

## Vitamin C and Risk of Coronary Heart Disease in Women

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<b>OBJECTIVES</b>	Our objective was to prospectively examine the relation between vitamin C intake and risk of coronary heart disease (CHD) in women.
<b>BACKGROUND</b>	Results from prospective investigations of the relation between vitamin C intake and risk of CHD have been inconsistent. The lack of clear evidence for a protective association despite a plausible mechanism indicates the need to evaluate further the association between vitamin C intake and risk of CHD.
<b>METHODS</b>	In 1980, 85,118 female nurses completed a detailed semiquantitative food-frequency questionnaire that assessed their consumption of vitamin C and other nutrients. Nurses were followed up for 16 years for the development of incident CHD (nonfatal myocardial infarction and fatal CHD).
<b>RESULTS</b>	During 16 years of follow-up (1,240,566 person-years), we identified 1,356 incident cases of CHD. After adjustment for age, smoking, and a variety of other coronary risk factors, we observed a modest significant inverse association between total intake of vitamin C and risk of CHD (relative risk [RR] = 0.73; 95% confidence interval [CI] 0.57 to 0.94). Among women who did not use vitamin C supplements or multivitamins, the association between intake of vitamin C from diet alone and incidence of CHD was weak and not significant (RR = 0.86; 95% CI 0.59 to 1.26). In multivariate models adjusting for age, smoking, and a variety of other coronary risk factors, vitamin C supplement use was associated with a significantly lower risk of CHD (RR = 0.72; 95% CI 0.61 to 0.86).
<b>CONCLUSIONS</b>	Users of vitamin C supplements appear to be at lower risk for CHD. (J Am Coll Cardiol 2003;42:246–52) © 2003 by the American College of Cardiology Foundation

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Vitamin C is the main water-soluble antioxidant in human plasma (1) and is hypothesized to have a protective role in the development of atherosclerotic heart disease (2) by inhibiting low-density lipoprotein oxidation (3,4). Oxidized low-density lipoprotein has been identified in atherosclerotic lesions (5,6) and may be atherogenic in the vessel wall through several mechanisms (7). In vitro, some studies have demonstrated a significant reduction in the oxidizability of low-density lipoprotein taken from the plasma of humans supplemented with vitamin C alone or in combination with vitamin E or beta-carotene (8–10).

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Several prospective studies have examined the relation between vitamin C intake or vitamin C supplement use and risk of coronary heart disease (CHD) (11). Higher dietary intake of vitamin C has been associated with a moderately lower risk of CHD among some study populations with a

substantial proportion of persons who have low or deficient intakes of vitamin C (12,13). However, most studies conducted with well-nourished populations have not demonstrated an inverse association (14–17). To date, data from primary prevention trials of supplementation are not available. The lack of clear evidence for a protective association despite a plausible mechanism indicates the need to evaluate further the association between vitamin C intake and risk of CHD. We therefore examined the relation between dietary and supplemental intake of vitamin C and risk of CHD in a cohort of U.S. women during 16 years of follow-up.

### METHODS

**Study population.** The Nurses' Health Study was initiated in 1976 when 121,700 female registered nurses 30 to 55 years of age and residing in 11 large U.S. states completed a mailed questionnaire on their medical history and lifestyle (18). Follow-up questionnaires have been sent every two years thereafter to ascertain information on potential risk factors and identify newly diagnosed cases of CHD and other diseases. A semiquantitative food-frequency questionnaire (SFFQ) was developed to assess intake of micronutrients and other components of diet.

A total of 98,482 women returned the diet questionnaire in 1980. A priori, we excluded respondents who had implausibly high (>3,500 kcal/day) or low (<500 kcal/day)

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#### Abbreviations and Acronyms

CHD	= coronary heart disease
CI	= confidence interval
MI	= myocardial infarction
RR	= relative risk
SFFQ	= semiquantitative food-frequency questionnaire

total energy intake or those who left 10 or more items blank. We further excluded women with cancer, except non-melanoma skin cancer ( $n = 3,499$ ), or cardiovascular diseases (i.e., angina, myocardial infarction [MI], stroke, or other cardiovascular diseases,  $n = 1,851$ ) diagnosed before 1980 because these diagnoses may have led to a recent change in diet. The final baseline sample consisted of 85,118 women who were followed up for 16 years for the occurrence of CHD. More than 90% responded to the subsequent biennial questionnaires, and about 80% completed the diet questionnaires at each follow-up assessment. The Nurses' Health Study was approved by the Institutional Review Board of the Brigham and Women's Hospital.

**Ascertainment of diet and other exposures.** Dietary intake of vitamin C and other aspects of diet were measured using the SFFQs administered in 1980, 1984, 1986, 1990, and 1994. For each food, a commonly used unit or portion size (e.g., one egg or one slice of bread) was specified, and the participant was asked how often, on average, during the previous year she had consumed that amount. Nine responses were possible, ranging from "never or <1 per month" to "≥6 times per day." The intake of specific nutrients was computed by multiplying the frequency of consumption of each unit of food by the nutrient content of the specified portion. Food composition values were obtained from the Harvard University Food Composition Database derived from U.S. Department of Agriculture sources (19) and supplemented with manufacturer information and other published values. We calculated the cumulative average intake of each nutrient from all dietary questionnaires available up to the start of every two-year follow-up interval as described elsewhere (20). When dietary data were missing at the start of a new interval, we carried forward the last available dietary data. The measurement of glycemic load in the Nurses' Health study was reported elsewhere (21). We also ascertained brand of breakfast cold cereal to take into account fortification with vitamins. A detailed description of the dietary questionnaires and documentation of their reproducibility and validity have been published elsewhere (22-24).

The biennial, mailed questionnaire collected information on several demographic, behavioral, and clinical variables proven or suspected to be associated with CHD. During each cycle, we asked participants to provide information on use of multiple vitamins, specific brand, and usual number of tablets taken per week. Information was also collected on the use of specific supplements, including vitamin C,

vitamin E, and beta-carotene (only in 1984 and thereafter), together with the dose of tablets and usual number of tablets taken per week. We calculated total nutrient intake of vitamin C, vitamin E, and beta-carotene as the sum of both dietary and supplemental sources. The number of years of past vitamin C supplement use was ascertained in 1980 and updated every two years thereafter.

**Ascertainment of end point.** The primary end point for this analysis was incident CHD, which included any non-fatal MI or fatal coronary event diagnosed after the return of the 1980 questionnaire but before June 1, 1996. For all women who reported a diagnosis of CHD on a biennial follow-up questionnaire, we requested permission to examine the medical records. An MI was considered confirmed if it met the World Health Organization criteria of symptoms and either typical electrocardiographic changes or elevated cardiac enzymes (25). Infarctions of indeterminate age were excluded. Infarctions that required hospital admission and for which confirmatory information was obtained by interview or letter, but for which no medical records were available, were designated as probable. We included all confirmed and probable cases in the analyses because results were not substantially different after excluding probable cases (data not shown).

Deaths were identified from state vital records and the National Death index or reported by the women's next of kin and the postal system (26). Fatal CHD was confirmed by hospital records or autopsy, or if CHD was listed as the cause of death on the death certificate and evidence of previous CHD was available. We designated as presumed fatal CHD those cases in which CHD was the underlying cause on the death certificate but for which no records were available. These cases constituted about 24% of fatal CHD cases. We also included sudden death within 1 h of onset of symptoms in women with no other plausible cause (other than coronary disease), which constituted 16% of fatal CHD cases. Analyses limited to confirmed cases yielded similar, although less precise results (data not shown).

**Statistical methods.** Person-time for each participant was calculated from the date of return of the 1980 diet questionnaire to the date of the first CHD event, death, or June 1, 1996. Nutrients were energy-adjusted using the residual method (27). For dietary exposures, women were categorized into five equal groups according to quintiles of an energy-adjusted nutrient. We used the cumulative average of repeated measures of diet to reduce the within-person variation in diet and more precisely represent long-term intakes (20). Incidence rates were calculated by dividing the number of events by the person-time of follow-up in each quintile. The relative risk (RR) of a coronary event was computed as the incidence rate in a specific category of energy-adjusted intake of vitamin C divided by the rate in the lowest category of intake, with adjustment for five-year age categories. For the analyses of use of vitamin C supplements, we compared the incidence rate in the category of current users of supplements to that of non-users.

**Table 1.** Characteristics of the Cohort According to Quintiles of Total Vitamin C Intake at Baseline (1980)

Characteristic	Quintile of Total Vitamin C Intake (mg)				
	1 (≤93 mg/day)	2 (94–132 mg/day)	3 (133–183 mg/day)	4 (184–359 mg/day)	5 (≥360 mg/day)
Median age (yrs)	45.0	45.0	46.0	46.5	48.0
Median body mass index (kg/m <sup>2</sup> )	23.2	24.4	24.5	24.4	24.1
High blood cholesterol* (%)	4.0	4.4	5.0	5.5	6.6
High blood pressure* (%)	12.4	14.1	16.4	17.9	16.6
Diabetes* (%)	1.4	2.1	2.2	2.5	2.2
Parental history of myocardial infarction before age 60 yrs (%)	15.0	14.4	14.6	14.0	13.7
Current smoker (%)	37.2	28.4	26.1	24.4	26.2
≥7 aspirin/week (%)	12.6	13.2	13.9	14.1	18.5
Multivitamin users (%)	4.1	12.5	28.9	52.3	73.2
Vitamin C supplement users (%)	0.1	0.6	1.7	13.2	81.1
Vitamin E supplement users (%)	2.3	3.0	4.9	10.5	44.8
Exercise ≥2 h/week (%)	69.3	74.5	76.7	77.8	77.6
Current postmenopausal hormone use (%)	5.1	5.6	6.5	6.9	9.2
Median total caloric intake (kcal)	1,457	1,518	1,536	1,539	1,495
Median alcohol intake (gm)	1.8	1.8	1.8	1.7	1.8
Median nutrient intakes†					
Saturated fat (g)	31.0	29.0	27.0	26.0	27.0
Polyunsaturated fat (g)	9.7	9.3	8.9	8.4	8.7
Transunsaturated fat (g)	4.4	4.1	3.8	3.5	3.5
Vitamin B6 (mg)	1.3	1.5	1.8	2.6	3.7
Folate (mcg)	172	237	306	418	452
Cereal fiber (g)	2.1	2.2	2.2	2.1	2.1
Glycemic load‡	108	117	122	130	120
Total carotene (IU)	4,416	6,067	7,518	8,469	7,794
Vitamin E (IU)	5.1	5.8	6.9	14.9	41.3
Vitamin C (mg)	70	113	155	228	704

\*Self-reported diagnosis of this condition. †Energy adjusted total nutrient intakes from 1980 semiquantitative food-frequency questionnaire. ‡Glycemic load was defined as an indicator of blood glucose induced by an individual's total carbohydrate intake. Each unit of glycemic load represents the equivalent of 1 g carbohydrate from white bread.

We used pooled logistic regression (28) with two-year follow-up periods, which is asymptotically equivalent to the Cox-proportional-hazard regression, to model the incidence of CHD in relation to the cumulative average of vitamin C intake and adjust simultaneously for potentially confounding variables shown in Table 1. Most non-dietary covariates were ascertained and updated every two years. Indicator variables were included for missing data on covariates. All models also included an indicator variable for each two-year time period during the study (8 periods). Tests of linear trend across increasing quintiles of vitamin C intake were conducted by assigning the medians of intake to categories that were treated as a continuous variable in the regression. All p values are two-sided.

To avoid a spurious finding due to the potential influence of disease or prodromal illness on women's diet, women with prior diagnoses of other cardiovascular diseases or cancer (except non-melanoma cancer) were excluded at baseline, and women with new diagnoses were also censored at the time of diagnosis during follow-up. Stratified analyses were conducted to examine potential interactions between use of vitamin C supplements and use of vitamin E supplements, alcohol intake, smoking status, and diagnosis of diabetes.

## RESULTS

During 16 years of follow-up (1,240,566 person-years) from 1980 to 1994, we identified 1,356 incident cases of CHD: 973 nonfatal MIs (813 confirmed nonfatal cases) and 383 deaths from coronary disease (209 confirmed CHD deaths). At baseline, mean energy-adjusted intake of vitamin C from both supplements and diet was 304 mg/day with substantially lower intakes from dietary sources alone (mean intake = 130 mg/day). Only 12% of women reported intakes below 75 mg/day, the current recommended daily allowance for non-smoking women, and approximately 19% of participants took vitamin C supplements. The distributions of energy-adjusted vitamin C intake from dietary sources only were similar for users and non-users of vitamin C supplements: median intake = 128 mg/day and 118 mg/day, respectively.

As shown in Table 1, median intake of vitamin C ranged from 70 mg/day in the lowest quintile to 704 mg/day in the highest quintile of intake. Participants with higher intakes of vitamin C were less likely to smoke cigarettes and more likely to exercise and take aspirin and supplements—including multivitamins, vitamin E, and vitamin C—than those with lower intakes. The majority of participants who took vitamin C supplements were in the highest quintile of

**Table 2.** Adjusted Relative Risks and 95% Confidence Intervals for Coronary Heart Disease (Nonfatal MI and Fatal CHD) According to Quintile of Vitamin C Intake\*

Variable	Quintile of Vitamin C Intake					p Value Trend
	1	2	3	4	5	
Total vitamin C intake (including supplements)						
Median intake (mg/day)	70	113	155	228	704	
Range	≤93	94–132	133–183	184–359	≥360	
No. of cases of CHD	296	261	281	302	216	
Relative risk						
Age adjusted	1.0	0.76	0.75	0.75	0.53	0.0001
95% CI	—	0.64–0.90	0.64–0.90	0.64–0.89	0.44–0.63	
Age- and smoking-adjusted	1.0	0.89	0.93	0.93	0.63	0.0001
95% CI	—	0.75–1.05	0.78–1.09	0.79–1.10	0.53–0.76	
Multivariate†	1.0	0.87	0.93	0.95	0.70	0.0008
95% CI	—	0.72–1.05	0.75–1.15	0.77–1.17	0.55–0.88	
Multivariate† plus total						
Vitamin E and carotene intake	1.0	0.87	0.94	0.98	0.73	0.005
95% CI	—	0.73–1.05	0.77–1.15	0.79–1.22	0.57–0.94	
Dietary vitamin C intake (without multivitamins or vitamin C supplements)‡						
Median intake (mg/day)	61	94	121	152	209	
Range	≤79	80–108	108–135	135–173	≥174	
No. of cases	119	106	106	109	118	
Relative risk						
Age-adjusted	1.0	0.79	0.74	0.69	0.73	0.03
95% CI	—	0.61–1.03	0.57–0.96	0.53–0.89	0.57–0.95	
Age- and smoking-adjusted	1.0	0.94	0.95	0.94	1.03	0.79
95% CI	—	0.72–1.22	0.73–1.24	0.72–1.22	0.79–1.33	
Multivariate†	1.0	0.90	0.85	0.83	0.85	0.46
95% CI	—	0.67–1.20	0.62–1.16	0.59–1.16	0.58–1.24	
Multivariate† plus total						
Vitamin E and carotene intake	1.0	0.91	0.86	0.84	0.86	0.52
95% CI	—	0.68–1.22	0.62–1.18	0.60–1.18	0.59–1.26	

\*Cumulative average intake of energy-adjusted nutrients. †Multivariate model adjusted for age, smoking, postmenopausal hormone use, parental history of myocardial infarction, history of high blood pressure, history of high cholesterol, diabetes, body mass index, regular exercise, aspirin use, alcohol intake, total caloric intake, saturated fat intake, polyunsaturated fat intake, transunsaturated fat intake, cereal fiber intake, folate intake, dietary glycemic load, and vitamin B6 intake. ‡Excludes women who take multivitamins or vitamin C supplements.

CHD = coronary heart disease; CI = confidence interval; MI = myocardial infarction.

total vitamin C intake. Those with higher total intakes of vitamin C also consumed more folate, vitamin B6, total carotene, and vitamin E—and somewhat less saturated fat.

Table 2 shows the RRs for CHD according to quintiles of vitamin C intake. In multivariate models, adjusting for a variety of other coronary risk factors and other dietary antioxidants, only women in the highest relative to the lowest quintile of intake were at moderately lower risk for CHD (RR = 0.73; 95% confidence interval [CI] 0.57 to 0.94). After excluding women who took vitamin C supplements or multivitamins, there was no significant association between vitamin C intake derived from diet only and risk of CHD (RR = 0.86; 95% CI 0.59 to 1.26 for the highest relative to lowest quintile of intake from diet only). We similarly found no association between intake of vitamin C from diet only and risk of CHD among the subgroup of vitamin C supplement users (multivariate RR = 0.94; 95% CI 0.56 to 1.60 for the highest relative to lowest quintile of intake from diet only).

We then examined the association between CHD and current vitamin C supplement use—including dose and

duration of use—among all participants. In general, women who took vitamin C supplements differed somewhat from those who did not (Table 3). Women who took vitamin C supplements tended to have substantially higher intakes of vitamin E, total carotene, folate, and vitamin B6. Vitamin C supplement users included a higher proportion of those who took vitamin E supplements and multivitamins. Women who took supplements were also somewhat older, more physically active, and less likely to smoke. In multivariate models adjusting for a variety of coronary risk factors and other dietary antioxidants, there was a significant 28% lower risk of CHD among users than non-users of supplements (RR = 0.72; 95% CI 0.61 to 0.86) (Table 4). The RR was essentially unchanged in multivariate models adjusting for vitamin E supplement use of 100 IU/day or more and two or more years duration (data not shown). Furthermore, we found that use of vitamin C supplements for less than two years was associated with no reduction in risk of CHD, but the CIs were broad because of the small number of users in this category. Use of vitamin C supplements for two to four years was associated with an approximately 23% lower risk,

**Table 3.** Characteristics of the Cohort According to Vitamin C Supplement Use at Baseline (1980)\*

Characteristic	Non-User of Vitamin C Supplements (n = 68,666)	User of Vitamin C Supplements (n = 16,186)
Median age (yrs)	46	48
Median body mass index (kg/m <sup>2</sup> )	24.4	24.0
High blood cholesterol† (%)	4.8	6.4
High blood pressure† (%)	15.4	15.8
Diabetes† (%)	2.0	2.1
Parental history of myocardial infarction before age 60 yrs (%)	14.6	13.2
Current smoker (%)	29.3	25.3
Exercise ≥2 h/week (%)	74.4	77.9
≥7 aspirin/week (%)	13.7	17.8
Current postmenopausal hormone use (%)	6.2	8.6
Vitamin E supplement users (%)	4.2	50.1
Multivitamin users (%)	26.0	67.2
Median alcohol intake (g/day)	1.8	1.8
Median total caloric intake (kcal/day)	1,506	1,522
Median nutrient intakes (U/day)‡		
Saturated fat (g)	28.0	27.0
Polyunsaturated fat (g)	9.0	8.9
Transunsaturated fat (g)	4.0	3.6
Folate (mcg)	259	450
Vitamin B6 (mg)	1.6	3.2
Cereal fiber (gm)	2.2	2.2
Glycemic load§	120	118
Total carotene (IU)	6,408	7,475
Vitamin E (IU)	6.3	52.3
Vitamin C (mg)	132	672

\*Excludes 266 participants with missing data on vitamin C supplement use. †Self-reported diagnosis of this condition. ‡Energy-adjusted total nutrient intakes from 1980 semiquantitative food-frequency questionnaire. §Glycemic load was defined as an indicator of blood glucose induced by an individual's total carbohydrate intake. Each unit of glycemic load represents the equivalent of 1 g carbohydrate from white bread.

and there was no consistent trend toward greater decrease in risk with longer duration of use. In addition, we found no significant differences in the RRs of CHD according to dose of vitamin C supplements; however, the reduction in risk was somewhat stronger among women who took at least 400 mg/day (Table 4).

Some investigators have suggested that antioxidants may be more important among subgroups with higher oxidative stress, such as cigarette smokers, those with high intakes of alcohol, and those with diabetes. We found that the inverse association between vitamin C supplement use and risk of CHD was somewhat stronger among never-smokers (RR = 0.54; 95% CI 0.39 to 0.77) and current smokers (RR = 0.72; 95% CI 0.55 to 0.94) than among former smokers (RR = 0.92; 95% CI 0.68 to 1.24); however, the variation in risk among subgroups of smokers was not statistically significant. Similarly, we found no statistically significant variation in risk of CHD among subgroups with different amounts of alcohol intake, including non-drinkers (RR = 0.74; 95% CI 0.56 to 0.96), women drinking 1 to 9 g/day (RR = 0.77; 95% CI 0.58 to 1.02), and women drinking ≥10 g/day (RR = 0.85; 95% CI 0.56 to 1.30). The inverse

**Table 4.** Adjusted Relative Risks and 95% Confidence Intervals for Coronary Heart Disease (Nonfatal MI and Fatal CHD)\* According to Use of Vitamin C Supplements†

	Vitamin C Supplement Users	
	No. of Cases Among Users	Relative Risk (95% CI)
Among vitamin C supplement users		
Age-adjusted	227	0.62 (0.54–0.73)
Age- and smoking-adjusted		0.65 (0.56–0.76)
Multivariate‡		0.71 (0.61–0.84)
Multivariate‡ plus total vitamin E and carotene intake		0.72 (0.61–0.86)
Among vitamin C supplement users, doses of§		
1–400 mg/day	45	0.82 (0.60–1.12)
401–749 mg/day	89	0.69 (0.55–0.87)
750 mg/day or more	79	0.71 (0.55–0.92)
Among vitamin C supplement users, durations of§		
<2 yrs	5	1.12 (0.46–2.77)
2–4 yrs	114	0.77 (0.63–0.94)
5–9 yrs	53	0.84 (0.63–1.13)
10 or more yrs	54	0.70 (0.51–0.94)

\*Self-reported diagnosis of this condition. †Analysis includes 729 cases of CHD among non-users of supplements and 956,579 total person years of follow-up. ‡Multivariate model adjusted for age, smoking, body mass index, postmenopausal hormone use, parental history of MI, history of high blood pressure, history of high cholesterol, diabetes, physical activity, aspirin use, alcohol intake, total caloric intake, glycemic load, saturated fat intake, transunsaturated fat intake, polyunsaturated fat intake, cereal fiber intake, folic acid intake, and vitamin B6 intake. Analysis excludes 14 cases missing dose information. §Multivariate model adjusted for age, smoking, body mass index, postmenopausal hormone use, parental history of MI, history of high blood pressure, history of high cholesterol, diabetes, physical activity, aspirin use, alcohol intake, total caloric intake, glycemic load, saturated fat intake, transunsaturated fat intake, polyunsaturated fat intake, cereal fiber intake, folic acid intake, vitamin B6 intake, vitamin E intake, and carotene intake. Analysis excludes 1 case missing duration-of-use information.

Abbreviations as in Table 2.

association between vitamin C supplement use and risk of CHD was somewhat stronger among women with diabetes (RR = 0.57; 95% CI 0.37 to 0.88) compared with women without diabetes (RR = 0.76; 95% CI 0.63 to 0.91), although the RRs were not significantly different. Vitamin C may play an important role in regenerating vitamin E by reducing the tocopheroxyl radical back to the active tocopherol form (29); therefore, antioxidants may act synergistically. However, we found similarly lower risks of CHD among vitamin C supplement users who also took vitamin E supplements (RR = 0.80; 95% CI 0.53 to 1.23) or did not (RR = 0.70; 95% CI 0.56 to 0.88).

## DISCUSSION

In this large prospective study of women, we observed a modest inverse association between intake of vitamin C and incidence of CHD. Women in the highest quintile of vitamin C intake (≥360 mg/day) from diet and supplements had a 27% lower risk of nonfatal MI and fatal CHD than women in the lowest quintile of intake (≤93 mg/day). The reduction in risk appeared to be limited to women who took vitamin C supplements. Among users of vitamin C supplements, we observed a significant 28% lower risk of nonfatal MI and fatal CHD than among non-users. Al-

though risk did not vary significantly according duration of use of supplements or dose of supplements, the reduction in risk was somewhat stronger for women taking at least 400 mg/day.

The lack of a relation between the risk of CHD and the dose and duration of use of vitamin C supplements is compatible with data on its bioavailability. Intestinal absorption of vitamin C is an active, saturable, and dose-dependent process (30). Pharmacokinetic data indicate that for doses as low as 100 to 200 mg/day, the amount is completely absorbed and tissues are saturated (31–33). In a sample of healthy women undergoing vitamin C repletion, steady-state plasma concentrations measured after the administration of a range of oral doses of pure vitamin C revealed a steep sigmoidal relationship that started to plateau at approximately 100 mg/day (33). Plasma and tissue saturation occurred between oral doses of 200 and 400 mg daily, and saturation was achieved within two months. As suggested by Levine *et al.* (32), high doses of vitamin C may, therefore, not impact body stores or disease risk.

Results from prospective investigations of the relationship between plasma levels or dietary intakes of vitamin C and the incidence of CHD have been mixed (11,31). An apparent benefit has been observed in some populations with relatively low or deficient intakes. The Kuopio Ischemic Heart Disease Study observed a significantly lower risk (63%) of fatal and nonfatal MI (RR = 0.37; 95% CI 0.18 to 0.77) among Finnish men whose baseline plasma vitamin C levels were above 64.8  $\mu\text{mol/l}$  than among those whose baseline plasma vitamin C levels were considered deficient (<11.4  $\mu\text{mol/l}$ ) (12). The Prospective Basel Study found a modest non-significant inverse relation with CHD mortality (RR = 0.80; 95% CI 0.50 to 1.33) among persons with relatively low plasma vitamin C levels (below vs. above 23  $\mu\text{mol/l}$ ) (34); however, the RR may have been weakened by comparing more broadly defined categories of plasma levels. With respect to diet, the Finnish Mobile Clinic Study found a significantly lower risk of death from CHD for women in the highest (>91 mg/day) relative to the lowest (<61 mg/day) tertile of intake (adjusted RR = 0.49; 95% CI 0.24 to 0.98) and no association in men (adjusted RR = 1.00; 95% CI 0.68 to 1.45), despite similar distributions of vitamin C intake (35). Results from other cohorts with similarly low intakes of vitamin C have shown either a modest non-significant inverse association (36–38) or no association (39).

Among cohorts similar to ours, with relatively higher distributions of vitamin C intake and substantial numbers of supplement users, data on the association between CHD and vitamin C intake or supplement use have been inconsistent. Sahyoun *et al.* (16) observed a significantly lower risk of death (62%) from CHD (RR = 0.38; 95% CI 0.19 to 0.75) for those in the highest (>388 mg/day) than for those in the lowest ( $\leq$ 90 mg/day) quintile of total intake in an elderly population. After excluding supplement users, there was no association with mortality; however, vitamin C

supplement use was not independently associated with CHD. The Health Professionals Follow-up Study ( $n = 39,910$ ) found a non-significant increased risk of CHD (RR = 1.25; 95% CI –0.91 to 1.71) among men in the highest (median intake 1,162 mg/day) compared with the lowest (median intake 92 mg/day) quintile of intake (14). Vitamin C supplement users were at moderately lower risk, although the association was not statistically significant. Kushi *et al.* (15) found a non-significant increased risk of death from CHD (RR = 1.49; 95% CI 0.96 to 2.30) for women in the highest ( $\geq$ 391 mg/day) compared with the lowest quintile ( $\leq$ 113 mg/day) of total vitamin C intake and no association with vitamin C supplement use. Similarly, Losconszy *et al.* (17) found no association between vitamin C supplement use and mortality from CHD in an elderly cohort of men and women. The First National Health and Nutrition Examination Study (NHANES I) Epidemiologic Follow-up Study (40) found a 25% lower risk of mortality from all cardiovascular disease (RR = 0.75; 95% CI 0.55 to 0.99) only among women who consumed 50 mg/day or more of vitamin C and took supplements.

The strengths of our study include its prospective design and high rates of follow-up. The prospective collection of information eliminates the possibility of biased recall of diet. High rates of cohort participation lessen the potential for differential losses to follow-up that threaten internal validity. Weaknesses include the use of dietary questionnaires to assess the dietary vitamin C intake that moderately correlates with plasma levels, and the fact that the population we examined was well nourished and had a relatively narrow range of intakes, especially among non-users of vitamin C supplements. Furthermore, our findings do not provide information about the possible benefits of vitamin C intake in patients with risk factors or known cardiovascular disease. In the present study, adjustment for several of the recognized physiologic and lifestyle risk factors for CHD attenuated the estimates of RR, demonstrating at least moderate confounding by the risk factors measured in our study. Nevertheless, we cannot exclude the possibility of residual confounding by an imprecisely measured risk factor or an unmeasured risk factor that is highly associated with vitamin C supplement use and a strong risk factor for CHD.

In conclusion, our findings suggest that vitamin C supplement users may be at lower risk of CHD. We found no evidence for a gradient in risk across the relatively narrow range of intakes of vitamin C from diet in our study population. Although we cannot exclude a physiologic benefit of supplemental vitamin C, we also cannot exclude the possibility that the association may be attributed to some unmeasured health-seeking characteristic among vitamin C supplement users. The inconsistent findings from available observational studies emphasize the need for further evidence from prospective studies and randomized clinical trials before public policy recommendations regarding the optimal intake of vitamin C or the need for supplements.

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