Plasma ascorbic acid concentrations and fat distribution in 19 068 British men and women in the European Prospective Investigation into Cancer and Nutrition Norfolk cohort study[1–3]

Dexter Canoy, Nicholas Wareham, Ailsa Welch, Sheila Bingham, Robert Luben, Nicholas Day, and Kay-Tee Khaw

ABSTRACT

Background: Antioxidants, such as ascorbic acid, play a role in scavenging free radicals to protect against oxidative endothelial damage. Excess fat may promote fatty acid oxidation and increase free radical concentrations, which could result in increased antioxidant use. Whether plasma ascorbic acid concentrations are associated with fat distribution remains unclear.

Objective: Our aim was to examine the association between abdominal obesity, as measured by the waist-to-hip ratio, and plasma ascorbic acid concentrations in the general population.

Design: We examined the cross-sectional relation between anthropometric measurements of fat distribution and plasma ascorbic acid concentrations in 19 068 men and women aged 45–79 y without known chronic illness. Dietary ascorbic acid intake was estimated for a subgroup of 8178 men and women who kept 7-d food diaries coded for nutrient intake.

Results: The waist-to-hip ratio was inversely related to plasma ascorbic acid concentrations in both men and women. This association was independent of body mass index, age, vitamin supplement use, cigarette smoking, and socioeconomic group. Waist and hip circumferences showed separate and opposite associations with plasma ascorbic acid concentrations, independent of body mass index and other covariates. Dietary ascorbic acid intake only partly explained the observed associations.

Conclusions: Plasma ascorbic acid was associated with fat distribution independent of body mass index. Differences in dietary intake and lifestyle habits, underlying systemic oxidative stress, or both may explain the inverse relation between fat distribution and plasma ascorbic acid concentrations. Additional studies are needed to determine the underlying explanation of these observations. *Am J Clin Nutr* 2005;82:1203–9.

KEY WORDS Obesity, body constitution, ascorbic acid

INTRODUCTION

Obesity is related to an increased risk of morbidity and mortality from various conditions, including cardiovascular disease (1–4). Excess fat may promote oxidative stress, and the free radicals generated may impair the endothelium and could predispose persons to atherosclerosis (5). Antioxidants scavenge free radicals and play a protective role against lipid peroxidation (5–8). However, it is unclear whether blood concentrations of antioxidants are lower in obese persons than in normal-weight persons. It has been suggested that concentrations of circulating antioxidants are inversely related to body mass index, but results have been inconsistent (9–12). Because abdominal obesity is associated with atherogenic factors independent of body mass index (13, 14), it is possible that fat distribution may be more related to obesity-related oxidative stress than is body mass index. Lower plasma concentrations of ascorbic acid, a known antioxidant (7, 15), have been shown to predict cardiovascular disease mortality (16). We examined whether plasma ascorbic acid is related to abdominal obesity independent of body mass index in a free-living population of men and women.

SUBJECTS AND METHODS

The European Prospective Investigation into Cancer and Nutrition (EPIC) study is a multicenter prospective population study of diet and cancer in Europe. The EPIC cohort in Norfolk, United Kingdom, expanded its aims to include other determinants of chronic diseases. The study was approved by the Norfolk Health District Ethics Committee. Details of participant recruitment and of the study procedures have been described previously (17). Briefly, participants aged 45–79 y were recruited between 1993 and 1997 with the use of age-sex registers from collaborating general practices in Norfolk. The participants answered health and lifestyle as well as dietary questionnaires. They were also examined by trained research nurses who measured baseline clinical data and obtained blood samples by venepuncture.

At the clinic visit, trained nurses used standard protocols to take anthropometric measurements of the participants while the participants were wearing light clothing and no shoes (18).

[1] From the Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom (DC, AW, RL, ND, and K-TK), and the MRC Epidemiology Unit (NW) and Dunn Human Nutrition Unit (SB), Cambridge, United Kingdom.

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[3] Reprints not available. Address correspondence to D Canoy, the Department of Public Health and Primary Care, University of Cambridge, Strangeways Site, Worts' Causeway, Cambridge CB1 8RN, United Kingdom. E-mail: dexter.canoy@srl.cam.ac.uk.

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Height was measured to the nearest 0.1 cm with a free-standing stadiometer. Weight was measured to the nearest 100 g with digital scales (Salter, Tonbridge, United Kingdom). Body mass index [weight (in kg)/height^2 (in m)] was calculated from weight and height measurements. A D loop nonstretch fiberglass tape was used for the circumference measures. The waist circumference was measured to the nearest 0.1 cm at the smallest circumference between the ribs and iliac crest while the participant was standing up, with the abdomen relaxed, and at the end of a normal expiration. If no natural waistline was present, the measurement was taken at the level of the umbilicus. The hip circumference was measured to the nearest 0.1 cm at the maximum circumference between the iliac crest and the crotch while participants were standing. The waist-to-hip ratio was then calculated from both the waist and hip measurements (waist circumference/hip circumference).

Nonfasting blood samples (40 mL) were taken from participants by venepuncture with monovettes and placed into plain or citrated bottles. The samples were then brought into the laboratory in an insulated box within 3–4 h of the blood draw and were stored at 4–7 °C. After an overnight storage, the samples in the bottle were spun in a centrifuge at 2100 × *g* for 15 min at 4 °C. The next day, these blood samples were prepared for different assays. For the plasma ascorbic acid concentration assay, plasma samples were stabilized in a standardized volume of metaphosphoric acid stored at −70 °C. The plasma ascorbic acid concentration was then estimated with a fluorometric assay (19) ≤1 wk from sampling. Plasma ascorbic acid concentrations may decrease after overnight storage; however, we previously reported that the plasma concentrations of ascorbic acid after an overnight storage were closely associated with the initial values, with a Spearman rank correlation of 0.84 (20). The CV was 5.6% at the lower end of the rage ($\bar{x}$: 33.2 μmol/L) and 4.6% at the upper end ($\bar{x}$: 102.3 μmol/L).

Dietary habits were assessed with a 7-d food diary, which was previously shown to both provide a valid estimate of dietary ascorbic acid (21–24) over short time periods as well as represent average intakes over much longer periods (25). The participants listed and quantified the food and drinks they had consumed the day before the health check, the day of the health check, and for 5 d afterward in food diaries. A pictorial guide was provided to aid in the estimation of portion sizes. A computer program was designed to quantify the different dietary components of the food, which included ascorbic acid, with the use of standard food tables (26).

From their responses to the questionnaire, the participants who reported having a doctor-diagnosed illness including cancer, heart disease (also heart attack or myocardial infarction), stroke, and diabetes mellitus were considered to have a medical history of a specific condition. The participants who answered yes to the question "Have you taken any vitamins, minerals, or other food supplements regularly during the past year (such as vitamin C, vitamin D, iron, calcium, fish oils, primrose oil, β-carotene, and vitamin E)? " were considered to be users of vitamin supplements. Participants were defined as current smokers if they were smoking ≥1 cigarette/d for ≥1 y at baseline, former smokers if they were not currently smoking but previously smoked ≥1 cigarette/d for ≥1 y, and nonsmokers if they neither currently nor previously smoked cigarettes. The participants were asked about their present and past occupations and were then classified into the following categories by their socioeconomic group: I, professional; II, managerial; IIIA, skilled nonmanual; IIIB, skilled manual; IV, partly skilled; and V, unskilled.

The baseline health check was attended by 25 623 participants. Because plasma ascorbic acid measurements only started in 1995, this measurement was only available for 21 558 participants. We additionally excluded participants who had known cardiovascular disease (history of heart disease, myocardial infarction, or stroke; $n = 946$), cancer (except nonmelanoma skin cancer; $n = 1173$), or diabetes mellitus ($n = 493$) and those who had missing anthropometric measurements ($n = 57$). The remaining 19 068 participants were included in the analyses.

Abdominal obesity was assessed from the waist-to-hip ratio. We used sex-specific waist-to-hip quartiles in the analyses because the distribution of waist-to-hip ratios differed between men and women. We also used linear regression models (27) to describe the association between waist-to-hip ratios and plasma ascorbic acid concentrations. We calculated mean plasma concentrations of ascorbic acid for each waist-to-hip ratio quartile. We also repeated the analysis but we plotted the mean plasma ascorbic acid concentration for all participants across the whole range of waist-to-hip ratio values. We then assessed the effect of an increase of 0.06 in the waist-to-hip ratio (1 SD = 0.059 in men and 0.062 in women) on the plasma ascorbic acid concentration using regression models. Covariates in our regression models included age, body mass index, cigarette smoking habit (never, former, or current), use of vitamin supplementation (yes or no), and socioeconomic group (I, II, IIIA, IIIB, IV, and V).

We also calculated the mean plasma ascorbic acid concentration by the waist-to-hip ratio after it was stratified by sex-specific body mass index quartiles. We then examined the separate effects of waist and hip circumferences on plasma ascorbic acid concentrations by stratifying the participants by sex-specific tertiles of waist and hip circumferences. We used tertiles to allocate an adequate number of participants in each subgroup.

Due to constraints in resources for entering food diary data, we only used the information from 8178 participants who had diaries that were fully coded and analyzed when the present study was conducted. For these persons, we calculated the total intake of dietary ascorbic acid by the waist-to-hip ratio quartile. To measure whether the relation between plasma ascorbic acid concentrations and waist-to-hip ratios could be explained by dietary ascorbic acid intake, we added dietary ascorbic acid and total energy intakes as covariates in the multivariate regression models.

We used an analysis of variance to calculate the statistical interaction between variables. Regression β coefficients and 95% CIs were calculated, and a P value < 0.05 was considered statistically significant. We used the statistical software STATA version 8 (Stata Corp, College Station, TX) for our analyses.

RESULTS

The characteristics of the men and women of the present study are shown in **Table 1**. The participants with a higher waist-to-hip ratio were slightly older, had higher body mass indexes, and were less likely to be vitamin supplement users than were the participants with lower waist-to-hip ratios. The waist-to-hip ratio was inversely associated with plasma concentrations and dietary intakes of ascorbic acid in both men and women.

An inversely linear relation between the waist-to-hip ratio and plasma ascorbic acid concentrations is shown in **Table 2** for both

TABLE 1
Characteristics of the participants by waist-to-hip ratio quartile[1]

Variables	Waist-to-hip ratio quartile 1	2	3	4
Men				
n	2151	2155	2139	2148
Waist-to-hip ratio	0.855 ± 0.031[2]	0.910 ± 0.011	0.947 ± 0.011	1.002 ± 0.033
BMI (kg/m^2)	24.1 ± 2.4	25.8 ± 2.4	27.0 ± 7.7	28.8 ± 3.2
Waist circumference (cm)	85.5 ± 6.0	92.9 ± 5.2	97.9 ± 5.8	105.2 ± 7.7
Hip circumference (cm)	100.0 ± 5.6	102.1 ± 5.5	103.5 ± 6.0	104.9 ± 6.6
Plasma ascorbic acid (μmol/L)	51.3 ± 19.1	49.0 ± 18.7	46.7 ± 17.8	42.6 ± 18.0
Dietary ascorbic acid (g/mL)[3]	86.0 ± 51.2	84.9 ± 45.7	82.2 ± 50.7	79.0 ± 46.6
Total energy intake (kJ/d)[3]	9425 ± 2031	9338 ± 2107	9061 ± 2103	8822 ± 2126
Age (y)	57.4 ± 8.6	59.0 ± 8.7	59.7 ± 8.5	62.0 ± 8.6
Current smokers [*n* (%)]	269 (12.5)	247 (11.5)	251 (11.7)	265 (12.3)
Vitamin supplement users [*n* (%)]	846 (39.3)	855 (39.7)	790 (36.9)	725 (33.8)
Social class IV and V [*n* (%)][4]	339 (15.8)	385 (17.9)	361 (16.9)	457 (21.3)
Women				
n	2619	2625	2613	2618
Waist-to-hip ratio	0.719 ± 0.023	0.768 ± 0.011	0.808 ± 0.012	0.874 ± 0.040
BMI (kg/m^2)	24.0 ± 3.2	25.2 ± 3.4	26.8 ± 4.1	28.6 ± 4.4
Waist circumference (cm)	72.5 ± 5.8	78.3 ± 6.3	84.2 ± 7.6	92.6 ± 9.6
Hip circumference (cm)	100.8 ± 7.4	101.9 ± 7.9	104.2 ± 9.3	105.9 ± 9.7
Plasma ascorbic acid (μmol/L)	62.3 ± 19.5	61.0 ± 19.6	58.0 ± 19.3	53.6 ± 20.1
Dietary ascorbic acid (g/mL)[3]	91.0 ± 49.6	89.1 ± 47.8	85.0 ± 44.9	82.1 ± 45.3
Total energy intake (kJ/d)[3]	7126 ± 1596	7105 ± 1574	6935 ± 1568	6843 ± 1653
Age (y)	55.5 ± 7.7	58.1 ± 8.4	60.4 ± 8.8	62.7 ± 8.6
Cigarette smoking habit [*n* (%)]	246 (9.4)	303 (11.5)	289 (11.1)	327 (12.5)
Vitamin supplement users [*n* (%)]	1460 (55.8)	1406 (53.6)	1342 (51.4)	1288 (49.2)
Social class IV and V [*n* (%)][4]	417 (15.9)	500 (19.1)	501 (19.2)	626 (23.9)

[1] All $P < 0.001$ (for trend for continuous variables or chi-square for categorical variables across waist-to-hip ratio categories). Total number may not sum to 100% for categorical variables because of missing variables. Waist-to-hip ratio ranges from the bottom to the top quartiles were 0.576–0.890, 0.891–0.929, 0.929–0.966, and 0.966–1.217 in men, and 0.607–0.748, 0.748–0.787, 0.787–0.831, and 0.831–1.242 in women.

[2] $\bar{x}$ ± SD (all such values).

[3] Based on a subgroup of 3953 men and 4225 women who had 7-d food diary data.

[4] Partly skilled and unskilled.

men and women even after adjustment for covariates. The magnitude of difference in plasma ascorbic acid concentrations that was associated with a 0.06 change in the waist-to-hip ratio was −2.3 μmol/L (95% CI: −2.8, −1.8) for men and −2.2 μmol/L (95% CI: −2.6, −1.8) for women after adjustment for covariates. The inverse association was apparent even when the data were restricted to only the nonobese, noncurrent smokers, and nonsupplement users. No 3-factor interactions were observed for the following: between sex, the waist-to-hip ratio, and obesity status (yes or no); between sex, the waist-to-hip ratio, and current smoking status (current, former, or never); between sex, the waist-to-hip ratio, and vitamin supplement use (yes or no); or between sex, the waist-to-hip ratio, and obesity status (yes or no), smoking status (current, former, or never), and vitamin supplement use (yes or no). However, a 2-factor interaction was observed between the waist-to-hip ratio and obesity ($P = 0.007$), between the waist-to-hip ratio and current smoking status and vitamin supplement use ($P = 0.004$), and between the waist-to-hip ratio and obesity, current smoking status, and vitamin supplement use ($P < 0.001$). Although the absolute concentration of plasma ascorbic acid was higher in the women than in the men, plasma ascorbic acid concentrations were inversely related across the whole range of waist-to-hip values for men and women (**Figure 1**). Moreover, a 10-cm increase in waist circumference (1 SD = 9.5 cm in men and 10.5 cm in women) was also associated with a plasma acid concentration difference of −3.4 μmol/L (95% CI: −4.1, −2.6) for men and −3.6 μmol/L (95% CI: −4.3, −3.0) for women after adjustment for body mass index and other covariates.

Compared with the participants who had 7-d food diary data, the participants without such data had lower waist-to-hip ratios, lower body mass indexes, and higher mean plasma ascorbic acid concentrations (all $P < 0.001$). For the participants with 7-d food diary data, the waist-to-hip ratio was inversely associated with dietary ascorbic acid intake in both men and women (Table 1). After adjustment for age, body mass index, vitamin supplement use, cigarette smoking habit, socioeconomic group, and total energy intake, the mean (±SE) dietary ascorbic acid intake (in mg/d) from the lowest to the highest waist-to-hip ratio quartiles were the following: 85.9 ± 1.8, 84.6 ± 1.6, 81.9 ± 1.5, and 80.0 ± 1.5 for men (P for trend = 0.009) and 87.7 ± 1.6, 87.7 ± 1.5, 85.6 ± 1.4, and 85.2 ±1.4 for women (P for trend = 0.173). When we added dietary ascorbic acid as an explanatory variable in the covariate-adjusted regression model, the R^2 increased >20% for both men and women (Table 2). Nevertheless, the inverse relation between the waist-to-hip ratio and plasma ascorbic acid concentrations persisted even after additional adjustment for dietary ascorbic acid intake (Table 2 and Figure 1).

TABLE 2
Estimated difference in plasma ascorbic acid associated with a 0.060 increase in the waist-to-hip ratio in the participants[1]

Regression models	Men n	Men β (95% CI)	Men R^2	Women n	Women β (95% CI)	Women R^2
		μmol/L			*μmol/L*	
All participants						
Unadjusted	8593	−3.3 (−3.7, −2.9)	3.0	10 475	−3.3 (−3.7, −3.0)	2.9
Age- and BMI-adjusted	8593	−2.9 (−3.4, −2.4)	3.1	10 475	−2.6 (−3.0, −2.1)	3.8
Covariate-adjusted[2]	8535	−2.3 (−2.8, −1.8)	11.4	10 384	−2.2 (−2.6, −1.8)	10.7
Obese participants[2,3]	1056	−1.6 (−2.8, −0.4)	6.2	1659	−2.2 (−3.1, −1.4)	7.1
Nonobese participants[2,4]	7479	−2.5 (−3.0, −1.2)	11.3	8725	−2.2 (−2.7, −1.7)	9.5
Smokers or vitamin supplement users[5]	3943	−2.2 (−2.8, −1.6)	5.3	6155	−2.7 (−3.3, −2.2)	5.1
Nonsmokers and non–vitamin supplement users[5]	4650	−2.2 (−2.8, −1.6)	5.4	4320	−2.3 (−2.8, −1.7)	5.3
Obese participants, smokers, or vitamin supplement users[5]	4584	−2.9 (−3.6, −2.2)	5.8	6972	−2.8 (−3.3, −2.2)	6.9
Nonobese participants, nonsmokers, and non–vitamin supplement users[5]	4009	−2.5 (−3.1, −1.8)	5.2	3503	−2.1 (−2.8, −1.4)	3.1
Participants with dietary ascorbic acid data						
Covariate-adjusted[2]	3928	−2.3 (−2.9, −1.6)	11.8	4189	−2.1 (−2.7, −1.5)	11.0
Covariate- and dietary ascorbic acid–adjusted[6]	3928	−2.0 (−2.7, −1.4)	25.6	4189	−1.9 (−2.5, −1.4)	22.9
Participants without dietary ascorbic acid data						
Covariate-adjusted[2]	4607	−2.3 (−2.9, −1.6)	10.8	6195	−2.1 (−2.7, −1.6)	10.5

[1] Data presented as regression coefficients with 95% CIs as derived from regression models. Statistical interactions, derived from analysis of variance, were as follows: $P > 0.05$ for sex × waist-to-hip ratio × obesity, $P > 0.05$ for sex × waist-to-hip ratio × current smoking status or vitamin supplement use, $P > 0.05$ for sex × waist-to-hip ratio × obesity or current smoking status or vitamin supplement use, $P = 0.007$ for waist-to-hip ratio × obesity, $P = 0.004$ for waist-to-hip ratio × current smoking status or vitamin supplement use, $P < 0.001$ for waist-to-hip ratio × obesity, current smoking status, or vitamin supplement use.

[2] Adjusted for age, BMI, vitamin supplement use (yes or no), cigarette smoking habit (never, former, or current), and social class (I, II, IIIA, IIIB, IV, and V).

[3] BMI (in kg/m^2) ≥30.

[4] BMI (in kg/m^2) <30.

[5] Adjusted for age, BMI, and social class (I, II, IIIA, IIIB, IV, and V).

[6] Adjusted for dietary ascorbic acid, total energy intake, age, BMI, vitamin supplement use (yes or no), cigarette smoking habit (never, former, or current), and social class (I, II, IIIA, IIIB, IV, and V).

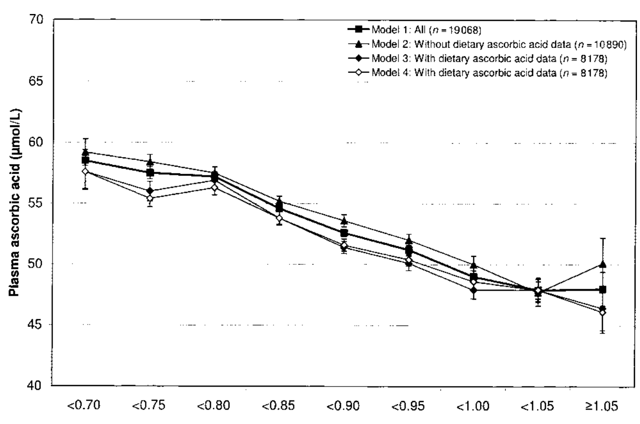

FIGURE 1. Plasma concentration of ascorbic acid (in μmol/L) by waist-to-hip ratio categories in 19 068 men and women aged 45–79 y without prevalent heart disease, stroke, or cancer and who took part in the European Prospective Investigation into Cancer and Nutrition Norfolk cohort study (1993–1997). P for trend < 0.001 for all. Means (±SEs) were obtained with regression models after adjustment for age, body mass index, vitamin supplement use (yes or no), cigarette smoking status (never, former, or current), and socioeconomic group (I, II, IIIA, IIIB, IV, or V) for models 1 to 3; additional adjustment for dietary ascorbic acid and total energy intake was made for model 4. The number of participants in the 9 waist-to-hip ratio categories (categories: <0.70, ≥0.70 to <0.75, ≥0.75 to <0.80, ≥0.80 to <0.85, ≥0.85 to <0.9, ≥0.9 to <0.95, ≥0.95 to <1.0, ≥1.0 to <1.05, and ≥1.05) from the lowest to the highest category were 501, 2213, 3504, 3207, 3118, 3364, 2178, 783, and 200 for model 1; 322, 1457, 2165, 1865, 1747, 1838, 1091, 325, and 80 for model 2; and 179, 756, 1339, 1342, 1371, 1526, 1087, 458, and 120 for models 3 and 4.

Plasma ascorbic acid concentrations also decreased with higher waist-to-hip ratio quartiles across all body mass index ranges (**Table 3**). The plasma concentration of ascorbic acid was also inversely related to higher body mass index quartiles across all ranges of waist-to-hip ratio in women. In men, a significant inverse association for body mass index was limited to those in the lowest waist-to-hip ratio quartile. Nevertheless, the participants in the highest waist-to-hip ratio and body mass index categories had the lowest plasma ascorbic acid concentrations.

After adjustment for waist circumference and other covariates, an 8-cm increase in hip circumference (1 SD = 6.2 cm in men and 8.9 cm in women) was associated with a higher plasma ascorbic acid concentration of 2.0 μmol/L (95% CI: 1.2, 2.8) for men and 1.2 μmol/L (95% CI: 0.8, 1.8) for women. The interrelation between mean plasma ascorbic acid and the tertiles of waist and hip circumference are shown in **Figure 2** and **Figure 3**. In the participants with dietary data, the estimated difference in plasma ascorbic acid concentration for every 8-cm increase in hip circumference was 1.6 μmol/L (95% CI: 0.3, 2.9) for men (n = 3953) and 0.8 μmol/L (95% CI: −0.3, 1.9) for women (n = 4225) after adjustment for waist circumference and other covariates. After additional adjustment for dietary ascorbic acid and total energy intakes, the estimates were 1.2 μmol/L (95% CI: 0.0, 2.4) for men and 0.8 μmol/L (95% CI: −0.3, 1.8) for women.

DISCUSSION

In the present cohort of men and women aged 45–79 y, higher waist-to-hip ratios were associated with lower plasma ascorbic

TABLE 3

Plasma concentration of ascorbic acid by quartiles of waist-to-hip ratio stratified by BMI categories in the participants[1]

	BMI quartile								
	1		2		3		4		
Waist-to-hip ratio quartile[2]	*n*	Ascorbic acid	*n*	Ascorbic acid	*n*	Ascorbic acid	*n*	Ascorbic acid	P^3
		μmol/L		*μmol/L*		*μmol/L*		*μmol/L*	
Men									
<0.891	1149	51.3 ± 0.5[4]	600	51.0 ± 0.7	302	47.7 ± 1.0	100	47.7 ± 1.8	0.003
0.891–0.929	596	48.0 ± 0.7	694	59.4 ± 0.7	562	50.5 ± 0.8	303	45.7 ± 1.0	> 0.05
0.929–0.966	282	47.1 ± 1.1	539	47.1 ± 0.8	697	47.2 ± 0.7	621	45.9 ± 0.7	> 0.05
>0.966	122	43.3 ± 1.4	317	43.8 ± 1.0	585	44.7 ± 0.7	1124	42.8 ± 0.5	> 0.05
P		< 0.001		< 0.001		< 0.001		< 0.001	
Women									
<0.748	1186	62.2 ± 0.6	740	62.0 ± 0.7	450	59.7 ± 0.9	243	61.4 ± 1.2	0.027
0.748–0.787	772	61.9 ± 0.7	783	61.4 ± 0.7	665	61.0 ± 0.7	405	57.5 ± 0.9	< 0.001
0.787–0.831	451	59.1 ± 0.9	660	58.9 ± 0.7	741	59.0 ± 0.7	761	56.0 ± 0.7	0.001
>0.831	210	55.8 ± 1.3	436	57.3 ± 0.9	763	55.5 ± 0.7	1209	52.1 ± 0.6	< 0.001
P		< 0.001		< 0.001		< 0.001		< 0.001	

[1] Means were obtained with regression models after adjustment for age, cigarette smoking status (never, former, or current), vitamin supplement use (yes or no), and socioeconomic class (I, II, IIIA, IIIB, IV, or V). Approximate BMI quartile ranges were <24.3, 24.3–26.2, 26.2–28.2, and >28.2 kg/m^2 for men, and <23.2, 23.2–25.5, 25.5–28.3, and >28.3 kg/m^2 for women.

[2] Ranges are approximate values; seemingly overlapping values are due to rounding off of numbers.

[3] *P* for trend across waist-to-hip ratio or BMI categories (ANOVA): $P = 0.050$ for sex × waist-to-hip ratio × BMI; $P = 0.030$ for sex × waist-to-hip ratio; $P > 0.05$ for waist-to-hip ratio × BMI; and $P > 0.05$ for sex × BMI.

[4] $\bar{x}$ ± SE (all such values).

acid concentrations. This inverse relation was continuous across the whole range of waist-to-hip ratios in both men and women. Although the plasma concentration of ascorbic acid may not necessarily reflect the usual plasma concentrations in these persons because it was measured only once, random measurement error would attenuate any association. Despite the possible large within-person variation of plasma ascorbic acid concentrations, a significant relation was still observed.

The inverse relation between the waist-to-hip ratio and plasma ascorbic acid concentrations may simply reflect the effect of total adiposity, as measured by body mass index. In 361 men and 426 women aged ≥18 y in a study conducted in France, body mass index was unrelated to plasma ascorbic acid concentrations (11). In the National Health and Nutrition Examination Survey II, however, 18–74-y-old participants showed a slight inverse relation between body mass index and ascorbic acid concentrations (12). Our findings suggest that the effect of the waist-to-hip ratio was independent of body mass index and was apparent even in the nonobese participants (those with a body mass index < 30).

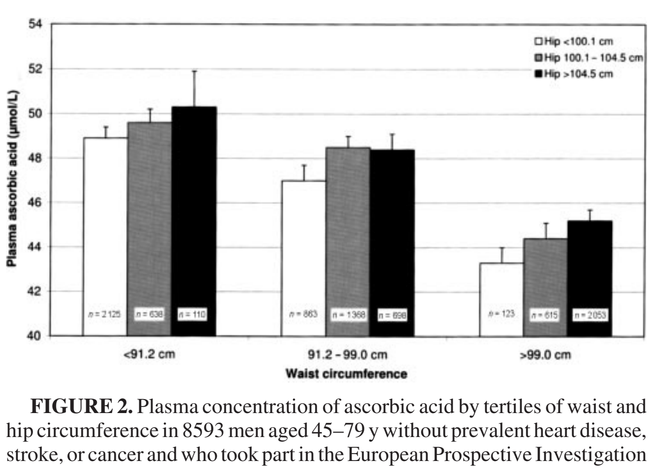

FIGURE 2. Plasma concentration of ascorbic acid by tertiles of waist and hip circumference in 8593 men aged 45–79 y without prevalent heart disease, stroke, or cancer and who took part in the European Prospective Investigation into Cancer and Nutrition Norfolk cohort study (1993–1997). Means (±SEs) were obtained from regression models after adjustment for age, body mass index, vitamin supplement use (yes or no), cigarette smoking status (never, former, or current), and socioeconomic group (I, II, IIIA, IIIB, IV, or V). For statistical interactions, data for both men and women were pooled before analysis. Statistical interactions as derived from analysis of variance: $P > 0.05$ for sex × waist × hip, $P = 0.022$ for sex × hip, $P = 0.014$ for waist × hip, and $P > 0.05$ for sex × hip.

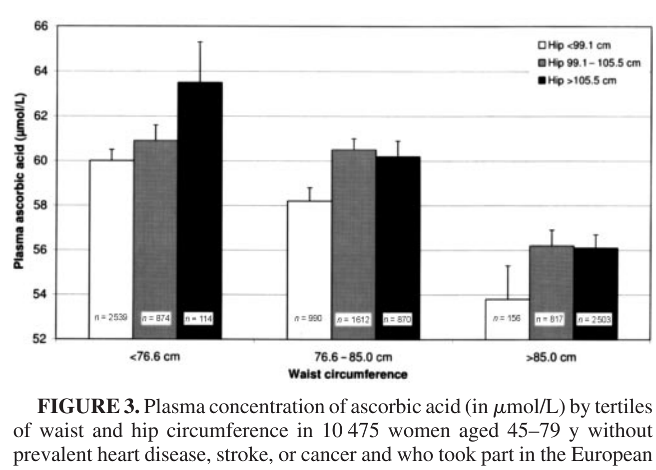

FIGURE 3. Plasma concentration of ascorbic acid (in μmol/L) by tertiles of waist and hip circumference in 10 475 women aged 45–79 y without prevalent heart disease, stroke, or cancer and who took part in the European Prospective Investigation into Cancer and Nutrition Norfolk cohort study (1993–1997). Means (±SEs) were obtained from regression models after adjustment for age, body mass index, vitamin supplement use (yes or no), cigarette smoking status (never, former, or current), and socioeconomic group (I, II, IIIA, IIIB, IV, or V). For statistical interactions, data for both men and women were pooled before analysis. Statistical interactions as derived from analysis of variance: $P > 0.05$ for sex × waist × hip, $P = 0.022$ for sex × hip, $P = 0.014$ for waist × hip, and $P > 0.05$ for sex × hip.

The association between fat distribution and plasma ascorbic acid concentrations could have common underlying factors, such as lifestyle habit and diet. Cigarette smoking is associated with both increased abdominal adiposity (28, 29) and lower plasma ascorbic acid concentrations (12, 30–35). However, our findings did not significantly change when we analyzed data only in nonsmokers. Adjustment for socioeconomic status, which may reflect underlying differences in lifestyle factors such as physical activity, cigarette smoking, and dietary habits, did not materially change our findings. Preexisting diseases in abdominally obese persons may affect plasma ascorbic acid concentrations, but we excluded persons with known chronic diseases from our analyses. Leaner persons are more likely to take vitamin supplements than are obese persons (34). Indeed, the proportion of vitamin supplement users was higher in the in the lower waist-to-hip ratio category. Our results remained significant after either adjustment for vitamin supplement use or limiting our analyses to the participants who were not using any vitamin supplements. When we adjusted for dietary ascorbic acid intakes, the inverse association between the waist-to-hip ratio and plasma ascorbic acid concentrations persisted. We may not have fully adjusted for dietary ascorbic acid intake, possibly due to biases associated with the underreporting of total energy intakes in obese persons (36), although micronutrients such as ascorbic acid are less correlated with total energy intake and are less affected by reporting biases that may be associated with total food intake (37). However, we could not rule out residual confounding due to errors associated with self-reported dietary intakes.

The cross-sectional associations we found need to be interpreted with caution. Although we have no reason to believe that ascorbic acid per se could affect fat distribution, plasma ascorbic acid is a known marker of fruit and vegetable intake (38–40). It is plausible that a higher intake of fruit and vegetables may form part of an overall dietary pattern of low-fat and high-fiber foods (41). Hence, a plasma ascorbic acid concentration is more likely to be an indicator of a particular diet and other lifestyle behaviors in health conscious persons, which may not only promote a leaner body mass but also a more favorable fat distribution pattern.

Alternatively, plasma ascorbic acid concentrations could also reflect the available pool (or the remaining pool) of ascorbic acid in the body (39). Unlike other antioxidants that may be stored in fat tissues, such as β-carotene and α tocopherols, no known mechanisms exist that show how ascorbic acid, which is water-soluble, could be stored differentially with increasing adiposity. However, ascorbic acid plays a role in scavenging free radicals (8) and inhibits lipid peroxidation (7). The systemic oxidative stress that is associated with obesity (42) or due to an underlying subclinical disease or ongoing atherosclerotic process may be associated with increased free radical concentrations. Antioxidants, which are involved in redox reactions, may be used up in the process. Hence, it is plausible that the plasma concentration of ascorbic acid reflects, to an extent, the ascorbic acid that is available for use by the body, the excess of what has already been used up, or both. Indeed, the lower plasma ascorbic acid concentrations that are observed in smokers, diabetics, and even undiagnosed angina patients would be consistent with the concept of an increase in the use of ascorbic acid and other antioxidants in these persons who are at a high risk of developing cardiovascular diseases (12, 30, 31, 43–45).

The separate and opposite relations observed between plasma ascorbic acid concentrations and waist and hip circumferences were intriguing. To our knowledge, these associations have not been previously reported. Indeed, a bigger hip or thigh circumference has been associated with less aortic calcification (46), better cardiovascular disease risk profile (47–49), and lower all-cause and cardiovascular disease mortality, especially in women (50, 51). Although the mechanism is unclear, it has been suggested that subcutaneous fat may play a role in fatty acid metabolism and peripheral fat mass may be less metabolically active (52–54). It is possible that peripheral fat mass is less involved in oxidative metabolic processes than is central fat mass. However, the clinical relevance of the association between peripheral adiposity and plasma ascorbic acid concentrations in our cohort remains to be elucidated, because the strength of this association was relatively small.

Clearly, more research has to be done to determine the underlying explanation to why abdominally obese persons have lower plasma ascorbic acid concentrations than do leaner persons. Furthermore, our observations need to be confirmed in other populations. The separate and opposite relations of plasma ascorbic acid concentration with waist and hip circumferences were intriguing, and the underlying explanation to these associations needs to be explored. Whether specific dietary patterns or lifestyle habits contribute to a better fat distribution pattern, or whether a reduction in abdominal obesity improves plasma ascorbic acid concentrations remains to be investigated.

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DC conceptualized the study, conducted the analyses and wrote the initial draft of the paper. RL managed and computed the data. AW and SB helped analyze the dietary and nutritional data. K-TK, NW, and AW assisted in the overall analyses. K-TK, ND, and SB originated and designed the cohort study. All authors contributed to the writing of the manuscript. None of the authors had any conflicts of interest.

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