Antioxidant vitamins and mortality in older persons: findings from the nutrition add-on study to the Medical Research Council Trial of Assessment and Management of Older People in the Community[1–3]

Astrid E Fletcher, Elizabeth Breeze, and Prakash S Shetty

ABSTRACT

Background: Older persons are at risk of both poor nutrition and increased oxidative stress. Plasma ascorbate concentrations fall with increasing age, and concentrations of other antioxidants may also be reduced.

Objective: The goal was to examine the association between antioxidants and mortality in older persons.

Design: We randomly selected persons aged 75–84 y from the lists of 51 British family practitioners taking part in a randomized trial of assessment of older persons. A total of 1214 participants provided a blood sample and were interviewed about their usual diet with the use of a food-frequency questionnaire. Statistical analyses were based on deaths after a median of 4.4 y of follow-up, and hazard ratios were estimated for quintiles of dietary or blood antioxidants.

Results: We found strong inverse trends for blood ascorbate concentrations with all-cause and cardiovascular disease mortality, which were only marginally reduced after adjustment for confounders or supplement use. Those in the lowest fifth ($<$ 17 μmol/L) had the highest mortality, whereas those in the highest fifth ($>$ 66 μmol/L) had a mortality risk nearly half that (hazard ratio = 0.54; 95% CI: 0.34, 0.84). Similar results were found after the exclusion of those subjects with cardiovascular disease or cancer at baseline (hazard ratio = 0.51; 0.28, 0.93). In fully adjusted models, there was no evidence for an influence of α-tocopherol, β-carotene, or retinol on total mortality. Dietary antioxidants measured by the food-frequency questionnaire were not associated with all-cause or cardiovascular disease mortality.

Conclusion: Low blood vitamin C concentrations in the older British population are strongly predictive of mortality. *Am J Clin Nutr* 2003;78:999–1010.

KEY WORDS Antioxidant vitamins, vitamin C, older persons, prospective study, mortality

INTRODUCTION

Studies conducted predominantly in middle-aged populations show associations between antioxidant vitamins and all-cause or cardiovascular disease (CVD) mortality, although much debate remains about the role of specific antioxidants and the benefit of supplementation (1, 2). Relatively few studies have been conducted in older age groups, however, especially in persons aged $\geq$ 75 y, who are at risk of both poor nutrition and increased oxidative stress (3). Blood concentrations of potent antioxidants, in particular plasma ascorbate (vitamin C), decrease with increasing age (4) such that by late life increasing proportions of the older population have concentrations indicating deficiency. In the British population, nearly 1 in 5 community-dwelling persons aged $\geq$ 75 y have ascorbate concentrations indicating severe biochemical depletion, and this figure increases to nearly one-half of those aged $>$ 85 y living in institutions (5). Low dietary intakes are considered to be the main cause of the reduced plasma concentrations observed in later life (4), and conditions of acute free radical generation, such as infection and inflammation, may dramatically reduce tissue stores of ascorbate (6, 7). The few studies that have investigated the associations of antioxidant concentrations in late life with mortality were mostly small and underpowered and showed varying results for the importance of vitamin C, β-carotene, or vitamin E (8–13). In the present article, we report the results for plasma antioxidants and subsequent mortality in participants aged 75–84 y in the nutrition substudy of a randomized trial conducted in Britain.

SUBJECTS AND METHODS

The Medical Research Council Trial of Assessment and Management of Older People in the Community is a cluster randomized trial conducted among family medical practitioners (known as general practitioners in the United Kingdom). The aim of the trial is to compare the cost-effectiveness of different methods of assessment and clinical management of older persons. A total of 106 general practices from the Medical Research Council General Practice Research Framework were recruited and selected to provide a representative sample of mortality experience (standardized mortality ratio) and deprivation level (a measure of the socioeconomic characteristics of

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[3] Reprints not available. Address correspondence to A Fletcher, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom. E-mail: astrid.fletcher@lshtm.ac.uk.

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the region) of the United Kingdom. The deprivation level was measured with the use of Jarman scores derived from the 1991 census data (14). All patients aged ≥ 75 y on each general practitioner's list were invited to participate in the trial unless they were resident in a long-stay hospital or nursing home or were terminally ill.

The practices were randomly divided into 2 groups: targeted or universal screening. In the universal screening practices, all participants underwent a detailed assessment conducted by the study nurse. In the targeted practices, only participants with a predetermined number and type of problems at the brief assessment underwent the detailed assessment. The detailed assessment included questionnaires for several health conditions, including the Rose Chest Pain Questionnaire (15). Patients were also asked about their current and past alcohol intake and smoking habits, sociodemographic factors (including marital status, living circumstances, and housing tenure), and medical history, including past and recent history of heart attack, stroke, cancer, and diabetes. Measurements taken at the detailed assessment included 2 measurements each of blood pressure (sitting and standing), height (with use of a stadiometer), and weight (with use of Soehnle scales; Leifheit AG, Nassau, Germany). Study nurses attended a 2-d training session. Participants were registered for mortality follow-up with the Office of National Statistics, who provided cause of death by using the 9th International Classification of Disease. The trial was approved by the relevant local research ethics committees.

The nutrition study was designed as an add-on study to the trial and was separately funded. Its main objective was to examine the association between blood concentrations of antioxidant vitamins and lipids (total, HDL, and LDL cholesterol) and mortality, especially from CVD. Dietary information was also collected. Written informed consent was obtained from the participants, and all relevant research ethics committees gave ethical approval for the nutrition study. Presented here are the results of the association of antioxidants with mortality.

Sample size

The nutrition study aimed to invite 3000 persons (with an expected response rate of 70%) aged 75–84 y from the universal screening arm of the trial because all of the participants in this arm would receive a full health assessment and would be a representative group of older persons. Patients in the targeted screening arm who had a detailed assessment were not included in the nutrition study because they were a selected group. The sample size was chosen to provide 80% power at a 5% significance level to detect a protective effect of ≤ 0.6 between the highest and the lowest quintile of antioxidant distribution, assuming a mortality rate of 60/1000 person-years. The upper age limit of 84 y was chosen because it was judged that an additional interview might be too burdensome in the oldest age groups (those aged ≥ 85 y). The nutrition and physical activity interview and nutrition study blood results were not part of the trial interventions, and no attempt was made to provide participants with any information or advice regarding their blood results or diet.

Sample selection

General practitioners in the 53 practices in the universal screening arm of the trial were invited to take part in the nutrition substudy. For each participating practice, persons with birth dates within the eligible range were identified from the age-sex registers, and a systematic random sample was taken by applying a sampling fraction that had been predetermined for each practice to obtain a similar number of participants for each practice. At the detailed assessment, the nurse invited the selected participants to take part in a further interview (to be held ≈4 wk after the assessment) and to provide an additional 8 mL blood. To take account of seasonal variations in diet, which might influence vitamin concentrations, the invitation dates were evenly spread across the year.

Blood collection

All nurses in the nutrition study were instructed how to take and process the blood samples. The nurses were asked to draw the blood under subdued lighting, to collect the sample into 7- or 9-mL EDTA-containing tubes, and to place the tubes immediately into an ice pack to be stored in a domestic refrigerator until shipment on ice in an insulated container to a local laboratory within 4 h of collection. At the laboratory, the blood was immediately centrifuged and divided into 7 aliquots. Metaphosphoric acid at a concentration of 10% was added to 2 of the aliquots to prevent oxidation of vitamin C. The aliquots were frozen to −80 °C. The local laboratories stored the blood samples for a maximum of 6 mo until they were sent in batches by 24-h courier on dry ice to Rowett Research Laboratories (Aberdeen, United Kingdom) for further storage at −70° C.

Plasma ascorbate was analyzed by HPLC by using the assay procedure of Ross (16). The CV was 3.7%. Retinol, α-tocopherol, and β-carotene were also analyzed by HPLC by using the method of Hess et al (17); the percentage relative error compared with National Institute of Standards and Technology (Gaithersburg, MD) reference values for high, medium, and low concentrations of the fat-soluble vitamins were < 5% for 11 of 12 comparisons. Serum total and HDL cholesterol were by measured using the KONE instruments kit (KoneLab Corporation, Helsinki). Blood results were sent to the London School of Hygiene and Tropical Medicine and were merged with the main data files. Additional funding from the European Union Biomed Programme permitted the analysis of homocysteine at the University Department of Pharmacology, University of Oxford, by using a fluorescence polarization immunoassay on an Abbott IMx autoanalyzer (Abbott Laboratories, Abbott Park, IL).

Interviews

The nutrition and physical activity interviews were carried out by the UK government's Office for National Statistics Social Survey Division and took place after the blood collection (median time of 28 d). The nutrition interview used the UK EPIC study (European Prospective Investigation into Cancer and Nutrition) version of a food-frequency questionnaire (FFQ) originally developed by Willett et al (18). We made some minor modifications to the questionnaire; in particular, we enquired about seasonal consumption of certain fruit and vegetables. The questionnaire included 139 food groups with a choice of 1 of 9 response codes of frequency. Respondents were asked about consumption over the previous year. Information on supplement use and type was also collected. Estimates of daily intakes of vitamin C, vitamin E, β-carotene, and

TABLE 1
Characteristics of persons eligible for the nutrition sample, of those selected for the present study, and of those who provided a blood sample and completed the questionnaire[1]

	All eligible persons	Selected sample	Respondents with blood sample and questionnaire
n (unweighted)	12 018	2167	1214
n (weighted)	—	2211.5	1195.7
Age (y)[2]	78.9 (76.7, 81.5)	78.8 (76.8, 81.3)	78.5 (76.7, 81.2)
Men (%)	40.3	42.1	45.5
Living alone (%)	43.7	45.8	44.3
Homeowner (%)	65.0	62.1	64.5
Systolic blood pressure (mm Hg)[3]	148.6 ± 22.1	149.4 ± 21.6	149.7 ± 21.6
BMI (kg/m^2)[3]	26.4 ± 4.4	26.5 ± 4.2	26.4 ± 4.2
Current smoker (%)	11.4	11.6	10.4
Exsmoker (%)	51.6	50.9	52.9
Alcohol consumption (units in past week)[2]	1 (0, 5)	1 (0, 4)	1 (0, 4)
No. of prescribed medicines[2]	3 (1, 4)	2 (1, 4)	2 (1, 4)
Diabetes (%)	6.8	7.4	6.5
History of cardiovascular disease (%)[4]	24.0	24.3	24.2
History of cancer (%)[5]	10.1	9.7	9.8

[1] There were no significant differences between groups.
[2] Median; interquartile range in parentheses.
[3] $\bar{x}$ ± SD.
[4] Ever had a heart attack or stroke or currently have probable or definite angina (as determined by the Rose angina questionnaire).
[5] Excludes basal cell carcinoma.

retinol were calculated from the food groups by using the nutrient databank that was made available to us by the investigators of the British National Diet and Nutrition Survey of Older Adults (NDNS; 5); estimates of portion sizes were based on the equivalent age group from the NDNS. Intakes from supplements could not be included in the estimates of daily intake because insufficient information on doses was obtained. Because no appropriate physical activity questionnaire for this UK age group was available, we adapted questions from the Allied Dunbar National Fitness Survey (19) to cover a range of activities from leisure activities, housework, and home maintenance. These were further categorized according to time spent and intensity of effort.

Statistical analysis

Analyses were performed for respondents with a full set of blood results, health assessments, and nutrition interviews to allow for adjustment for potential confounders. The results presented are weighted to allow for the differing planned probabilities of selection in the practices. Analyses were performed using STATA 6 software (20). Mortality analyses used Cox regression models and modified Wald tests for statistical significance. Analyses took account of the cluster design in the estimation of 95% CIs (21). Hazard ratios were estimated for quintiles of plasma antioxidants referent to the lowest quintile and were adjusted for age and sex. The *P* values for test for trend were obtained from a logistic regression model in which the quintiles were scored from 1 to 5 and a log-linear model for odds of the outcome assumed. Further models took account of possible confounders from data collected at the detailed assessment and described above. Smoking was classified as current, ex, and never and pack-years were calculated from information on lifetime smoking consumption. α-Tocopherol concentrations were divided by total cholesterol to estimate the α-tocopherol ratio, and all analyses were based on the ratio of α-tocopherol to cholesterol. CVD was classified as a death from an underlying cause due to hypertensive disease (ICD 401–405), ischemic heart disease (ICD 410–414), other heart diseases (ICD 420–429), cerebrovascular disease (ICD 430–439), and diseases of the arteries (440–447). The analyses were based on deaths reported by September 2001; the median follow-up time was 4.4 y.

RESULTS

Of 53 practices in the universal arm of the study, 51 agreed to participate in the nutrition study. A total of 2959 persons were randomly sampled for the nutrition study, of whom 2167 attended the detailed assessment. One hundred twenty-seven were not invited either because of delays in obtaining ethics approval or because of administrative errors. The overall response rate to the invitation to the interview was 68% (1387) and that to the blood collection was 75% (1529). A total of 120 blood samples were unusable or were not transported by the local laboratory. The number of participants with both interviews and blood samples was 1214. Taking into account all of the subjects sampled for the nutrition study, the response rate was 47% for the interview and 52% for the blood sample.

The characteristics of those who provided a blood sample and completed an interview were not significantly different from those of either subjects in the universal arm of the study in the comparable age range or subjects sampled to take part in the nutrition study (**Table 1**). Of those with both a blood sample and a completed interview, 290 (24%) had died by September 2001, of whom 44% had died of CVD.

TABLE 2
Characteristics of the participants by quintiles of plasma ascorbate

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend
Ascorbate						
Cutoffs (μmol/L)	<17.00	17.00, 32.80	32.81, 49.74	49.75, 66.28	>66.28	
Median (μmol/L)	10.61	24.55	41.65	58.03	79.58	
Mean (μmol/L)	10.48	24.64	41.11	57.75	87.79	
n (unweighted), total *n* = 1175	232	239	235	229	240	
n (weighted)	236.6	226.7	240.5	229.7	223.8	
Age (y)[1]	79.2 (77.2, 81.6)	78.4 (76.8, 81.4)	78.7 (76.8, 81.3)	78.4 (76.6, 81.1)	78.3 (76.7, 81.0)	0.01
Men (%)	51.2	52.2	54.0	41.6	26.8	<0.01
Living alone (%)	46.1	42.8	40.3	47.1	46.2	0.38
Homeowner (%)	55.4	55.0	73.6	65.4	73.3	<0.01
Systolic blood pressure (mm Hg)[2]	148.0 ± 23.6	150.6 ± 20.8	149.9 ± 21.7	149.3 ± 20.4	151.1 ± 21.9	0.33
Total cholesterol (mmol/L)[2]	5.52 ± 1.18	5.81 ± 1.11	5.67 ± 1.15	6.02 ± 1.21	6.07 ± 1.25	<0.01
HDL cholesterol (mmol/L)[2]	1.13 ± 0.35	1.16 ± 0.38	1.18 ± 0.35	1.22 ± 0.35	1.34 ± 0.42	<0.01
BMI (kg/m^2)[2]	25.9 ± 4.6	26.9 ± 4.5	26.8 ± 3.7	26.9 ± 3.9	25.5 ± 4.2	0.43
Current smoker (%)	19.2	12.0	5.1	9.5	4.2	<0.01
Exsmoker (%)	50.3	51.9	57.1	55.4	51.2	
Alcohol consumption (drinks/wk)[1]	0 (0, 2)	0 (0, 3)	0 (0, 4)	1 (0, 3)	1 (0, 3)	<0.01
Physical activity (units/wk)[1,3]	1 (0, 5)	2 (0, 5)	3 (0, 6)	3.75 (1, 7)	4 (0, 7)	<0.01
Diabetes (%)	7.2	6.3	8.3	7.1	3.8	0.06
History of cardiovascular disease (%)[4]	28.2	23.3	25.0	21.6	21.3	0.11
History of cancer (%)[5]	5.7	8.3	9.1	6.0	10.0	0.60
Supplement user (%)[6]	24.5	36.3	43.2	49.3	64.2	<0.01
Dietary vitamin C (mg/d)[1,7]	52.1 (34.8, 80.0)	72.0 (48.3, 103.6)	89.3 (61.0, 117.4)	97.2 (66.2, 135.3)	103.5 (71.5, 139.1)	<0.01
Dietary vitamin E (mg/d)[1,7]	7.98 (5.49, 12.71)	9.00 (6.01, 13.90)	8.83 (6.01, 13.90)	7.93 (5.78, 13.24)	7.79 (5.94, 11.81)	0.48
Dietary β-carotene (mg/d)[1,7]	1.97 (1.19, 2.55)	2.14 (1.40, 2.96)	2.24 (1.54, 3.11)	2.21 (1.52, 3.19)	2.21 (1.67, 3.02)	<0.01
Dietary retinol (mg/d)[1,7]	0.69 (0.49, 1.79)	0.67 (0.47, 1.69)	0.81 (0.55, 1.77)	0.71 (0.49, 1.76)	0.72 (0.47, 1.52)	0.12
≥ 5 Portions fresh fruit and vegetables/d (%)	18.2	33.9	44.4	51.6	55.3	<0.01

[1] Median; interquartile range in parentheses.
[2] $\bar{x}$ ± SD.
[3] Units of activity defined by time and activity level.
[4] Stroke, heart attack, or definite or probable angina on Rose chest pain questionnaire.
[5] Excludes basal cell carcinoma.
[6] Regular user of any supplements.
[7] Dietary intakes do not include supplements.

Inverse associations existed between increasing blood ascorbate concentrations and age, the proportion of men, and current smoking, and positive associations existed with the proportion of homeowners, levels of physical activity, supplement use, alcohol consumption, and total and HDL cholesterol (**Table 2**). Ascorbate concentrations were associated with dietary vitamin C and β-carotene intakes and with the proportion consuming ≥ 5 fresh fruit and vegetables daily. There were fewer trends for associations with α-tocopherol (**Table 3**). Trends similar to those observed for ascorbate were seen for β-carotene (**Table 4**), but fewer were seen for retinol (**Table 5**).

We observed a strong inverse trend for all-cause mortality and blood ascorbate, which was only marginally reduced after adjustment for confounders, including sex and supplement use (**Table 6**). Forty-three percent of the subjects reported taking some form of vitamin supplement; the most common was cod liver oil, which was taken by 25%, mainly on its own (21%). Vitamin C alone was reported by only 5%, and the total taking vitamin C either alone or as part of a multivitamin preparation was 17%. Adjustment for any use of supplements had little effect on the results. Separate analyses using sex-specific quintiles confirmed the associations for men and women with ascorbate and mortality (data not shown); there was no evidence for a differential effect for men compared with women (*P* value for test for interaction in the fully adjusted model = 0.83).

α-Tocopherol and retinol were not associated with mortality, and a nonlinear association with β-carotene disappeared after adjustment for confounders. The results were essentially similar after the exclusion of those with prevalent CVD or cancer at baseline (Table 6).

The results for CVD mortality also showed decreasing hazard ratios with increasing ascorbate concentrations, with no extra benefit in the top fifth compared with the fourth. For α-tocopherol, there was weak evidence for a protective effect on CVD mortality for concentrations > 3.92 μmol/mmol cholesterol in the fully adjusted models, whereas for β-carotene, a nonsignificant reduction in risk with increasing concentrations disappeared when adjusted for confounders. The hazard ratios for a 20-μmol/L increase in ascorbate were 0.82 for all-cause and CVD mortality, respectively, and 0.76 and 0.74, respectively, after the exclusion of those with prevalent CVD or cancer at baseline (**Table 7**). The hazard ratios for ascorbate were little altered by including all plasma antioxidants in the

TABLE 3
Characteristics of the participants by quintiles of plasma α-tocopherol

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend
α-Tocopherol						
Cutoffs (μmol/mmol cholesterol)	<3.08	3.08, 3.52	3.52, 3.92	3.92, 4.49	>4.49	
Median (μmol/mmol cholesterol)	2.80	3.32	3.72	4.15	4.95	
Mean (μmol/mmol cholesterol)	2.68	3.32	3.71	4.18	5.29	
n (unweighted), total *n* = 1166	233	229	227	233	244	
n (weighted)	216.5	216.9	222.6	230.3	260.6	
Age (y)[1]	78.3 (77.1, 81.6)	79.0 (77.0, 81.6)	79.3 (76.7, 81.7)	78.1 (76.7, 81.0)	78.4 (76.5, 80.6)	0.02
Men (%)	42.8	46.2	44.6	42.8	50.1	0.89
Living alone (%)	46.3	46.9	45.8	47.3	38.3	0.43
Homeowner (%)	62.3	64.4	67.0	64.6	66.8	0.27
Systolic blood pressure (mm Hg)[2]	149.0 ± 21.8	148.5 ± 19.6	148.0 ± 22.4	152.0 ± 21.3	150.0 ± 22.5	0.31
HDL cholesterol (mmol/l)[2]	1.28 ± 0.39	1.26 ± 0.39	1.21 ± 0.35	1.19 ± 0.36	1.11 (0.39)	<0.01
BMI (kg/m^2)[2]	26.6 ± 4.8	26.5 ± 3.7	26.3 ± 3.9	26.5 ± 4.3	26.3 ± 4.2	0.68
Current smoker (%)	14.3	7.4	12.1	11.7	6.5	0.16
Exsmoker (%)	50.8	50.7	49.2	51.4	59.8	
Alcohol consumption (drinks/wk)[1]	0 (0, 3)	1 (0, 4)	0 (0, 3)	0 (0, 4)	0 (0, 3)	0.58
Physical activity (units/wk)[1,3]	1.75 (0, 5.75)	3 (0, 6)	3 (0, 7)	2 (0, 6)	3.5 (0, 6.5)	0.28
Diabetes (%)	5.2	6.6	4.5	7.0	8.0	0.27
History of cardiovascular disease (%)[4]	19.4	21.2	24.1	19.5	31.3	0.06
History of cancer (%)[5]	7.9	10.6	5.6	6.4	9.3	0.96
Supplement user (%)[6]	31.5	34.5	46.3	47.9	54.1	<0.01
Dietary vitamin C (mg/d)[1,7]	71.3 (44.4, 103.9)	84.8 (55.8, 122.4)	83.9 (54.7, 121.1)	76.5 (54.7, 121.1)	85.2 (55.1, 118.0)	0.05
Dietary vitamin E (mg/d)[1,7]	7.11 (5.60, 10.88)	7.81 (5.83, 10.94)	8.22 (5.64, 12.94)	8.68 (5.82, 14.41)	9.74 (6.90, 14.90)	<0.01
Dietary β-carotene (mg/d)[1,7]	2.06 (1.40, 2.81)	2.13 (1.48, 2.99)	2.17 (1.32, 2.97)	2.19 (1.48, 2.92)	2.19 (1.67, 3.09)	0.16
Dietary retinol (mg/d)[1,7]	0.75 (0.51, 1.69)	0.69 (0.49, 1.72)	0.65 (0.45, 1.50)	0.69 (0.49, 1.7)	0.75 (0.50, 1.82)	0.26
≥ 5 Portions fresh fruit and vegetables/d (%)	37.7	43.6	37.1	39.3	42.7	0.44

[1] Median; interquartile range in parentheses.
[2] $\bar{x}$ ± SD.
[3] Units of activity defined by time and activity level.
[4] Stroke, heart attack, or definite or probable angina on Rose chest pain questionnaire.
[5] Excludes basal cell carcinoma.
[6] Regular user of any supplements.
[7] Dietary intakes do not include supplements.

model, either in adjusted or unadjusted analyses. For example, in a fully adjusted model (adjusted for age, sex, BMI, cholesterol, systolic blood pressure, smoking, alcohol, diabetes, history of CVD or cancer, physical activity, housing tenure, and supplement use) that included α-tocopherol, β-carotene, and retinol, the hazard ratios by increasing fifths of ascorbate compared with the lowest quintile were 0.97 (0.72, 1.31), 0.59 (0.40, 0.86), 0.63 (0.36, 1.08), and 0.54 (0.34, 0.85) (*P* for trend = 0.004). None of the other antioxidants was significantly associated with mortality in this model.

The results were also essentially unchanged in other analyses substituting HDL for total cholesterol or adjusting for folate concentrations or using pack-years of smoking (data not shown). In analyses restricted to 417 never smokers, the fully adjusted (age, sex, BMI, cholesterol, systolic blood pressure, alcohol, diabetes, history of CVD or cancer, physical activity, housing tenure, and supplement use) hazard ratios for a 20-μmol/L increase in ascorbate were 0.73 (95% CI: 0.57, 0.93; *P* = 0.012) for all-cause mortality. We found a small attenuation of the estimates in analyses that additionally adjusted for

TABLE 4
Characteristics of the participants by quintiles of plasma β-carotene

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend
β-Carotene						
Cutoffs (μmol/L)	<0.206	0.206, 0.315	0.316, 0.429	0.430, 0.596	>0.596	
Median (μmol/L)	0.153	0.261	0.372	0.501	0.772	
Mean (μmol/L)	0.143	0.262	0.370	0.505	0.936	
n (unweighted), total *n* = 1195	240	233	250	236	236	
n (weighted)	221.4	228.7	247.8	236.4	245.0	
Age (y)[1]	78.4 (76.7, 81.0)	78.1 (76.8, 81.5)	79.3 (77.0, 81.7)	78.1 (76.6, 80.7)	79.4 (77.0, 81.7)	0.17
Men (%)	60.5	52.2	49.6	38.9	27.6	<0.01
Living alone (%)	39.0	39.5	41.4	50.2	51.3	<0.01
Homeowner (%)	55.8	55.4	70.7	70.2	70.2	<0.01
Systolic blood pressure (mm Hg)[2]	148.3 ± 21.0	148.2 ± 20.2	150.1 ± 21.8	147.9 ± 21.2	152.9 ± 22.8	0.05
Total cholesterol (mmol/L)[2]	5.13 ± 1.04	5.63 ± 1.00	5.80 ± 1.15	6.00 ± 1.20	6.44 ± 1.21	<0.01
HDL cholesterol (mmol/L)[2]	1.15 ± 0.38	1.11 ± 0.30	1.20 ± 0.37	1.24 ± 0.38	1.32 ± 0.41	<0.01
BMI (kg/m^2)[2]	26.8 ± 4.82	27.3 ± 4.06	26.7 ± 3.97	26.1 ± 4.27	25.2 ± 3.46	<0.01
Current smoker (%)	16.5	13.6	7.8	8.0	5.0	<0.01
Exsmoker (%)	57.8	57.6	58.4	50.1	41.2	
Alcohol consumption (drinks/wk)[1]	0 (0, 4)	0 (0, 4)	0 (0, 3)	0 (0, 4)	1 (0, 3)	0.92
Physical activity (units/wk)[1,3]	2 (0, 5.5)	2.5 (0, 6)	3 (0, 6)	3 (0, 7)	3 (0.5, 7)	<0.01
Diabetes (%)	12.5	6.1	4.8	4.6	4.2	<0.01
History of cardiovascular disease (%)[4]	23.1	26.6	27.0	19.6	22.3	0.41
History of cancer (%)[5]	7.4	10.2	8.2	7.4	6.4	0.27
Supplement user (%)[6]	28.0	33.5	44.5	51.6	58.2	<0.01
Dietary vitamin C (mg/d)[1,7]	69.7 (41.4, 104.7)	70.4 (45.0, 103.7)	84.5 (54.2, 117.0)	91.9 (59.3, 128.3)	93.9 (68.7, 127.4)	<0.01
Dietary vitamin E (mg/d)[1,7]	9.21 (5.82, 13.38)	7.78 (5.74, 13.01)	8.05 (5.81, 14.54)	8.43 (5.67, 13.30)	7.96 (6.21, 12.94)	0.87
Dietary β-carotene (mg/d)[1,7]	1.94 (1.18, 2.60)	1.96 (1.24, 2.59)	2.11 (1.43, 3.00)	2.20 (1.61, 3.21)	2.40 (1.89, 3.47)	<0.01
Dietary retinol (mg/d)[1,7]	0.71 (0.48, 1.79)	0.66 (0.48, 1.66)	0.71 (0.50, 1.76)	0.73 (0.48, 1.67)	0.76 (0.51, 1.80)	0.45
≥ 5 Portions fresh fruit and vegetables/d (%)	27.0	32.9	38.1	50.3	51.9	<0.01

[1] Median; interquartile range in parentheses.
[2] $\bar{x}$ ± SD.
[3] Units of activity defined by time and activity level.
[4] Stroke, heart attack, or definite or probable angina on Rose chest pain questionnaire.
[5] Excludes basal cell carcinoma.
[6] Regular user of any supplements.
[7] Dietary intakes do not include supplements.

homocysteine (available for 78%). The fully adjusted hazard ratios for a 20-μmol/L increase in ascorbate were reduced to 0.88 (95% CI: 0.76, 1.02) for all-cause mortality and 0.84 (95% CI: 0.66, 1.08) for CVD mortality in the subset of those with homocysteine results. Dietary antioxidants were not associated with either all-cause or CVD mortality (**Table 8**).

DISCUSSION

In the present study of an older British population, we found strong associations between plasma vitamin C concentrations and mortality, with individuals having higher concentrations also having considerably reduced mortality. In common with the results of the British NDNS (5) and with other studies, which were conducted mainly in younger population groups (4, 22, 23), we found lower plasma vitamin C concentrations in men, in current smokers, in those of lower socioeconomic status, and in those with lower levels of physical activity. However, we found no clear associations with diabetes, history of CVD or cancer, systolic blood pressure, or BMI, for which associations were reported in some but not all studies, although

TABLE 5
Characteristics of the participants by quintiles of plasma retinol

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P* for trend
Retinol						
Cutoffs (μmol/L)	<1.54	1.54, 1.78	1.78, 1.99	2.00, 2.31	>2.31	
Median (μmol/L)	1.34	1.66	1.89	2.13	2.62	
Mean (μmol/L)	1.30	1.66	1.89	2.14	2.71	
n (unweighted), total *n* = 1199	228	242	245	240	244	
n (weighted)	225.4	235.4	239.9	234.0	248.0	
Age (y)[1]	79.0 (77.2, 81.5)	79.2 (77.1, 81.9)	78.1 (76.7, 81.5)	78.1 (76.3, 81.0)	78.7 (76.6, 81.0)	0.02
Men (%)	49.4	47.2	47.3	36.7	46.7	0.18
Living alone (%)	47.7	38.8	46.3	45.3	44.0	0.60
Homeowner (%)	59.8	63.9	67.1	68.5	64.2	0.09
Systolic blood pressure (mm Hg)[2]	146.2 ± 20.1	150.7 ± 22.6	150.1 ± 20.9	150.5 ± 21.6	150.1 ± 22.0	0.32
Total cholesterol (mmol/L)[2]	5.21 ± 1.12	5.57 ± 1.09	5.78 ± 1.00	6.19 ± 1.12	6.28 ± 1.33	<0.01
HDL cholesterol (mmol/L)[2]	1.21 ± 0.37	1.20 ± 0.40	1.21 ± 0.35	1.24 ± 0.42	1.17 ± 0.35	0.62
BMI (kg/m^2)[2]	26.2 ± 4.8	26.3 ± 4.1	26.3 ± 4.0	26.6 ± 4.2	26.6 ± 4.0	0.26
Current smoker (%)	12.8	10.4	7.5	9.7	10.7	0.20
Exsmoker (%)	51.4	49.8	55.8	50.9	56.8	
Alcohol consumption (drinks/wk)[1]	0 (0, 2)	0 (0, 4)	0 (0, 3)	0 (0, 3)	0 (0, 4)	0.21
Physical activity (units/wk)[1,3]	1.5 (0, 5)	2 (0, 5.75)	4 (1, 7)	2.5 (0, 7)	3 (0, 6)	0.05
Diabetes (%)	6.6	5.5	6.8	7.5	5.2	1.0
History of cardiovascular disease (%)[4]	22.7	22.5	22.4	18.4	32.1	0.11
History of cancer (%)[5]	8.0	8.6	8.9	6.4	7.5	0.48
Supplement user (%)[6]	34.1	45.4	42.9	45.9	48.3	0.01
Dietary vitamin C (mg/d)[1,7]	80.4 (48.3, 121.7)	75.9 (50.1, 10.1)	78.9 (50.8, 123.9)	87.7 (61.7, 118.6)	83.4 (56.9, 123.4)	0.11
Dietary vitamin E (mg/d)[1,7]	8.43 (5.94, 13.54)	8.58 (5.76, 14.77)	8.06 (5.60, 13.01)	8.07 (5.99, 12.79)	7.97 (5.93, 12.27)	0.15
Dietary β-carotene (mg/d)[1,7]	2.20 (1.54, 2.97)	2.18 (1.40, 3.01)	2.09 (1.39, 2.96)	2.06 (1.53, 2.64)	2.13 (1.33, 3.31)	0.84
Dietary intake of retinol (mg/d)[1,7]	0.67 (0.44, 1.28)	0.69 (0.50, 1.73)	0.72 (0.50, 1.78)	0.69 (0.49, 1.62)	0.78 (0.52, 1.84)	0.02
≥ 5 Portions fresh fruit and vegetables/d (%)	36.1	40.2	36.8	42.6	45.5	0.12

[1] Median; interquartile range in parentheses.
[2] $\bar{x}$ ± SD.
[3] Units of activity defined by time and activity level.
[4] Stroke, heart attack, or definite and probable angina on Rose chest pain questionnaire.
[5] Excludes basal cell carcinoma.
[6] Regular user of any supplements.
[7] Dietary intakes do not include supplements.

in inconsistent directions. We observed a positive association between ascorbate and total cholesterol, as in the National Health and Nutrition Examination Survey (23) but in contrast with the Norfolk EPIC study, which reported an inverse association (22). For HDL cholesterol, we also observed a positive association with ascorbate concentrations that was similar to the association reported in some studies (22), including those in elderly persons (4). However, adjustment for these variables only marginally affected our results. Homocysteine concentrations were negatively correlated with ascorbate ($r = -0.27$), but adjustment for homocysteine led to only a small attenuation of the hazard ratios.

The response rate in our study was 75% of those invited; taking into account the original numbers sampled, the response rate was just > 50%, equivalent to that of the Norfolk EPIC cohort of 45% (22). Our respondents were similar both to those randomly selected for the nutrition study and to the participants in the universal arm of the trial and are therefore likely representative of the British elderly in this age range. Ascorbate concentrations in our sample were comparable with those of community-dwelling older persons of similar ages in the British NDNS, in which median values were 36 μmol/L for men and 47 μmol/L for women (5) compared with 35 and 47 μmol/L, respectively, in our study. Our study group, however, included fewer persons with very low concentrations (< 11 μmol/L): 13% of men and 9.5% of women in the present study compared with 19% of men and 17% of women in the NDNS.

TABLE 6
Hazard ratios (95% CI) for all-cause and cardiovascular disease mortality by quintile (Q) of plasma antioxidant referent to the first quintile

	Q1	Q2	Q3	Q4	Q5	*P* for trend
All-cause mortality						
Ascorbate						
Median values (μmol/L)	10.61	24.55	41.65	58.03	79.58	
n = 1115[1] (deaths = 258)	71	64	50	39	34	
Hazard ratios[2]	1	0.87 (0.65, 1.16)	0.53 (0.38, 0.74)	0.48 (0.31, 0.74)	0.43 (0.29, 0.64)	< 0.001
Hazard ratios[3]	1	0.97 (0.71, 1.33)	0.60 (0.44, 0.83)	0.55 (0.34, 0.90)	0.49 (0.32, 0.77)	< 0.001
Hazard ratios[4]	1	0.94 (0.70, 1.28)	0.60 (0.43, 0.83)	0.60 (0.37, 0.98)	0.51 (0.34, 0.78)	< 0.001
Hazard ratios[5]	1	0.96 (0.70, 1.31)	0.59 (0.42, 0.82)	0.61 (0.37, 0.99)	0.51 (0.34, 0.78)	< 0.001
Hazard ratios[6]	1	0.98 (0.72, 1.33)	0.60 (0.43, 0.85)	0.62 (0.38, 1.02)	0.54 (0.34, 0.84)	0.001
CVD or cancer at baseline excluded						
n = 786 (deaths = 150)	44	41	22	23	20	
Hazard ratios[2]	1	0.95 (0.67, 1.36)	0.41 (0.24, 0.68)	0.46 (0.26, 0.80)	0.41 (0.23, 0.75)	< 0.001
Hazard ratios[6]	1	0.94 (0.62, 1.43)	0.45 (0.28, 0.73)	0.54 (0.31, 0.95)	0.51 (0.28, 0.93)	0.004
α-Tocopherol						
Median values (μmol/mmol cholesterol)	2.80	3.32	3.72	4.15	4.95	
n = 1140[1] (deaths = 264)	55	48	55	43	63	
Hazard ratios[2]	1	0.82 (0.56, 1.20)	0.98 (0.62, 1.55)	0.74 (0.48, 1.15)	1.03 (0.68, 1.55)	0.97
Hazard ratios[7]	1	0.97 (0.65, 1.46)	1.10 (0.70, 1.72)	0.79 (0.50, 1.25)	1.03 (0.68, 1.56)	0.80
Hazard ratios[8]	1	1.04 (0.71, 1.53)	1.22 (0.76, 1.96)	0.86 (0.55, 1.34)	1.14 (0.76, 1.72)	0.82
Hazard ratios[9]	1	1.06 (0.72, 1.56)	1.22 (0.76, 1.95)	0.86 (0.55, 1.35)	1.15 (0.77, 1.73)	0.82
Hazard ratios[10]	1	1.06 (0.73, 1.56)	1.27 (0.79, 2.04)	0.89 (0.57, 1.40)	1.21 (0.81, 1.80)	0.61
CVD or cancer at baseline excluded						
n = 809 (deaths = 154)	39	24	29	28	34	
Hazard ratios[2]	1	0.61 (0.36, 1.04)	0.79 (0.47, 1.34)	0.73 (0.42, 1.28)	0.86 (0.50, 1.49)	0.78
Hazard ratios[10]	1	0.81 (0.46, 1.43)	1.08 (0.62, 1.88)	0.97 (0.55, 1.70)	1.09 (0.59, 2.01)	0.65
β-Carotene						
Median values (μmol/L)	0.153	0.261	0.372	0.501	0.772	
n = 1136[1] (deaths = 263)	68	56	48	52	39	
Hazard ratios[2]	1	0.86 (0.61, 1.21)	0.61 (0.42, 0.90)	0.77 (0.56, 1.07)	0.55 (0.33, 0.91)	0.01
Hazard ratios[3]	1	1.00 (0.70, 1.14)	0.75 (0.50, 1.14)	0.97 (0.70, 1.36)	0.68 (0.43, 1.08)	0.12
Hazard ratios[4]	1	0.98 (0.71, 1.36)	0.78 (0.51, 1.20)	1.00 (0.71, 1.41)	0.73 (0.46, 1.14)	0.23
Hazard ratios[5]	1	0.98 (0.71, 1.36)	0.78 (0.51, 1.21)	0.99 (0.70, 1.40)	0.72 (0.45, 1.14)	0.22
Hazard ratios[6]	1	0.99 (0.72, 1.38)	0.79 (0.51, 1.22)	1.03 (0.74, 1.43)	0.76 (0.47, 1.23)	0.34
CVD or cancer at baseline excluded						
n = 806[1] (deaths = 154)	42	27	24	37	24	
Hazard ratios[2]	1	0.77 (0.44, 1.34)	0.56 (0.34, 0.92)	1.03 (0.70, 1.53)	0.64 (0.36, 1.16)	0.36
Hazard ratios[6]	1	0.88 (0.51, 1.51)	0.79 (0.44, 1.41)	1.30 (0.85, 2.00)	0.82 (0.46, 1.45)	0.89
Retinol						
Median values (μmol/L)	1.34	1.66	1.89	2.13	2.62	
n = 1140[1] (deaths = 264)	58	53	49	58	46	
Hazard ratios[2]	1	1.05 (0.67, 1.65)	0.83 (0.51, 1.37)	1.10 (0.71, 1.72)	0.85 (0.56, 1.28)	0.58
Hazard ratios[3]	1	1.15 (0.76, 1.76)	0.90 (0.56, 1.44)	1.26 (0.87, 1.82)	0.92 (0.61, 1.38)	0.83
Hazard ratios[4]	1	1.22 (0.79, 1.88)	1.03 (0.65, 1.63)	1.34 (0.94, 1.91)	0.98 (0.64, 1.49)	0.83
Hazard ratios[5]	1	1.21 (0.79, 1.87)	1.02 (0.64, 1.62)	1.32 (0.93, 1.88)	0.98 (0.65, 1.50)	0.90
Hazard ratios[6]	1	1.25 (0.81, 1.93)	1.03 (0.65, 1.64)	1.36 (0.95, 1.95)	1.02 (0.67, 1.55)	0.79
CVD or cancer at baseline excluded						
n = 809 (deaths = 154)	34	30	32	35	23	
Hazard ratios[2]	1	1.01 (0.56, 1.83)	1.05 (0.56, 1.96)	1.19 (0.65, 2.15)	0.72 (0.40, 1.29)	0.55
Hazard ratios[6]	1	1.32 (0.78, 2.25)	1.32 (0.73, 2.36)	1.32 (0.81, 2.15)	0.87 (0.50, 1.49)	0.76
Cardiovascular disease mortality						
Ascorbate						
Median values (μmol/L)	10.61	24.55	41.65	58.03	79.58	
n (deaths = 113)	34	23	22	16	18	
Hazard ratios[2]	1	0.67 (0.40, 1.12)	0.55 (0.33, 0.91)	0.36 (0.19, 0.67)	0.46 (0.26, 0.83)	0.001
Hazard ratios[3]	1	0.69 (0.37, 1.30)	0.60 (0.36, 1.00)	0.39 (0.19, 0.81)	0.53 (0.27, 1.05)	0.020

(*Continued*)

TABLE 6 (*Continued)*

	Q1	Q2	Q3	Q4	Q5	*P* for trend
Hazard ratios[4]	1	0.69 (0.37, 1.27)	0.62 (0.38, 1.04)	0.46 (0.22, 0.94)	0.57 (0.29, 1.11)	0.046
Hazard ratios[5]	1	0.71 (0.38, 1.32)	0.61 (0.37, 1.01)	0.46 (0.22, 0.96)	0.58 (0.30, 1.13)	0.049
Hazard ratios[6]	1	0.70 (0.38, 1.27)	0.60 (0.35, 1.05)	0.46 (0.22, 0.94)	0.57 (0.29, 1.12)	0.053
CVD or cancer at baseline excluded						
n (deaths = 65)	21	15	8	8	13	
Hazard ratios[2]	1	0.77 (0.46, 1.28)	0.31 (0.12, 0.79)	0.25 (0.10, 0.64)	0.51 (0.24, 1.07)	0.009
Hazard ratios[6]	1	0.77 (0.49, 1.20)	0.33 (0.12, 0.94)	0.29 (0.11, 0.77)	0.62 (0.30, 1.32)	0.05
α-Tocopherol						
Median values (μmol/mmol cholesterol)	2.80	3.32	3.72	4.15	4.95	
n (deaths = 115)	27	24	29	13	22	
Hazard ratios[2]	1	0.79 (0.44, 1.40)	1.08 (0.60, 1.95)	0.50 (0.21, 1.16)	0.74 (0.41, 1.36)	0.20
Hazard ratios[7]	1	0.87 (0.46, 1.66)	1.12 (0.62, 2.05)	0.47 (0.20, 1.12)	0.67 (0.36, 1.24)	0.077
Hazard ratios[8]	1	0.92 (0.48, 1.76)	1.25 (0.66, 2.36)	0.51 (0.21, 1.20)	0.73 (0.39, 1.37)	0.13
Hazard ratios[9]	1	0.95 (0.50, 1.81)	1.24 (0.66, 2.36)	0.51 (0.21, 1.20)	0.73 (0.39, 1.38)	0.12
Hazard ratios[10]	1	0.95 (0.50, 1.81)	1.25 (0.66, 2.37)	0.51 (0.22, 1.19)	0.73 (0.39, 1.37)	0.11
CVD or cancer at baseline excluded						
n (deaths = 67)	20	13	13	9	12	
Hazard ratios[2]	1	0.56 (0.27, 1.15)	0.74 (0.36, 1.54)	0.46 (0.18, 1.17)	0.56 (0.29, 1.09)	0.14
Hazard ratios[10]	1	0.73 (0.34, 1.56)	0.92 (0.43, 1.97)	0.50 (0.18, 1.36)	0.59 (0.26, 1.33)	0.16
β-Carotene						
Median values (μmol/L)	0.153	0.261	0.372	0.501	0.772	
Deaths = 114	31	22	24	20	17	
Hazard ratios[2]	1	0.68 (0.35, 1.33)	0.62 (0.37, 1.04)	0.67 (0.36, 1.23)	0.49 (0.21, 1.13)	0.09
Hazard ratios[3]	1	0.73 (0.38, 1.42)	0.71 (0.40, 1.25)	0.83 (0.43, 1.61)	0.58 (0.24, 1.38)	0.31
Hazard ratios[4]	1	0.72 (0.39, 1.33)	0.76 (0.43, 1.36)	0.87 (0.43, 1.77)	0.63 (0.26, 1.52)	0.47
Hazard ratios[5]	1	0.72 (0.39, 1.32)	0.78 (0.44, 1.37)	0.86 (0.43, 1.74)	0.63 (0.26, 1.54)	0.47
Hazard ratios[6]	1	0.72 (0.39, 1.33)	0.77 (0.44, 1.37)	0.86 (0.44, 1.68)	0.62 (0.25, 1.55)	0.46
CVD or cancer at baseline excluded						
n (deaths = 67)	21	8	13	15	10	
Hazard ratios[2]	1	0.39 (0.13, 1.17)	0.53 (0.28, 1.00)	0.78 (0.38, 1.56)	0.50 (0.18, 1.35)	0.43
Hazard ratios[6]	1	0.38 (0.13, 1.10)	0.77 (0.36, 1.65)	0.94 (0.42, 2.11)	0.54 (0.17, 1.68)	0.72
Retinol						
Median values (μmol/L)	1.34	1.66	1.89	2.13	2.62	
n (deaths = 115)	20	23	23	29	20	
Hazard ratios[2]	1	1.20 (0.67, 2.13)	1.10 (0.60, 2.02)	1.52 (0.85, 2.72)	0.96 (0.51, 1.81)	0.80
Hazard ratios[3]	1	1.29 (0.75, 2.21)	1.16 (0.66, 2.04)	1.63 (0.95, 2.79)	1.01 (0.52, 1.96)	0.71
Hazard ratios[4]	1	1.39 (0.80, 2.44)	1.37 (0.76, 2.44)	1.78 (1.05, 3.01)	1.08 (0.54, 3.01)	0.55
Hazard ratios[5]	1	1.38 (0.78, 2.45)	1.33 (0.74, 2.40)	1.71 (1.01, 2.90)	1.10 (0.56, 2.17)	0.54
Hazard ratios[6]	1	1.40 (0.79, 2.45)	1.34 (0.74, 2.40)	1.73 (1.02, 2.92)	1.11 (0.56, 2.21)	0.54
CVD or cancer at baseline excluded						
n (deaths = 67)	14	12	12	19	10	
Hazard ratios[2]	1	0.86 (0.36, 2.02)	0.92 (0.36, 2.34)	1.26 (0.59, 2.69)	0.66 (0.29, 1.47)	0.75
Hazard ratios[6]	1	1.06 (0.48, 2.37)	1.18 (0.45, 3.09)	1.39 (0.68, 2.84)	0.83 (0.32, 2.15)	0.92

[1] Participants with complete data on all variables in the models.
[2] Adjusted for age and sex.
[3] Adjusted as for model 2 and additionally for BMI, cholesterol, systolic blood pressure, smoking, alcohol, diabetes, and history of cardiovascular disease or cancer.
[4] Adjusted as for model 3 and additionally for physical activity.
[5] Adjusted as for model 4 and additionally for housing tenure.
[6] Adjusted as for model 5 and additionally for vitamin supplementation.
[7] Adjusted as for model 2 and additionally for BMI, systolic blood pressure, smoking, alcohol, diabetes, and history of cardiovascular disease or cancer.
[8] Adjusted as for model 7 and additionally for physical activity.
[9] Adjusted as for model 8 and additionally for housing tenure.
[10] Adjusted as for model 9 and additionally for vitamin supplementation.

TABLE 7
Hazard ratio per 20-μmol/L change in plasma ascorbate

	All-cause mortality		Cardiovascular disease mortality	
	Ratio (95% CI)	*P*	Ratio (95% CI)	*P*
All participants (n = 1115)[1]				
Model 1[2]	0.77 (0.69, 0.85)	<0.001	0.76 (0.64, 0.90)	0.001
Model 2[3]	0.80 (0.71, 0.89)	<0.001	0.79 (0.66, 0.95)	0.013
Model 3[4]	0.81 (0.73, 0.90)	<0.001	0.82 (0.69, 0.99)	0.034
Model 4[5]	0.82 (0.73, 0.92)	0.001	0.82 (0.68, 0.99)	0.038
Excluding those with a history of cardiovascular disease or cancer at baseline (n = 786)[6]				
Model 1[2]	0.72 (0.62, 0.84)	<0.001	0.69 (0.54, 0.88)	0.003
Model 2[7]	0.75 (0.64, 0.87)	<0.001	0.71 (0.55, 0.91)	0.008
Model 3[8]	0.77 (0.67, 0.89)	<0.001	0.76 (0.60, 0.96)	0.021
Model 4[9]	0.76 (0.66, 0.89)	<0.001	0.74 (0.59, 0.94)	0.015
Norfolk EPIC study[10]	0.80 (0.73, 0.88)	<0.001	0.70 (0.60, 0.82)	<0.001

[1] Participants with complete data on all variables in the models. n = 258 deaths and 113 deaths, respectively.
[2] Adjusted for age and sex.
[3] Adjusted for age, sex, BMI, cholesterol, systolic blood pressure, smoking, alcohol, diabetes, history of cardiovascular disease, and history of cancer.
[4] Adjusted as for model 3 and additionally for physical activity and housing tenure.
[5] Adjusted as for model 4 and additionally for vitamin supplementation.
[6] n = 150 deaths and 65 deaths, respectively.
[7] Adjusted for age, sex, BMI, cholesterol, systolic blood pressure, smoking, alcohol, and diabetes.
[8] Adjusted as for model 6 and additionally for physical activity and housing tenure.
[9] Adjusted as for model 7 and additionally for vitamin supplementation.
[10] From reference 2.

Ascorbate concentrations in the present study were also lower than in the Norfolk EPIC cohort (which had a mean age 60 y), but the association with mortality was similar (Table 7). The Norfolk EPIC investigators were unable to adjust for socioeconomic status or physical activity because they did not have this information. We showed that taking these variables into account had little effect on the results.

We found no clear evidence from the dietary data of an association between vitamin C or other dietary antioxidants and all-cause or CVD mortality. Although plasma antioxidant concentrations were correlated with the corresponding dietary antioxidant intakes, our correlations were lower than those reported by others [in our study the correlation between ascorbate and dietary vitamin C was 0.3 compared with 0.6 in the NDNS (5) and 0.4 in the Norfolk EPIC study (22)]. Those 2 studies used 4-d weighed intakes or 7-d diet histories, respectively, whereas our source of dietary vitamin intakes was an FFQ that asked about usual food intake over the previous year. The median time between blood collection and completion of the questionnaire in our study was 1 mo, so it is unlikely that the weaker correlations were substantially affected by this time difference. The Norfolk EPIC investigators also reported a correlation of 0.28 for ascorbate with dietary vitamin C intakes derived from an FFQ (24) and concluded there would be substantial measurement error in estimates derived from FFQs. Our experience also suggests that FFQs may not reliably categorize dietary antioxidant intakes in older age groups. Compared with the subjects of the NDNS, both the men and the women in our study had higher dietary intakes of vitamin C (72 mg/d in men and 85 mg/d in women compared with 50 and 43 mg/d, respectively, for the equivalent sample in the NDNS). Our respondents may have overreported their intakes, because plasma concentrations were similar in the 2 samples. We did

TABLE 8
Hazard ratios (95% CI) by quintile (Q) of dietary antioxidant referent to the first quintile[1]

Mortality	Q1	Q2	Q3	Q4	Q5	*P*
All-cause mortality						
Vitamin C	1	0.92 (0.59, 1.45)	1.15 (0.72, 1.82)	0.87 (0.52, 1.45)	0.88 (0.56, 1.39)	0.57
Vitamin E	1	0.80 (0.50, 1.26)	0.81 (0.43, 1.53)	1.03 (0.70, 1.50)	0.70 (0.41, 1.18)	0.41
β-Carotene	1	1.06 (0.72, 1.56)	1.07 (0.75, 1.53)	0.88 (0.61, 1.27)	0.88 (0.61, 1.27)	0.97
Retinol	1	0.98 (0.72, 1.34)	0.80 (0.46, 1.37)	0.76 (0.52, 1.10)	0.73 (0.50, 1.09)	0.053
Cardiovascular disease mortality						
Vitamin C	1	1.24 (0.72, 2.14)	1.39 (0.71, 2.69)	1.13 (0.63, 2.02)	0.91 (0.54, 1.57)	0.69
Vitamin E	1	0.36 (0.16, 0.80)	0.41 (0.17, 0.97)	0.83 (0.44, 1.54)	0.47 (0.26, 0.88)	0.39
β-Carotene	1	1.06 (0.60, 1.96)	1.07 (0.62, 1.82)	0.90 (0.48, 1.70)	1.32 (0.89, 1.96)	0.40
Retinol	1	0.74 (0.46, 1.19)	0.75 (0.33, 1.70)	0.78 (0.42, 1.46)	0.80 (0.47, 1.36)	0.55

[1] Adjusted for age, sex, total energy intake, BMI, cholesterol, systolic blood pressure, smoking, alcohol, diabetes, history of cardiovascular disease or cancer, supplement use, physical activity, and housing tenure.

not find strong evidence for associations for α-tocopherol, β-carotene, or retinol with mortality.

The limited evidence for an association between plasma antioxidant concentrations and mortality in older persons is more convincing for vitamin C than for other antioxidants. In a 20-y follow-up of participants in the first Diet and Nutrition Study of the British Elderly, lower death rates from stroke (30% reduction) were found in those with ascorbate concentrations $>$ 28 μmol/L (10). A study in a Massachusetts population (with a mean age of 72 y) showed a lower risk of total mortality and a trend for CVD mortality in the highest and combined middle fifths of ascorbate compared with the lowest, smaller and nonsignificant protective effects for total plasma carotenoids (8), but no association with α-tocopherol. A 7-y follow-up of a Dutch cohort of persons aged 65–85 y found the highest risks for total plasma carotenoids and mortality, specifically, for β-cryptoxanthin and lutein but not for β-carotene, lycopene, or α-tocopherol (11), whereas a Finnish study found no effect of plasma α-tocopherol (12). Ascorbate was not measured in either study. We did not have funds to measure carotenoids other than β-carotene.

We found strong positive correlations between ascorbate concentrations and reporting of consumption of $\geq$ 5 fresh fruit and vegetables daily. The main foods associated with plasma vitamin C concentrations in our population were oranges, broccoli, and sweet peppers. It is therefore possible that the association between ascorbate and mortality was, at least in part, due to other dietary micronutrients.

Studies showing associations between plasma concentrations and outcomes may be prone to biases resulting from reverse causation, ie, lower concentrations of antioxidant vitamins reflect depletion as a result of concomitant disease, itself a marker for subsequent mortality and morbidity. It is unlikely that reverse causation explains our results, however: the association was linear across the ascorbate distribution, the estimates agreed well with those found in prospective studies of younger cohorts, and the associations remained after the exclusion of those with prior CVD or cancer. The concentrations of vitamin C observed at older ages along with the increased stresses on the antioxidant defense system has led to concerns that concentrations in older populations are too low (25) and to recommendations to increase the dietary allowance for vitamin C (26). The older British population is a special worry because ascorbate concentrations, which are generally low in both the British population and in the older population, are low compared with concentrations in some other countries. The lowest quintile of plasma ascorbate at highest risk in the Massachusetts elderly study ($<$ 52 μmol/L) would have included $\approx$60% of our study population, whereas $<$ 10% would have been in the most protected quintile ($>$ 89 μmol/L) (8).

A key question is how to increase concentrations of ascorbate in older age groups. Enthusiasm for vitamin supplementation has been tempered by the negative results from randomized trials, which were conducted predominantly in middle-aged populations, although the largest trial did include persons up to the age of 80 y (27). Supplementation with chemical forms of a few antioxidants cannot substitute for the richness and variety of dietary sources of antioxidants. Antioxidants act in synergy, and many antioxidants (of which vitamin C is one of the most powerful) appear to be involved in a cascade of radical-quenching reactions (28). Thus, the best recommendation for older persons, as for middle-aged and younger persons, is to maintain a diet rich in a variety of antioxidant micronutrients. At older ages, however, several factors, such as reduced appetite and taste, poor dentition, physical and economic barriers to food sources, and lack of motivation, present formidable challenges to this strategy (29). The evidence for the success of interventions to promote healthy eating in elderly persons is weak, at best, and nonexistent for the United Kingdom (30). More attention needs to be given to addressing the barriers to the adoption of healthy diets in old age.

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AEF and PSS designed the nutrition study. EB coordinated the study and carried out the statistical analyses. AEF and EB specified the analyses, and AEF wrote the paper. PSS and EB contributed critical comments to the paper. None of the authors had a conflict of interest to report.

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