and risk of (a): Hip fracture and (b): Non-vertebral osteoporotic fracture in the elderly men and women of the Framingham Osteoporosis Study b

Squares represent HR for hip fracture and non-vertebral osteoporotic fracture
Lines represent 95% CI

HR is significantly different from HR of tertile 1: * $P < 0.05$, † $P = 0.1$

P for trend = 0.02 for hip fracture and 0.07 for non-vertebral osteoporotic fracture

^a Vitamin C from supplements was categorized as (group 1: non-supplement users, group 2: intake < 75 mg/d, group 3: intake $\geq$ 75 mg/d)

^b Parsimonious models were adjusted for dietary vitamin C intake (mg), sex and estrogen use (group 1: men, group 2: never or former estrogen users, group 3: current estrogen users), age at exam 20 (yr), BMI (kg/m^2), height at exam 1 (m), total energy intake (MJ), Physical Activity Index, and multivitamin use (yes/no)

Table 1Characteristics of study participants of the Framingham original cohort at the 20th examination ^a

Descriptive variables	Study participants
Women (%)	60.9
Age (yr)	75.3 ± 5.0 ^b
BMI (kg/m ²)	25.5 ± 4.4
Physical Activity Index	33.4 ± 5.4
Education group (%)	
○ No high school diploma	30.3
○ High school diploma	36.8
○ Higher education	32.9
Smoking status (%)	
○ Current smokers	10.9
○ Former smokers	52.0
Alcohol use (%)	
○ Moderate	39.1
○ High	17.7
Multivitamin supplement use (%)	25.3
Vitamin C supplement use (%)	30.5
Current estrogen use (%), women only	4.7

Descriptive variables	Men and women
Intake of:	
○ Total Energy (MJ/d)	7.3 ± 2.4 ^b
○ Total calcium (mg/d) ^c	803 ± 428
○ Total vitamin D (IU/d) ^c	326 ± 263
○ Total vitamin C (mg/d) ^c	244 ± 268
○ Dietary vitamin C (mg/d)	152 ± 80
○ Vitamin C from supplements (mg/d)	92 ± 246
○ Fruit & vegetables (servings/d)	5.4 ± 2.7

^aSample sizes varied from 917 to 946 for men and women^bMean ± SD^cTotal nutrient intake= Dietary intake + Intake from supplements

Baseline vitamin C intake and risk of hip fracture after adjustment for baseline femoral neck BMD, among men and women in the Framingham original cohort.

Vitamin C intake	n	Hazard Ratio ^a for hip fracture by tertiles of Vitamin C intake (mg/d) ^b			P for trend ^c
		Tertile 1 (Ref.)	Tertile 2	Tertile 3	
Total ^d	837	1.00	0.69	0.52*	0.03*
Supplemental ^e	835	1.00	0.61	0.36*	0.02*
Dietary ^e	835	1.00	0.89	0.79	0.44

^aHR significantly different from HR in the first tertile, * $P < 0.05$

^bTotal and dietary vitamin C intakes were energy-adjusted residuals added to a constant, where the constant equals the nutrient intake for the mean energy intake of the study population. Logarithmic and square root transformations were applied to the total and dietary vitamin C intake respectively before creating residuals

^c* P for trend < 0.05

^dParsimonious models were adjusted for sex and estrogen use (group 1: men, group 2: never or former estrogen users, group 3: current estrogen users), age at exam 20 (yr), Body Mass Index (BMI, kg/m²), height at exam 1 (m), total energy intake (MJ), and multivitamin use (yes/no)

^eParsimonious models for supplemental (group 1: non-supplement users, group 2: intake < 75 mg/d, group 3: intake ≥ 75 mg/d) and dietary vitamin C intake were additionally adjusted for Physical Activity Index. Supplemental and dietary vitamin C intakes were adjusted for each other when examined