Association Between Plasma Vitamin C Concentrations and Blood Pressure in the European Prospective Investigation Into Cancer-Norfolk Population-Based Study

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Abstract—The effect of fruit and vegetable consumption and blood pressure is unclear. A population-based cross-sectional study was conducted in 20 926 men and women aged 40 to 79 years participating in the European Prospective Investigation Into Cancer-Norfolk who completed a health questionnaire and attended a clinic from 1993 to 1997. The relationship between plasma vitamin C concentrations, as an indicator of fruit and vegetable intake, and systolic BP was examined. The magnitude of their association was assessed using dichotomized values of high (≥140 mm Hg) and low (<140 mm Hg) systolic blood pressure. A total of 20 926 participants (46% men; mean [SD] 58.5 years [9.2 years]) were included after excluding participants with any missing data for variables of interest. People with high vitamin C concentrations had lower clinic blood pressure. The likelihood of having high blood pressure was 22% lower (odds ratio: 0.78 [95% CI: 0.71 to 0.86]) for those who were in the top quartiles of plasma vitamin C levels compared with the bottom quartiles after adjusting for age, sex, body mass index, cholesterol, prevalent medical conditions, smoking, physical activity, alcohol consumption, social class, education, use of vitamin C–containing supplement, and antihypertensive medication. Sex-specific analysis, as well as repeated analysis after exclusion of people who used vitamin C–containing supplements or who were taking antihypertensive medication, did not alter the results. There appears to be a strong association between vitamin C concentrations, an indicator of fruit and vegetable consumption, and a lower level of blood pressure. This may provide further evidence for health benefits of dietary patterns with higher fruit and vegetable consumption. **(*Hypertension*. 2011;58:372-379.)**

Key Words: blood pressure ■ hypertension ■ ascorbic acid ■ diet ■ antioxidant

Hypertension is one of the major risk factors for cardiovascular disease (CVD),[1] which is responsible for a third of global deaths with increasing disease burden attributed to increasing aging of populations across the world.[2] Hypertension has been well recognized as a major risk factor for CVD. The World Health Organization defines hypertension as blood pressure ≥140/90 mm Hg regardless of age or sex.[3] There also appears to be a linear and direct relationship between blood pressure and CVD incidence, as well as mortality.[4–6]

Fresh fruits and vegetables are a richer source of ascorbic acid compared with cooked/boiled fruit and vegetables. Ascorbic acid in the food is also easily destroyed (eg, cooking in water, roasting, or grilling).[7] and has a short half-life (≈30 minutes) in the blood.[8,9] Furthermore, the main source of vitamin C (ascorbic acid) in humans is from food consumption, predominantly fruits and vegetables, because they cannot synthesize ascorbic acid in the body.[7] Therefore, plasma concentration of vitamin C is highly related to the individual's habitual dietary pattern and method of food preparation. Although randomized trials indicate that supplementation with antioxidant vitamins including β-carotene, vitamin E, or vitamin C does not reduce cardiovascular risk,[10,11] prospective studies indicate that high fruit and vegetable intake, of which plasma vitamin C is a good biomarker, is inversely related to mortality and incident CVD, especially stroke.[12–14]

The association between fruit and vegetable intake and blood pressure is less well known. Because hypertension is the major risk factor for stroke, we hypothesize that plasma vitamin C concentrations, which are derived from fruit and vegetable intake, may reduce stroke incidence through blood pressure–lowering effect. Therefore, in this study, we explored the cross-sectional association between plasma vitamin C concentrations and blood pressure using a large United

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Table 1. Distribution of Sex-Combined and Sex-Specific Sample Characteristics by Ascorbic Acid Quartiles in 20 926 Men and Women of the European Prospective Investigation Into Cancer-Norfolk Cohort at the Baseline (1993–1997)

Variable	Plasma Vitamin C Concentration Quartiles				*P* for Trend
	1 (<41 μmol/L)	2 (41 to 53 μmol/L)	3 (54 to 65 μmol/L)	4 (≥66 μmol/L)	
All	n=5082	n=5095	n=5353	n=5396	
Age, mean (SD), y	59.8 (9.4)	58.6 (9.4)	57.8 (9.0)	58.1 (9.1)	<0.0001
Systolic blood pressure, mean (SD), mm Hg	139 (18.4)	136 (18.2)	134 (17.7)	132 (17.9)	<0.0001
Diastolic blood pressure, mean (SD), mm Hg	84 (11.5)	83 (11.2)	82 (11.0)	80 (11.0)	<0.0001
Body mass index, mean (SD), kg/m^2	26.9 (4.0)	26.7 (3.8)	26.1 (3.7)	25.4 (3.5)	<0.0001
Cholesterol level, mean (SD), mmol/L	6.2 (1.2)	6.2 (1.1)	6.2 (1.2)	6.2 (1.2)	0.055
Daily alcohol intake, mean (SD), g	8.9 (14.5)	9.0 (13.0)	8.5 (12.2)	8.6 (12.1)	0.099
Vitamin C level, mean (SD), μmol/L	27.4 (9.4)	47.5 (3.7)	59.3 (3.4)	78.1 (13.1)	<0.0001
Daily fruit and vegetable intake, mean (SD), mg	350 (201)	441 (219)	489 (252)	528 (276)	<0.0001
Smoking, n (%)					<0.0001*
Current	1056 (20.8)	509 (10.0)	414 (7.7)	374 (6.9)	
Former	2302 (45.3)	2272 (44.6)	2201 (41.1)	2105 (39.0)	
Never smoked	1724 (33.9)	2314 (45.4)	2738 (51.1)	2917 (54.1)	
Occupational social class, n (%)					<0.0001*
I	272 (5.4)	330 (6.5)	419 (7.8)	458 (8.5)	
II	1576 (31)	1814 (35.6)	2099 (39.2)	2247 (41.6)	
III nonmanual	764 (15.0)	879 (17.3)	916 (17.1)	909 (16.8)	
III manual	1418 (27.9)	1221 (24.0)	1119 (20.9)	1039 (19.3)	
IV	801 (15.8)	679 (13.3)	645 (12.0)	620 (11.5)	
V	251 (4.9)	172 (3.4)	155 (2.9)	123 (2.3)	
Education, n (%)					<0.0001*
None/less than O level	2241 (44.1)	1968 (38.6)	1908 (35.6)	1983 (36.7)	
O level	551 (10.8)	645 (12.7)	726 (13.6)	783 (14.5)	
A level	1828 (36.0)	1873 (36.8)	1905 (35.6)	1786 (33.1)	
Degree	462 (9.1)	609 (12.0)	814 (15.2)	844 (15.6)	
Physical activity level, n (%)					<0.0001*
Inactive	1881 (37)	1505 (29.6)	1450 (27.1)	1338 (24.8)	
Moderately inactive	1311 (25.8)	1459 (28.6)	1597 (29.8)	1657 (30.7)	
Moderately active	1071 (21.1)	1186 (23.3)	1258 (23.5)	1321 (24.5)	
Active	819 (16.1)	945 (18.5)	1048 (19.6)	1080 (20.0)	
Prevalent myocardial infarction, n (%)	255 (5.0)	167 (3.3)	133 (2.5)	90 (1.7)	<0.0001
Prevalent diabetes mellitus, n (%)	183 (3.6)	136 (2.7)	91 (1.7)	52 (1.0)	<0.0001
Prevalent stroke, n (%)	113 (2.2)	65 (1.3)	47 (0.9)	53 (1.0)	<0.0001
Prevalent cancer, n (%)	276 (5.4)	251 (4.9)	243 (4.5)	337 (6.2)	0.001
Vitamin C–containing supplement user, n (%)	96 (1.9)	204 (4.0)	287 (5.4)	873 (16.2)	<0.0001
Antihypertensive medication use, n (%)	1098 (21.6)	998 (19.6)	896 (16.7)	833 (15.4)	<0.0001
Men	n=3274	n=2763	n=2172	n=1402	
Age, mean (SD), y	59.9 (9.3)	58.8 (9.3)	58.3 (8.9)	58.6 (9.4)	<0.0001
Systolic blood pressure, mean (SD), mm Hg	140 (17.9)	137 (17.3)	135 (16.7)	135 (17.2)	<0.0001
Diastolic blood pressure, mean (SD), mm Hg	86 (11.5)	85 (10.9)	83 (10.4)	83 (10.7)	<0.0001
Body mass index, mean (SD), kg/m^2	26.8 (3.5)	26.7 (3.2)	26.2 (3.0)	25.6 (2.9)	<0.0001
Cholesterol level, mean (SD), mmol/L	6.1 (1.1)	6.0 (1.1)	6.0 (1.1)	5.9 (1.1)	0.001
Daily alcohol intake, mean (SD), g	11.4 (16.5)	12.1 (15.4)	12.6 (15.3)	14.3 (16.8)	<0.0001
Vitamin C level, mean (SD), μmol/L	27.0 (9.5)	47.1 (3.7)	58.9 (3.4)	76.5 (12.1)	<0.0001
Daily fruit and vegetable intake, mean (SD), mg	333 (191)	415 (201)	446 (233)	470 (237)	<0.0001

(*Continued*)

Table 1. Continued

Variable	Plasma Vitamin C Concentration Quartiles				*P* for Trend
	1 (<41 μmol/L)	2 (41 to 53 μmol/L)	3 (54 to 65 μmol/L)	4 (≥66 μmol/L)	
Smoking, n (%)					<0.0001*
Current	634 (19.4)	239 (8.7)	144 (6.6)	93 (6.6)	
Former	1766 (53.9)	1533 (55.5)	1145 (52.7)	795 (56.7)	
Never smoked	874 (26.7)	991 (35.9)	883 (40.7)	514 (36.7)	
Occupational social class, n (%)					<0.0001*
I	193 (5.9)	199 (7.2)	213 (9.8)	137 (9.8)	
II	1062 (32.4)	1085 (39.3)	953 (43.9)	627 (44.7)	
III nonmanual	414 (12.6)	360 (13.0)	249 (11.5)	171 (12.2)	
III manual	979 (29.9)	696 (25.2)	463 (21.3)	284 (20.3)	
IV	487 (14.9)	352 (12.7)	249 (11.5)	161 (11.5)	
V	139 (4.2)	71 (2.6)	45 (2.1)	22 (1.6)	
Education, n (%)					<0.0001*
None/less than O level	1200 (36.7)	841 (30.4)	511 (23.5)	337 (24.0)	
O level	277 (8.5)	247 (8.9)	200 (9.2)	113 (8.1)	
A level	1448 (44.2)	1264 (45.7)	1018 (46.9)	662 (47.2)	
Degree	349 (10.7)	411 (14.9)	443 (20.4)	290 (20.7)	
Physical activity level, n (%)					<0.0001*
Inactive	1167 (35.6)	815 (29.5)	583 (26.8)	341 (24.3)	
Moderately inactive	768 (23.5)	706 (25.6)	549 (25.3)	342 (24.4)	
Moderately active	713 (21.8)	637 (23.1)	524 (24.1)	361 (25.7)	
Active	626 (19.1)	605 (21.9)	516 (23.8)	358 (25.5)	
Prevalent myocardial infarction, n (%)	216 (6.6)	140 (5.1)	98 (4.5)	55 (3.9)	<0.0001
Prevalent diabetes mellitus, n (%)	137 (4.2)	91 (3.3)	47 (2.2)	23 (1.6)	<0.0001
Prevalent stroke, n (%)	84 (2.6)	39 (1.4)	24 (1.1)	16 (1.1)	<0.0001
Prevalent cancer, n (%)	134 (4.1)	96 (3.5)	62 (2.9)	67 (4.8)	0.014
Vitamin C–containing supplement user, n (%)	51 (1.6)	93 (3.4)	103 (4.7)	241 (17.2)	<0.0001
Antihypertensive medication use, n (%)	681 (20.8)	515 (18.6)	363 (16.7)	189 (13.5)	<0.0001
Women	n=1808	n=2332	n=3181	n=3994	
Age, mean (SD), y	59.5 (9.4)	58.3 (9.5)	57.5 (9.1)	57.9 (8.9)	<0.0001
Systolic blood pressure, mean (SD), mm Hg	137 (19.1)	135 (19.0)	133 (18.4)	131 (18.0)	<0.0001
Diastolic blood pressure, mean (SD), mm Hg	82 (11.3)	81 (11.2)	81 (10.8)	80 (10.8)	<0.0001
Body mass index, mean (SD), kg/m^2	27.1 (4.9)	26.7 (4.4)	26.0 (4.1)	25.3 (3.7)	<0.0001
Cholesterol level, mean (SD), mmol/L	6.4 (1.2)	6.3 (1.2)	6.3 (1.2)	6.2 (1.2)	<0.0001
Daily alcohol intake, mean (SD), g	4.3 (7.8)	5.2 (8.0)	5.6 (8.4)	6.6 (9.1)	<0.0001
Vitamin C level, mean (SD), μmol/L	28.1 (9.3)	47.9 (3.7)	59.6 (3.4)	78.7 (13.4)	<0.0001
Daily fruit and vegetable intake, mean (SD), mg	383 (216)	474 (234)	519 (260)	549 (286)	<0.0001
Smoking, n (%)					<0.0001*
Current	422 (23.3)	270 (11.6)	270 (8.5)	281 (7.0)	
Former	536 (29.6)	739 (31.7)	1056 (33.2)	1310 (32.8)	
Never smoked	850 (47.0)	1323 (56.7)	1855 (58.3)	2403 (60.2)	
Occupational social class, n (%)					<0.0001*
I	79 (4.4)	131 (5.6)	206 (6.5)	321 (8.0)	
II	514 (28.4)	729 (31.3)	1146 (36.0)	1620 (40.6)	
III nonmanual	350 (19.4)	519 (22.3)	667 (21.0)	738 (18.5)	
III manual	439 (24.3)	525 (22.5)	656 (20.6)	755 (18.9)	
IV	314 (17.4)	327 (14.0)	396 (12.4)	459 (11.5)	
V	112 (6.2)	101 (4.3)	110 (3.5)	101 (2.5)	

(*Continued*)

Table 1. Continued

Variable	Plasma Vitamin C Concentration Quartiles				*P* for Trend
	1 (<41 μmol/L)	2 (41 to 53 μmol/L)	3 (54 to 65 μmol/L)	4 (≥66 μmol/L)	
Education, n (%)					<0.0001*
None/less than O level	1041 (57.6)	1127 (48.3)	1397 (43.9)	1646 (41.2)	
O level	274 (15.2)	398 (17.1)	526 (16.5)	670 (16.8)	
A level	380 (21.0)	609 (26.1)	887 (27.9)	1124 (28.1)	
Degree	113 (6.3)	198 (8.5)	371 (11.7)	554 (13.9)	
Physical activity level, n (%)					<0.0001*
Inactive	714 (39.5)	690 (29.6)	867 (27.3)	997 (25.0)	
Moderately inactive	543 (30.0)	753 (32.2)	1048 (32.9)	1315 (32.9)	
Moderately active	358 (19.8)	549 (23.5)	734 (23.1)	960 (24.0)	
Active	193 (10.7)	340 (14.6)	532 (16.7)	722 (18.1)	
Prevalent myocardial infarction, n (%)	39 (2.2)	27 (1.2)	35 (1.1)	35 (0.9)	<0.0001
Prevalent diabetes mellitus, n (%)	46 (2.5)	45 (1.9)	44 (1.4)	29 (0.7)	<0.0001
Prevalent stroke, n (%)	29 (1.6)	26 (1.1)	23 (0.7)	37 (0.9)	0.024
Prevalent cancer, n (%)	142 (7.9)	155 (6.6)	181 (5.7)	270 (6.8)	0.029
Vitamin C–containing supplement user, n (%)	45 (2.5)	111 (4.8)	184 (5.8)	632 (15.8)	<0.0001
Antihypertensive medication use, n (%)	417 (23.1)	483 (20.7)	533 (16.8)	644 (16.1)	<0.0001

General linear model was used for continuous variables, and χ^2 test was used for categorical variables.
*Data show the overall *P* value.

Kingdom population sample, the European Prospective Investigation Into Cancer (EPIC)-Norfolk Study.

Methods

Participants

Participants were drawn from the EPIC-Norfolk prospective population study, which recruited men and women aged between 40 to 79 years from general practice age-sex registers at the study baseline from 1993 to 1997 resident in Norfolk, United Kingdom. The detailed recruitment method and study protocol of EPIC-Norfolk have been described previously.[15] Briefly, all of the eligible community dwelling adults from 35 participating general practices were invited to participate. A total of 25 639 participants (99.6% white British) attended a baseline health examination. They provided written consent to participate in the study. The Norwich Local Research Ethics Committee approved the study.

Measurements

Trained nurses examined individuals at a baseline clinic visit. Blood pressure (BP) was measured with an Accutorr monitor after the participant had been seated for 5 minutes. We used the mean of 2 measurements for analysis. Height and weight were measured, and body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters squared). Nonfasting venous blood samples were taken into plain and citrate bottles. After overnight storage in a dark box at 4°C to 7°C, sample bottles were centrifuged at 2100 *g* for 15 minutes at 4°C. Approximately 1 year after the start of the study, when funding became available, extra blood samples from participants were taken for ascorbic acid assays. Plasma vitamin C was measured from blood taken into citrate bottles, and plasma was stabilized in a standardized volume of metaphosphoric acid stored at −70°C. We estimated plasma vitamin C concentration with a fluorometric assay within 1 week of sampling.[16] The coefficient of variation was 5.6% at the lower end of the range (mean: 33.2 μmol/L) and 4.6% at the upper end (102.3 μmol/L). Other blood samples for assay were stored at 4°C and assayed at the Department of Clinical Biochemistry, University of Cambridge, within 1 week after samples were taken. We measured serum total cholesterol, high-density lipoprotein cholesterol, and triacylglycerol with the RA 1000 (Bayer Diagnostics, Basingstoke, United Kingdom) and calculated low-density lipoprotein cholesterol values with the Friedewald formula.[17]

At the baseline, survey participants completed a detailed health and lifestyle questionnaire. Participant educational status, prevalent medical conditions, smoking status, vitamin C–containing supplement, and antihypertensive medication use were obtained from the survey responses. Social class was classified according to the Registrar General's occupation-based classification scheme.[18,19] Alcohol consumption was derived from a food frequency questionnaire collected at the baseline.[20] A 4-level physical activity index was derived from the validated EPIC short physical activity questionnaire designed to assess combined work and leisure activity.[21]

Statistical Analysis

We excluded participants with any missing data for any of the variables included in the analysis. Statistical analyses were carried out using SPSS for Windows version 14.0 (SPSS, Inc). We used logistic regression models to determine the associations between quartiles of vitamin C concentrations and likelihood of having systolic BP ≥140 mm Hg. Multiple logistic regression models were constructed using the bottom quartile as the reference category.

Multivariate adjustments were made to examine how far the association between plasma ascorbic acid concentrations and the BP might be explained by known cardiovascular risk factors. We adjusted for age in model A, age (and sex in sex-combined model) in model B; age (sex), BMI, cholesterol level, and history of prevalent conditions including diabetes mellitus, stroke, myocardial infarction, and cancer in model C; and additionally adjusted for lifestyle factors such as smoking status, physical activity, and alcohol consumption in model D and additional adjustment for social class and educational attainment in model E, including the use of vitamin C–containing supplement use in model F, and antihypertensive medication use in model G. We further constructed 2 models, model H (as in model E) after excluding people who took vitamin C–containing supplements and model I (as in model E) after excluding people who were taking antihypertensive medications.

Multiple linear regression models were constructed to examine the association between every increase in 1 SD of vitamin C concentration (20 μmol/L), which is the equivalent of 1 portion of fruits and

Table 2. Odds Ratios and 95% CIs for Risk of Systolic Blood Pressure ≥140 mm Hg by Quartiles of Plasma Vitamin C Concentration at Baseline in European Prospective Investigation Into Cancer-Norfolk Population (1993/1997–2005)

	Plasma Vitamin C Quartiles				
Models	Q1 (<41 μmol/L)	Q2 (41 to 53 μmol/L)	Q3 (54 to 65 μmol/L)	Q4 (≥66 μmol/L)	*P*
All					
Model A	1.00	0.88 (0.81 to 0.96)	0.78 (0.72 to 0.85)	0.64 (0.59 to 0.70)	<0.0001
Model B	1.00	0.89 (0.82 to 0.97)	0.80 (0.74 to 0.88)	0.68 (0.62 to 0.74)	<0.0001
Model C	1.00	0.91 (0.84 to 0.99)	0.86 (0.79 to 0.94)	0.78 (0.71 to 0.85)	<0.0001
Model D	1.00	0.90 (0.83 to 0.98)	0.85 (0.77 to 0.92)	0.76 (0.69 to 0.83)	<0.0001
Model E	1.00	0.91 (0.84 to 0.99)	0.87 (0.79 to 0.95)	0.78 (0.71 to 0.85)	<0.0001
Model F	1.00	0.91 (0.84 to 0.99)	0.86 (0.79 to 0.94)	0.77 (0.70 to 0.85)	<0.0001
Model G	1.00	0.91 (0.83 to 0.99)	0.87 (0.79 to 0.95)	0.78 (0.71 to 0.86)	<0.0001
Model H	1.00	0.92 (0.84 to 1.00)	0.86 (0.79 to 0.94)	0.76 (0.69 to 0.84)	<0.0001
Model I	1.00	0.88 (0.80 to 0.97)	0.84 (0.76 to 0.93)	0.77 (0.70 to 0.86)	<0.0001
Men					
Model A	1.00	0.90 (0.81 to 1.00)	0.76 (0.68 to 0.85)	0.68 (0.59 to 0.77)	<0.0001
Model B	1.00	0.91 (0.82 to 1.01)	0.81 (0.72 to 0.91)	0.77 (0.67 to 0.89)	<0.0001
Model C	1.00	0.91 (0.81 to 1.02)	0.81 (0.71 to 0.91)	0.76 (0.66 to 0.87)	<0.0001
Model D	1.00	0.92 (0.82 to 1.03)	0.83 (0.73 to 0.93)	0.78 (0.67 to 0.90)	0.001
Model E	1.00	0.92 (0.82 to 1.03)	0.82 (0.73 to 0.93)	0.77 (0.66 to 0.89)	0.001
Model F	1.00	0.92 (0.82 to 1.03)	0.82 (0.73 to 0.93)	0.77 (0.67 to 0.90)	0.001
Model G	1.00	0.92 (0.82 to 1.03)	0.81 (0.72 to 0.92)	0.76 (0.65 to 0.88)	<0.0001
Model H	1.00	0.91 (0.80 to 1.03)	0.83 (0.72 to 0.95)	0.82 (0.70 to 0.95)	0.016
Women					
Model A	1.00	0.89 (0.78 to 1.02)	0.85 (0.75 to 0.97)	0.69 (0.61 to 0.78)	<0.0001
Model B	1.00	0.93 (0.81 to 1.06)	0.93 (0.81 to 1.05)	0.80 (0.70 to 0.91)	0.002
Model C	1.00	0.91 (0.79 to 1.04)	0.90 (0.79 to 1.03)	0.77 (0.70 to 0.88)	0.001
Model D	1.00	0.92 (0.80 to 1.06)	0.93 (0.81 to 1.06)	0.80 (0.70 to 0.91)	0.002
Model E	1.00	0.92 (0.80 to 1.06)	0.93 (0.81 to 1.06)	0.79 (0.69 to 0.91)	0.002
Model F	1.00	0.92 (0.80 to 1.05)	0.93 (0.81 to 1.07)	0.80 (0.70 to 0.91)	0.003
Model G	1.00	0.94 (0.81 to 1.08)	0.93 (0.81 to 1.07)	0.78 (0.68 to 0.89)	0.001
Model H	1.00	0.84 (0.72 to 0.99)	0.85 (0.73 to 0.99)	0.74 (0.64 to 0.87)	0.002

Models A was adjusted for age; B, adjusted for age and sex; C, adjusted for age, sex (for all), body mass index, cholesterol, and prevalent conditions (myocardial infarction, stroke, diabetes mellitus, and cancer); D, as in model C and additionally adjusted for smoking, physical activity, and alcohol consumption; E, as in model D and additionally adjusted for social class and education; F, as in model E additionally adjusted for vitamin C–containing supplement use; G, as in model F with additional adjustment for antihypertensive use; H, as in model E after exclusion of vitamin C supplement users; model I, as in model E after exclusion of those who were on antihypertensive medication.

vegetables and BP first adjusting for age and sex and second adjusting for all of the covariates as in model E of the logistic regression model. To examine the impact of smoking on the relationship between vitamin C concentrations and BP, we also analyzed the linear relationship between every 1-SD (20 μmol/L) increase in vitamin C concentrations and BP stratified by smoking status.

Results

Of 30 445 who consented to participate in the EPIC-Norfolk (40% of the eligible sample population), 25 579 participants attended health check and had their BPs measured. Of them, vitamin C levels were available in 22 474 participants. A total of 20 926 participants were included in the current study after excluding those who had missing data for any of the variables included in the analysis. The numbers of missing values for each variable were 32 for BMI, 217 for cholesterol, 173 for smoking status, 1 for physical activity level, 11 for education level, 476 for social class, and 697 for alcohol consumption. There were no missing data for antihypertensive medications, vitamin C–containing supplement use, and prevalent medical conditions. Some had >1 missing value.

Table 1 shows the distribution of sample characteristics by quartiles of plasma vitamin C concentrations by sex-combined and then sex-specific analyses. Quartile 1 represents the lowest quartile, although quartile 4 represents the highest plasma vitamin C concentration. Men and women who were in the top quartile category had both lowest systolic and diastolic BPs compared with the other categories. They tend to be younger and had lower BMI. People in the highest quartile were less likely to be smokers, more likely to be in

Table 3. Level of Blood Pressure Reduction Associated With Every Increase 1 SD (20 μmol/L) of Ascorbic Acid Concentrations in Middle and Older Aged Men and Women of European Prospective Investigation Into Cancer Norfolk (49 to 70 y) at the Baseline

Models	Every 20-μmol/L Increase in Vitamin C Concentration	Every Increase in 1 y of Age
Systolic blood pressure		
Age- and sex-adjusted model	−1.5 mm Hg	+0.7 mm Hg
Fully adjusted model (as in model G)	−0.9 mm Hg	+0.6 mm Hg
Diastolic blood pressure		
Age- and sex-adjusted model	−0.8 mm Hg	+0.2 mm Hg
Fully adjusted model (as in model G)	−0.5 mm Hg	+0.1 mm Hg

nonmanual occupations, had higher level of educational attainment, were physically more active, consumed more fruits and vegetables, were more likely to take vitamin C–containing supplements, were more likely to be on antihypertensive medication, and had lower prevalence of chronic diseases except cancer (showed reversed trend) compared with those in the lower quartile categories. Sex-specific analyses showed similar trends. Cholesterol levels were lower in the highest quartile group compared with others when data were analyzed separately for men and women. There were no significant trends in the proportion of people with a diagnosis of cancer among vitamin C concentration categories.

Table 2 shows the odds ratios and their corresponding 95% CIs for likelihood of having systolic BP of ≥140 mm Hg adjusting for age (A); age and sex (B); age, sex (for all), BMI, cholesterol, and prevalent conditions (myocardial infarction, stroke, diabetes mellitus, and cancer) (C); and additionally adjusting for smoking, physical activity, and alcohol consumption (D); with further adjustment for social class and education (E); additionally adjusting for vitamin C–containing supplement use (F); and additionally adjusting for antihypertensive use (G). After age and sex adjustment, there was little change in odds ratio estimates. In a fully adjusted model, men and women in the highest quartile of vitamin C concentrations were 23% and 20% less likely to be in the hypertensive range (systolic BP ≥140 mm Hg), respectively. Further sensitivity analyses by excluding people who were taking vitamin C–containing supplements (model H) and those who were taking antihypertensive medication (model I) showed similar results for men and women.

Table 3 shows the difference in BP associated with every increase in 1 SD (20 μmol/L) of vitamin C concentrations in this cohort of middle and older ages. An increase in 1 year of age is associated with 0.7-mm Hg (age and sex adjusted) and 0.6-mm Hg (fully adjusted for all the variables above) higher systolic BP; the corresponding values for every 1-SD increase in 20 μmol/L of ascorbic acid were lower systolic BP of 1.5 mm Hg and 0.9 mm Hg, respectively, suggesting an equivalent of 2.5 to 3.0 chronological years in BP difference with every 1-SD increase in vitamin C concentrations.

Table 4 shows the difference in BP associated with every increase in 1 SD (20 μmol/L) of vitamin C concentrations by smoking status adjusting for age and sex. The lower level of BP associated with higher vitamin concentrations appeared to be most significant in those who never smoked or have given up smoking.

Discussion

We found a strong linear association between plasma vitamin C concentrations and systolic BP. This was independent of known biological, social, and lifestyle risk factors hat are associated with fruit and vegetable consumption and high BP. Interestingly, the association between vitamin C concentrations and the BP is stronger in never/former smokers compared with current smokers. The current study is a large population-based study with >20 000 participants and is able to take into account biological (age, sex, BMI, and cholesterol), social (occupational social class and education), and lifestyle behaviors (smoking, alcohol consumption, physical activity, and vitamin C supplement use) and has the additional ability to take into account of prevalent illnesses and the use of antihypertensive medication. We addressed potential confounding issues in this study by adjusting for these possible confounders. Furthermore, we examined the multivariate adjusted relationship after excluding those people who took vitamin C–containing supplements and those who were taking antihypertensive medications.

Interestingly, antioxidant supplementation, including vitamin C, did not produce substantial benefit in clinical trial settings in high-risk individuals.[10,22] The recent Women's Health Initiative also reported no reduction in CVD in the group allocated to a low-fat and higher fruit and vegetable target diet.[23] There are some plausible explanations why the

Table 4. Level of Blood Pressure Reduction Associated With Every Increase 1 SD (20 μmol/L) of Ascorbic Acid Concentrations in Middle and Older Aged Men and Women of European Prospective Investigation Into Cancer Norfolk (49 to 70 y) at the Baseline by Smoking Status Adjusted for Age and Sex

	Lower Blood Pressure Level (in mm Hg) Associated With Every 20-μmol/L Increase in Vitamin C Concentrations (β, 95% CI)			
Smoking Status	Systolic Blood Pressure	*P*	Diastolic Blood Pressure	*P*
Current smokers	−0.61 (0.00 to −1.22)	0.05	−0.29 (0.11 to −0.69)	0.158
Former smokers	−1.59 (−1.23 to −1.95)	<0.0001	−0.97 (−0.74 to −1.21)	<0.0001
Those who never smoked	−1.69 (−1.35 to −2.03)	<0.0001	−1.00 (−0.78 to −1.22)	<0.0001

discrepancy exists between cohort studies and trials. Many of the supplementation trials, such as the Heart Protection Study and the Finnish Alpha-Tocopherol Beta-Carotene Trial, were conducted in high-risk or highly selected rather than general populations.[22,24,25] In addition, combinations of antioxidants, some of them in pharmacological doses, such as vitamin E, may have unpredicted biological effects. Moreover, the lack of benefit of vitamin C in clinical trials could be explained by the relationship between vitamin C dose and plasma concentration. At doses <100 mg/day, there is a large change in plasma concentration for small changes in dose. Above 100 mg/day, there is little change in plasma concentration despite large changes in dose. If control (ie, lowest quartile subjects) consumed 100 mg/day, then further increases in dose would be predicted to cause little change in concentration. Outcome, therefore, may not be affected at higher doses. This problem was first pointed out by Levine et al[26] in 1999.

Plasma vitamin C concentration is a good biomarker for plant food, namely, fruit and vegetable intake, in our cohort. The 20 μmol/L or 1 SD increase in plasma vitamin C concentration is associated with ≈1 additional serving of fruit and vegetables daily (the correlation coefficient $r^2=0.38$).[12] In this study, every increase in 1 SD (20 μmol/L) of plasma vitamin C concentration is associated with a lower level of systolic BP, and the observed effect seems to be the equivalent of 2 to 3 years younger. Because average fruit and vegetable consumption in the United Kingdom is ≈3 portions per person, the increased fruit and vegetable consumption to 5 portions per day as recommended by the Department of Health in England could potentially have a substantial impact on CVD risk reduction. Interestingly, there is an ongoing discussion in literature on whether plasma vitamin C concentration is codetermined or influenced by genetic factors, such as haptoglobin genotype and its polymorphism,[27,28] and the more controversial factor of iron overload.[29]

Vitamin C is well known as a potent antioxidant and acts as a vasodilator through increased bioavailability of NO. Oxidative stress has been implicated as a factor that plays a major role in renovascular hypertension.[30] There has been ongoing basic science research in the area of link between antioxidants and BP. Nishi et al[31] reported recently that chronic antioxidant treatment with vitamin C improves arterial renovascular hypertension and oxidative stress markers in Wistar rats. The cardioprotective effect of vitamin C during isoproterenol-induced acute myocardial infraction appears to be associated with inducible NO synthase downregulation and improvement in the autonomic balancing of the heart.[32] However, interestingly, an acute intake of vitamin C appears to have no effect on oxidative stress, arterial stiffness, or BP in human subjects.[33] The study examining the effect of a single large dose of vitamin C was tested in 26 healthy volunteers, and vitamin C showed no effect on vasodilatation measured by augmentation index, forearm blood flow, or several markers of oxidative stress compared with placebo.[33] However, there has been recent evidence of an association between vitamin C and BP in a longitudinal study of young black and white women aged 18 to 21 years (n=242) at baseline (with 10-year follow-up),[34] as well as in a clinical trial setting involving 110 hypertensive men with a mean age of 46 years (range: 35 to 60 years).[35] Therefore, it is possible that the inverse relationship between vitamin C levels and CVD outcomes may be related to a BP-lowering effect of vitamin C.

Naturally there are limitations to our study. Because of the requirement to provide detailed health and lifestyle information and to be able to attend a health examination, the response rate was modest at ≈40%. This could introduce a healthy responder bias. Nevertheless, baseline characteristics of the study population are similar to other United Kingdom population samples, except with a slightly lower prevalence of smokers.[15] Moreover, truncation of distribution because of healthy responders is likely to attenuate the associations, but this should not affect the vitamin C-BP association observed within the study participants; if anything, truncation of the distribution is likely to reduce power for any associations. BP measurement values were based on research clinic–based measures. This may overestimate the people in higher BP category because of so-called white coat hypertension. However, the association between vitamin C concentration and BP appears linear and consistent across various lifestyle and social strata regardless of age and sex. There were only single measurements of plasma vitamin C and other covariates, such as cholesterol and BP. Moreover, the blood sample taken was a nonfasting sample and, therefore, less standardized for some of the parameters (eg, cholesterol level) compared with fasting blood sample. Nevertheless, random measurement error is likely only to attenuate any associations observed between plasma vitamin C and BP.

Perspectives

Given current evidence, it unlikely that long-term randomized, controlled trials of isolated vitamin C supplementation and CVD end points will be conducted. Nevertheless, the magnitude of the association between fruit and vegetable consumption depicted by plasma vitamin C concentration and BP is considerable and independent of known major risk factors for high BP. The vitamin C levels in serum are most likely to be contributed by the plant foods. Future studies perhaps should be focused not only on quantity but on quality and type of fruit and vegetable consumption to better understand the association between dietary lifestyle behavior and BP.

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Disclosures

None.

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