TABLE 1
Estimated daily energy intake and energy distribution from macronutrients across empirically derived dietary clusters for Whitehall II participants in 1991–1993

	Dietary patterns			
	Unhealthy	Sweet British	Mediterranean-like	Healthy
Participants (*n*)	2665	1042	1361	2663
Energy intake (MJ)				
Men	8.23 ± ±2.15[1]	11.53 ± 2.35	10.43 ± 2.34	9.16 ± 2.35
Women	7.31 ± 2.15	10.56 ± 2.47	9.69 ± 2.11	7.75 ± 2.15
Energy distribution (%)				
Protein	16.8 ± 3.4	15.2 ± 2.4	16.3 ± 2.7	17.3 ± 3.5
Carbohydrate	46.8 ± 6.7	48.6 ± 5.3	46.5 ± 5.5	50.4 ± 6.2
Alcohol	4.3 ± 5.6	3.6 ± 3.7	6.1 ± 4.9	2.8 ± 3.8
Total fat	32.1 ± 5.4	32.6 ± 4.3	31.1 ± 4.6	29.5 ± 5.5
Saturated fat	13.0 ± 3.2	13.5 ± 2.7	11.9 ± 2.6	10.6 ± 2.6
Monounsaturated fat	10.0 ± 1.8	9.9 ± 1.5	9.6 ± 1.6	8.7 ± 1.9
Polyunsaturated fat	6.0 ± 2.0	5.8 ± 1.7	6.2 ± 1.8	6.9 ± 2.3

[1] $\bar{x}$ ± SD (all such values).

diabetes incidence. The relative proportions of participants and events within each of these 2 clusters are important to an interpretation of the results obtained at this stage of follow-up.

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Erratum

Agudo A, Cabrera L, Amiano P, et al. Fruit and vegetable intakes, dietary antioxidant nutrients, and total mortality in Spanish adults: findings from the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC–Spain). Am J Clin Nutr 2007;85:1634–42.

In Table 2 (page 1638), the units for the 4 indexes of Total antioxidant capacity were incorrectly shown as “mmol TE.” They should have been “μmol TE.” All other analyses of these variables were done by quartile, taking their ranks instead of absolute values, and all of those results are correct.

Fruit and vegetable intakes, dietary antioxidant nutrients, and total mortality in Spanish adults: findings from the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain)[1–3]

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ABSTRACT

Background: Epidemiologic data suggest that persons with diets rich in fruit and vegetables are at a lower risk of several chronic diseases and mortality than are persons with diets poor in fruit and vegetables. Often, this effect is attributed to antioxidant micronutrients found in plant foods.

Objective: We aimed to assess the relation of mortality to the consumption of fruit, vegetables, and other plant foods and to the dietary intake of vitamin C, vitamin E, and carotenoids.

Design: The study was a prospective study in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition. During 6.5 y of follow-up, 562 deaths occurred in 41 358 subjects aged 30–69 y. Proportional hazards regression analysis was used to assess the relation between dietary factors and total mortality.

Results: After adjustment for age, sex, and several potential confounders, the hazard ratio for the highest versus the lowest quartile of consumption was 0.79 (95% CI: 0.62, 1.00; *P* for trend = 0.029) for fresh fruit, 0.72 (0.56, 0.91; *P* for trend = 0.006) for root vegetables, and 0.77 (0.60, 0.98; *P* for trend = 0.015) for fruiting vegetables (ie, vegetables that contain the "fruit" part of the plant, the seeds). The corresponding figures for antioxidant nutrients were 0.74 (0.58, 0.94; *P* for trend = 0.009) for vitamin C, 0.68 (0.53, 0.87; *P* for trend = 0.006) for provitamin A carotenoids, and 0.65 (0.51, 0.84; *P* for trend 0.001) for lycopene. The effect of vitamin C and provitamin A disappeared after adjustment for total antioxidant capacity in plant foods.

Conclusions: A high intake of fresh fruit, root vegetables, and fruiting vegetables is associated with reduced mortality, probably as a result of their high content of vitamin C, provitamin A carotenoids, and lycopene. Antioxidant capacity could partly explain the effect of ascorbic acid and provitamin A but not the association with lycopene. *Am J Clin Nutr* 2007;85:1634–42.

KEY WORDS Mortality, fruit, vegetables, antioxidants, cohort studies

INTRODUCTION

It is widely accepted that fruit and vegetables are important components of a healthy diet and that their consumption helps prevent a wide range of diseases. Epidemiologic data have shown that persons with a high consumption of fruit and vegetables are at a lower risk of several types of cancers (1) and of cardiovascular disease (CVD) and stroke (2) than are persons with a low consumption of fruit and vegetables. There have been attempts to identify the specific components that are responsible for such effects. One of the most common hypotheses points to the ability of antioxidant nutrients, such as vitamin C, vitamin E, and carotenoids, to prevent oxidative damage, which is thought to be involved in the pathophysiology of many chronic diseases (3). However, despite the substantial body of evidence, from observational studies, of the beneficial effects of diets rich in the antioxidant nutrients found in plant foods, trials of supplementation with any single nutrient or combination of nutrients have not shown any benefit of primary or secondary prevention of CVD and have shown inconsistent or discouraging results regarding cancer (3).

Although beneficial effects of plant foods have mainly been reported for cancer, CVD, and other chronic conditions, the potential effects of fruit, vegetables, and antioxidant nutrients have been considered in several prospective studies of overall mortality. An increment of 230 g vegetables/d and 200 g fruit/d was associated with a significant decrease in mortality of 12% and

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18%, respectively, in a Greek population (4). A high consumption of fruit and vegetables (considered together) was also associated with reduced all-cause mortality in white and African American adults in 3 communities in the United States (5). Lower mortality was associated with greater adherence to a Mediterranean diet in elderly from several European countries (6) and with the recommended foods behavior score (RFBS) in the National Health Interview Surveys from the United States (7); both scores included high intakes of fruit and vegetables. A dietary oxidative balance score including vitamin C and β-carotene was also associated with lower mortality in male Belgian smokers (8). In contrast, no differences in mortality were seen between vegetarians and nonvegetarians in a British population (9). Furthermore, plasma concentrations of ascorbic acid were significantly and inversely associated with mortality in 2 British cohorts (10, 11) and in one cohort in the United States (12). Plasma carotene was also associated with lower mortality in the elderly populations of several European countries (13), whereas, in Dutch elderly, the protective effect was found with oxygenated carotenoids (β-cryptoxanthin, lutein, and zeaxanthin) but not carotene (14).

Our group previously showed that the adult Spanish population has a higher consumption of both fruit and vegetables than do the populations of several other European countries (15). In the same population, we found that vegetables and fruit are the sources of nutrients with redox properties: fruit, mainly citrus, accounts for half of the total vitamin C intake, whereas vegetables account for almost 70% of provitamin A carotenoids, and both, together with nuts, seeds, and vegetable oils, substantially contribute to total vitamin E intake (16). In this study, we aimed to assess the relation of overall mortality in the adult Spanish cohort from the European Prospective Investigation into Cancer and Nutrition (EPIC-Spain) to the consumption of fruit, the main types of vegetables, and other plant foods and the relation to the dietary intakes of vitamin C, vitamin E, and carotenoids. Moreover, we tried to evaluate the extent to which the potential beneficial effects of such vitamins may be explained by the total antioxidant capacity (TAC) measured in foods of plant origin.

SUBJECTS AND METHODS

Study design and population

The study population is the Spanish cohort of EPIC, a large prospective European study investigating the relation between diet and cancer (17). The EPIC-Spain cohort included 41 440 healthy volunteers aged 29–69 y who were recruited between 1992 and 1996 in 5 regions in Spain—Asturias, Guipúzcoa, and Navarra in the north and Granada and Murcia in the south. The participation rate varied among centers from 55% to 60%. For each participant, information on usual diet, a questionnaire on lifestyle factors, anthropometric measurements, and a blood sample were obtained at baseline. To ascertain the vital status, annual record linkages were carried out with the national databases of the Instituto Nacional de Estadística. For each cohort member identified as having died during the study, the date and cause of death were collected. For this analysis, the follow-up for vital status was complete until 31 December 2002; the mean follow-up was 6.5 y. After the exclusion of 82 subjects because of implausible dietary information, the final population studied consisted of 41 358 subjects (15 610 M, 25 748 F), of whom 562 died during the follow-up period.

All subjects provided written informed consent. The study protocol was approved by the Ethics Committee of the Bellvitge University Hospital.

Dietary information

Information on usual intake over the previous year was collected by means of a computerized questionnaire that was based on a previously validated dietary history method (18, 19) and administered by trained interviewers. It was structured by meals, and it recorded the frequency of consumption of foods eaten at least twice a month, taking seasonal variation into account; although the questionnaire was open, it contained a list of the most common foods and recipes. In addition to frequency, the method of preparation and the amount of each food item consumed were reported; portion size was assessed by means of a photo series, natural units, and household measures. The final amount of each food consumed was reported as daily intake (in g). Four groups of plant foods were considered: vegetables, legumes, potatoes and other tubers, and fruit. Vegetables were classified as total vegetables and then divided into 5 main subgroups: leafy vegetables, fruiting vegetables (ie, vegetables that contain the "fruit" part of the plant, the seeds), root vegetables, cabbage family, and onion and garlic. The total fruit group included nuts, seeds, and olives, but the main subgroup largely consisted of fresh fruit, which accounted for ≈90% of total fruit intake. A detailed description of the classification and the main foods included in each group or subgroup was presented elsewhere (15).

Data on the vitamin C, vitamin E, β-carotene, α-carotene, lycopene, lutein, β-cryptoxanthin, and zeaxanthin composition of foods were obtained from a computerized database of >700 food items compiled for EPIC in Spain (20), although values for some carotenoids were also obtained from other sources (21, 22). Provitamin A carotenoid intake was expressed as μg β-carotene equivalents/d (1 β-carotene equivalent = 1 β-carotene + 0.5 α-carotene + 0.5 β-cryptoxanthin). Data on TAC from plant foods were gathered from published databases that provided the antioxidant capacity measured in foods by 4 different assays: total radical–trapping antioxidant parameter (TRAP), ferric-reducing antioxidant power (FRAP), trolox equivalent antioxidant capacity (TEAC) (23), and oxygen radical absorbance capacity (ORAC) (24).

Lifestyle and other factors

Information on lifestyle and other factors was obtained by means of personal interview, and measurements of height and weight were taken at the time of recruitment. Body mass index (BMI; in kg/m^2) was calculated. Subjects were classified as lean (below normal weight), normal-weight, overweight, or obese (BMIs of 20, 25, and 30 were used as cutoffs). Education was categorized into 4 levels, from uncompleted primary school to university. The physical activity section consisted of questions on occupational and leisure activities. Current job was classified as sedentary, standing, manual, or heavy manual work. Leisure activities included questions on time spent during the past year walking, cycling, gardening, practicing hobbies, sports, and housework. A metabolic equivalent (MET) defined as the ratio of a working metabolic rate to a standard resting metabolic rate of ($4184\ kJ \cdot kg^{-1} \cdot h^{-1}$), was assigned to each reported activity (25). The mean number of hours per week of each activity was estimated and then multiplied by the appropriate values to obtain

MET-h/wk of activity. A combination of occupational activity with quartiles of MET-h/wk week was used to classify subjects as inactive, moderately inactive, moderately active, or active. Subjects were classified according to their smoking habits as never smokers of any type of tobacco products, exclusive smokers of pipe or cigars at any time during their lifetime, and cigarette smokers; the latter were further classified as former or current smokers at the time of recruitment. Finally, daily alcohol intake (in g) was obtained from the information on the consumption of alcoholic beverages included in the diet history.

Statistical analysis

Because the dietary intakes of fruit, vegetables, other plant foods, and nutrients and TAC indicators had a right-skewed distribution, the median and the interquartile range (IQR) were used to describe those variables. Furthermore, all the variables were categorized into quartiles, and we calculated the mean of each quartile to obtain a better description of the range and variation of the dietary intake of antioxidant foods and nutrients in the study population. The association between dietary variables and mortality was assessed by means of the hazard ratio (HR) by using the Cox proportional hazards model (26). Age was used as the primary time variable, with age at recruitment as the entry time and age at the date of death or the end of follow-up (31 December 2002), whichever came first, as the exit time. All the models were stratified by center. The assumption of proportional hazards over time was assessed by a test based on scaled Schoenfeld residuals. To compare models that are not nested, we used the Akaike's information criterion (AIC) that penalizes the deviance of each model to reflect the number of estimated parameters. The preferred model is the one with the smallest AIC value; however, there is no a statistical test to compare ≥2 AIC. The HR with corresponding 95% CIs was estimated for each quartile of dietary variables (foods, nutrients, and TAC indicators) by using the lowest quartile as the reference. Trend tests were calculated on the basis of quartile-based scores 1–4 used as continuous variables. Furthermore, all the dietary variables were also analyzed as continuous, either in natural units (g/d) or after $\log_2$ transformation. The models with the log-transformed variable showed always better fit to the data, and thus only the HRs for the log-transformed variable are presented. The natural logarithm is the most common transformation used to normalize right-skewed data; however we used a $\log_2$ transformation because it produces the same normalizing effect, but the HR is more easily interpretable because it corresponds to the reduction of mortality for doubling the intake.

The association of mortality with foods and antioxidant nutrients was assessed separately for men and women, and interaction terms of the main dietary variables with sex were estimated; because no modification of these associations was observed, all the analyses are adjusted for sex. In addition, all of the models included terms for educational level, BMI, physical activity, cigarette smoking, and alcohol consumption. These factors are potential determinants of mortality, and all have been shown to be associated with fruit and vegetable intakes in the same population (27). Thus, they may act as confounders of any relation between mortality and antioxidant foods or nutrients. All models including dietary variables were further adjusted for total energy intake; although the foods or nutrients considered do not contribute substantially to caloric intake, total energy was included partly to control for the error in the estimated food intake due to correlation between errors in the estimation of different dietary components (28). All the analyses were conducted by using STATA/SE statistical software (version 9.0; StataCorp LP, College Station, TX).

RESULTS

During the follow-up period, a total of 268 825 person-years were accrued by the 41 358 study participants, and 562 deaths occurred, of which 295 were due to cancer and 123 to CVD. Of the other 144 deaths, 66 were due to external causes (mainly accidents), and 31 were due to diseases of the respiratory or digestive system. The age at recruitment ranged from 39 to 69 y [$\bar{x}$ age: 49.3 y (50.8 in men and 48.4 in women)]. A description of the main features of our study population and its mortality experience is shown in **Table 1**. Significantly lower mortality was seen in women than in men and in subjects with the highest educational level than in those with the lowest educational level; the risk of dying was 71% higher for current smokers than for never smokers. More active people seem to have a lower mortality, although the estimates were not significant. No clear pattern of mortality was found for BMI or alcohol intake.

Subjects from our population consumed a daily average of ≈250 g vegetables and >300 g fruit (**Table 2**). This consumption is by far larger than the average Spanish consumption of potatoes and legumes. The list of subgroups of vegetables is not exhaustive, and only the main types are shown; however, the 5 subgroups included account for 85% of total vegetable intake. For the 4 groups of plant foods considered (total vegetables, potatoes, legumes, and total fruit), the intake of subjects in the highest quartile is between 5 and 8 times as high as the corresponding intake in the lowest quartile. For antioxidant nutrients and TAC from plant foods, the intake in the highest quartile is ≈4 times as high as that in the first quartile and approximately twice the median consumption of the population.

The association between mortality and plant food groups and subgroups after adjustment for age, sex, education, BMI, physical activity, cigarette smoking, alcohol consumption, and total energy intake is shown in **Table 3**. A clear dose-response relation was evident for reduced mortality with increasing intake of fruiting and root vegetables (mostly tomatoes and carrots, respectively). There was a significant association both when intake was categorized into quartiles and when it was entered into the model as a continuous variable after $\log_2$ transformation. There was a significant decrease in mortality for increased intake of total vegetables as a continuous variable, but there was not a clear dose-response relation. No clear patterns were seen for other subgroups, although an inverse relation with leafy vegetable consumption is suggested. For fruit, mainly the subgroup of fresh fruit, there was a significant trend for a reduction of mortality with increased consumption. There was no association with the intakes of potatoes and legumes. The intake of every group was also analyzed as a continuous variable in natural units (g/d), but the fit was better for the $\log_2$-transformed variable. Given that, in some cases, the association was weaker for the highest levels of intake—ie, the HR for the fourth quartile was higher than that for the third quartile—a quadratic term was entered into the model when food intake was analyzed as a continuous variable in natural units (g/d). Nevertheless, the models with the food intake variable after $\log_2$ transformation always yielded the best fit.

TABLE 1
Mortality in the EPIC-Spain cohort (aged 30–69 y) according to demographic, anthropometric, and lifestyle variables[1]

Characteristic	Proportion of cohort (n = 41 358)	Deaths (n = 562)	HR (95% CI)[2]	P for trend
	%	n		
Sex				
Male	37.7	350	1.00	
Female	62.3	212	0.54 (0.41, 0.70)	
Education				
Primary not complete	34.7	229	1.00	
Primary	38.9	212	0.99 (0.81, 1.22)	
Secondary	14.8	74	0.86 (0.65, 1.14)	
University	11.6	43	0.67 (0.48, 0.96)	0.019
BMI				
Below normal, <20	0.7	6	2.20 (0.96, 5.04)	
Normal, ≥20 and <25	21.5	99	1.00	
Overweight, ≥25 and <30	47.7	252	0.72 (0.56, 0.91)	
Obese, ≥30	30.1	205	0.85 (0.66, 1.10)	0.52[3]
Physical activity				
Inactive	13.2	104	1.00	
Moderately inactive	21.0	165	1.01 (0.79, 1.30)	
Moderately active	26.8	153	0.85 (0.65, 1.11)	
Active	38.9	140	0.80 (0.58, 1.09)	0.064
Cigarette smoking				
Never smoker	55.7	248	1.00	
Former smoker	18.6	132	1.26 (0.98, 1.60)	
Current smoker	23.3	164	1.71 (1.36, 2.15)	
Cigar or pipe exclusively	2.5	17	0.79 (0.47, 1.33)	<0.001[4]
Alcohol				
0 g/d	37.7	180	1.00	
<10 g/d	26.9	113	0.81 (0.64, 1.03)	
>10 and <20 g/d	10.9	59	0.81 (0.59, 1.11)	
≥20 and <40 g/d	11.8	82	0.85 (0.64, 1.14)	
≥40 g/d	12.8	128	0.98 (0.75, 1.29)	0.70

[1] EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio.
[2] Derived by Cox regression and stratified by center after adjustment for age (time axis), and mutually adjusted for all variables in the table.
[3] Estimated with categories ordered as below normal, normal, overweight, and obese.
[4] Estimated by using only 3 categories (never, former, or current smoker); exclusive smokers of cigar or pipe were not taken into account.

The relation between total mortality and antioxidant nutrient intakes and TAC from plant foods intake is shown in **Table 4**. Vitamin C is inversely associated with the risk of death, with significant estimates for the third and fourth quartiles and a significant trend both for the categorized or continuous ($\log_2$-transformed) variables, whereas there was no association with dietary consumption of vitamin E. There was also an inverse association with mortality for provitamin A carotenoids (α- and β-carotene and β-cryptoxanthin) and for lycopene and total carotenoids, whereas no association was found for lutein and zeaxanthin. All of the indicators of TAC from plant food intake were associated with a reduced mortality with similar patterns. These results are not surprising, because all of these variables are highly correlated: pairwise correlation coefficients between TRAP, FRAP, and TEAC are 0.99, and correlation coefficients between ORAC and the other 3 indicators range from 0.75 to 0.82. TRAP was selected as the indicator of TAC from plant foods because it showed the best fit as given by its lowest AIC. Both for TAC and most antioxidant nutrients (except lycopene), the dose-response relation seems not to be linear: there is no reduction in mortality beyond the third quartile, and, in many cases, the HR for the fourth quartile is actually higher than that for the third quartile, which suggests a U-shaped relation. Introduction of a quadratic term improved the model as compared with the linear relation, but the model with the lowest AIC was always the one with $\log_2$ transformation of the continuous variable (results not shown).

Given that most antioxidant nutrients have common sources and are likely to be correlated, we tried to find the best reduced model accounting for the effects of antioxidant nutrients on total mortality—ie, the model having the best fit to the data with the smallest number of parameters (**Table 5**). From the results mentioned above, the 3 carotenoids with provitamin A activity (α-, β-carotene, and β-cryptoxanthin) are associated with lower mortality; the model with a single variable for total provitamin A activity measured as β-carotene equivalents (model 2) showed better fit (lower AIC) than the one including the tree carotenoids (model 1). Among carotenoids other than provitamin A, only lycopene showed a significant effect, whereas total carotenoids were also strongly associated with lower mortality. Although the difference in AIC was small, the model with total carotenoids only (model 4) had a worse fit than the one including provitamin A and lycopene (model 3). Thus, model 3 best reflects the effect of carotenoids on mortality. Vitamin C was strongly associated with reduced mortality as well, but the addition of vitamin C to provitamin A and lycopene (model 5) did not produce an improvement in terms of AIC. Furthermore, the effects of both

TABLE 2
Daily intake of selected foods groups or subgroups, vitamins, and carotenoids and total antioxidant capacity in the EPIC-Spain cohort[1]

	Median	Interquartile range	Mean (by quartile)			
			Q1	Q2	Q3	Q4
Food group or subgroup (g)						
Leafy vegetables	53.1	69.8	12.1	38.6	71.8	155.7
Fruiting vegetables	89.1	91.8	28.1	69.2	113.2	208.7
Root vegetables	3.9	7.2	0.4	2.7	5.9	24.3
Cabbage family	1.2	9.4	0.0	1.9	9.2	42.5
Onion and garlic	18.1	20.9	5.7	13.7	24.0	43.6
Vegetables, total	224.2	186.2	92.9	183.2	272.0	453.3
Legumes	45.1	44.6	13.5	35.7	56.1	103.7
Potatoes and other tubers	70.1	62.7	24.4	56.4	86.4	149.8
Fresh fruit	275.8	271.0	73.2	225.0	345.7	624.5
Fruit, total	285.3	272.1	79.6	233.0	355.0	634.0
Nutrients						
Vitamin C (mg)	137.2	96.9	64.8	115.8	161.8	261.3
Vitamin E (mg)	8.5	6.1	4.9	7.4	10.2	19.1
β-Carotene (μg)	1678.6	1329.1	830.4	1405.7	2032.7	3707.2
α-Carotene (μg)	146.2	212.5	43.6	109.4	204.5	696.3
β-Cryptoxanthin (μg)	495.4	652.3	91.4	362.8	668.5	1418.3
Provitamin A (μg)[2]	1547.6	1224.9	698.3	1279.0	1867.8	3210.8
Lutein (μg)	547.1	560.1	221.3	439.0	698.9	1722.9
Zeaxanthin (μg)	109.7	106.0	40.5	87.7	137.9	260.9
Lycopene (μg)	1797.6	1725.3	621.8	1425.1	2255.1	4047.4
Total carotenoids (μg)	5274.5	3735.6	2632.3	4466.8	6247.5	10182.8
Total antioxidant capacity						
FRAP (mmol FE)	5931	4395	2668	4964	7064	11325
TRAP (mmol TE)	1804	918	817	1514	2138	3395
TEAC (mmol TE)	2138	1651	918	1773	2563	4201
ORAC (mmol TE)	11139	7567	5372	9447	13073	20438

[1] EPIC, European Prospective Investigation into Cancer and Nutrition; FRAP, ferric-reducing antioxidant power; TRAP, total radical–trapping antioxidant parameter; TEAC, trolox equivalent antioxidant capacity; ORAC, oxygen radical absorbance capacity; FE, Fe2-equivalents; TE, trolox-equivalents.
[2] As β-carotene equivalents; β-carotene + 0.5 α-carotene + 0.5 β-cryptoxanthin.

provitamin A and vitamin C became nonsignificant because of their high correlation (r = 0.73). To ascertain the extent to which the effect of the 3 relevant nutrients could be explained by the antioxidant capacity of plant foods, we added a term for TRAP to models including these nutrients (Table 5). The inclusion of TRAP improved the fitting, as can be seen from the fact that models 6–9 in the table had lower AIC values than did models 1–5. On the other hand, the protective effect of both provitamin A and vitamin C disappeared after the inclusion of TRAP in models with each single nutrient (models 6 and 8, respectively), whereas the effect of lycopene remained almost unchanged and significant (model 7). The same pattern held when TRAP was added to the model including the 3 nutrients altogether (model 9). Thus, a model with lycopene

TABLE 3
Association between mortality and consumption of fruit and vegetables in the EPIC-Spain cohort[1]

Food groups or subgroups	HR (95% CI) by quartile[2] Q2	Q3	Q4	P for trend	HR (95% CI) continuous[2] ($\log_2$)
Vegetables (total)	0.75 (0.59, 0.96)	0.81 (0.64, 1.03)	0.84 (0.66, 1.06)	0.23	0.91 (0.83, 0.99)
Leafy vegetables	0.87 (0.69, 1.11)	0.79 (0.62, 1.00)	0.79 (0.62, 1.02)	0.046	0.96 (0.91, 1.01)
Fruiting vegetables	0.93 (0.74, 1.17)	0.78 (0.61, 0.99)	0.77 (0.60, 0.98)	0.015	0.93 (0.87, 0.98)
Root vegetables	0.82 (0.65, 1.10)	0.80 (0.63, 1.00)	0.72 (0.56, 0.91)	0.006	0.94 (0.89, 1.00)
Cabbage family	0.89 (0.66, 1.20)	0.91 (0.70, 1.17)	1.02 (0.81, 1.29)	0.94	1.00 (0.96, 1.04)
Onion and garlic	1.13 (0.89, 1.43)	0.93 (0.73, 1.19)	0.82 (0.64, 1.06)	0.047	0.97 (0.90, 1.05)
Legumes	0.95 (0.75, 1.20)	0.81 (0.62, 1.05)	0.91 (0.71, 1.17)	0.37	0.96 (0.91, 1.02)
Potatoes and tubers	0.99 (0.78, 1.26)	0.80 (0.61, 1.03)	0.94 (0.72, 1.22)	0.38	0.95 (0.89, 1.01)
Fruit (total)	0.83 (0.66, 1.05)	0.74 (0.58, 0.94)	0.82 (0.64, 1.04)	0.061	0.96 (0.92, 1.00)
Fresh fruit	0.87 (0.69, 1.09)	0.77 (0.60, 0.97)	0.79 (0.62, 1.00)	0.029	0.96 (0.93, 1.00)

[1] EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio.
[2] Derived by Cox regression stratified by center after adjustment for age (time axis), sex, total energy intake, education, BMI, physical activity, cigarette smoking, and alcohol consumption. The lowest quartile (Q1) was used as the reference category (HR = 1).

TABLE 4
Association between mortality and the consumption of vitamins and carotenoids and total antioxidant capacity of fruit and vegetables in the EPIC-Spain cohort[1]

Nutrients and total antioxidant capacity	HR (95% CI) by quartile[2] Q2	Q3	Q4	*P* for trend	HR (95% CI) (continuous)[2] ($\log_2$)
Vitamin C	0.72 (0.57, 0.91)	0.65 (0.51, 0.83)	0.74 (0.58, 0.94)	0.009	0.87 (0.78, 0.96)
Vitamin E	0.95 (0.75, 1.20)	0.83 (0.65, 1.08)	0.83 (0.64, 1.08)	0.12	0.90 (0.79, 1.02)
β-Carotene	0.76 (0.60, 0.96)	0.72 (0.56, 0.92)	0.74 (0.58, 0.95)	0.022	0.89 (0.80, 0.98)
α-Carotene	0.86 (0.68, 1.08)	0.84 (0.67, 1.06)	0.75 (0.59, 0.96)	0.023	0.95 (0.91, 1.00)
β-Cryptoxanthin	0.73 (0.57, 0.92)	0.77 (0.61, 0.98)	0.75 (0.59, 0.95)	0.034	0.94 (0.90, 0.99)
Provitamin A[3]	0.66 (0.52, 0.83)	0.70 (0.55, 0.89)	0.68 (0.53, 0.87)	0.006	0.88 (0.80, 0.97)
Lutein	0.76 (0.60, 0.98)	0.86 (0.68, 1.09)	0.83 (0.65, 1.05)	0.23	0.97 (0.90, 1.03)
Zeaxanthin	0.78 (0.61, 1.00)	0.75 (0.59, 0.96)	0.91 (0.72, 1.16)	0.48	0.96 (0.89, 1.04)
Lycopene	0.79 (0.63, 0.99)	0.76 (0.60, 0.96)	0.65 (0.51, 0.84)	0.001	0.93 (0.89, 0.97)
Total carotenoids	0.74 (0.59, 0.93)	0.70 (0.55, 0.89)	0.69 (0.55, 0.88)	0.003	0.85 (0.76, 0.94)
TRAP	0.69 (0.55, 0.87)	0.61 (0.48, 0.78)	0.77 (0.61, 0.97)	0.015	0.84 (0.77, 0.92)
FRAP	0.70 (0.56, 0.89)	0.56 (0.44, 0.72)	0.77 (0.61, 0.97)	0.010	0.84 (0.77, 0.92)
TEAC	0.72 (0.57, 0.91)	0.59 (0.46, 0.76)	0.78 (0.62, 1.00)	0.019	0.85 (0.78, 0.93)
ORAC	0.81 (0.64, 1.03)	0.75 (0.59, 0.96)	0.81 (0.64, 1.04)	0.089	0.88 (0.79, 0.97)

[1] EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; FRAP, ferric-reducing antioxidant power; TRP, total radical–trapping antioxidant parameter; TEAC, trolox equivalent antioxidant capacity; ORAC, oxygen radical absorbance capacity.
[2] HR (and 95% CI) by Cox regression stratified by center after adjustment for age (time axis), sex, total energy intake, education, BMI, physical activity, cigarette smoking, and alcohol consumption. The lowest quartile (Q1) was used as the reference category (HR = 1).
[3] As β-carotene equivalents: β-carotene + 0.5 α-carotene + 0.5 3 β-cryptoxanthin.

and TRAP seems the most appropriate to explain the inverse relation between antioxidant nutrients from plant foods and mortality. This model was indeed the one with the best fit, according to its lowest AIC value.

The multivariate model for the 3 food subgroups associated with mortality in the univariate analysis and the best model for the effects on total mortality of antioxidant nutrients and TAC from plant foods are shown in **Table 6**. For the 3 subgroups of foods (fruiting and root vegetables and fresh fruit), the protective effects were rather attenuated when they were considered simultaneously, although an inverse relation with mortality was clearly suggested for all of them. As already seen, both lycopene and TRAP were significantly associated with a lower mortality, and the association was stronger for TRAP when the variables were modeled as $\log_2$-transformed variables, whereas the trend was better for lycopene when the variables were categorized by quartiles, which probably reflects the linear relation of lycopene with mortality and the rather U-shaped relation of TAC.

DISCUSSION

In a large prospective study, we have observed that a reduction in mortality is associated with increased intakes of fresh fruit and vegetables, mainly root vegetables and fruiting vegetables. A lower risk of dying also seems to be associated with high intakes of vitamin C, provitamin A carotenoids, and lycopene. Whereas the effects of provitamin A and ascorbic acid could be explained by the antioxidant activity of plant foods, the effect of lycopene could be explained at least partly by other mechanisms. No association was seen for other plant-based foods, such as potatoes and legumes, or for vitamin E intake.

Overall, our results are quite consistent with those from analyses of prospective studies of mortality risk. Cohort studies in Greece (4) and the United States (5) reported an inverse relation of mortality with fruit and vegetable intakes. In the Greek study, the association was observed with both fruit and vegetables, whereas no association appeared with legumes or potatoes; in the US study, the results reported referred to a broad group including vegetables and fruit and to potatoes and some legumes. Other studies based on dietary information reported an inverse association of mortality with scores including either fruit and vegetables (6, 7) or ascorbic acid and β-carotene (8), whereas, in the United Kingdom, mortality did not differ significantly between vegetarians and nonvegetarians (9). In studies dealing with plasma concentrations of antioxidant nutrients, vitamin C has consistently been reported as associated with lower mortality (10–12). An inverse relation with carotene was found in one European study (13) but not in a study in the United Kingdom (11); neither study observed any association with vitamin E. Only one study analyzed mortality in relation with serum carotenoids (14): an inverse association was observed with concentrations of β-cryptoxanthin, lutein, and total oxygenated carotenoids (including those previously reported plus zeaxanthin) but not with carotene or lycopene.

Advantages of our study are its prospective design and relatively large sample size, although, in a prospective study, the power is mainly determined by the number of cases: 562 deaths were ascertained in our study, whereas, in the abovementioned cohort studies, deaths ranged from 275 to 1217. We also had a relatively good assessment of dietary intake: in the validation study, comparison of the diet history with the average of twelve 24-h diet recalls (reference) showed correlation coefficients from 0.65 to 0.76 for fruit and vegetables (18) and from 0.65 to 0.84 for vitamins C and E in men and women; the lowest correlation was for β-carotene, with coefficients of 0.51 and 0.59 (19). A complete list of potential confounders was taken into account, including important lifestyle and other dietary factors associated with mortality, which are also known to be associated with fruit and vegetable intake in the EPIC-Spain population (27). An inverse association may occur in prospective studies when some

TABLE 5
Models for the effect on mortality of the consumption of carotenoids and vitamin C and the total antioxidant capacity (TAC) of fruit and vegetables in the EPIC-Spain cohort[1]

Model	HR (95% CI)[2]	*P*	AIC
Nutrients			
Model 1			
β-Carotene	0.92 (0.80, 1.06)	0.241	
α-Carotene	0.99 (0.93, 1.06)	0.862	
β-Cryptoxanthin	0.96 (0.91, 1.00)	0.057	7961.6
Model 2			
Provitamin A[3]	0.88 (0.80, 0.97)	0.009	7959.9
Model 3			
Provitamin A[3]	0.91 (0.82, 1.01)	0.063	
Lycopene	0.94 (0.89, 0.97)	0.013	7956.3
Model 4			
Total carotenoids	0.85 (0.76, 0.94)	0.002	7957.2
Model 5			
Provitamin A[3]	0.94 (0.80, 1.11)	0.470	
Lycopene	0.94 (0.90, 0.99)	0.018	
Vitamin C	0.95 (0.80, 1.13)	0.557	7958.0
Nutrients and TAC			
Model 6			
Provitamin A[3]	1.00 (0.87, 1.15)	0.994	
TRAP	0.84 (0.73, 0.96)	0.012	7955.8
Model 7			
Lycopene	0.95 (0.90, 0.99)	0.028	
TRAP	0.87 (0.79, 0.95)	0.003	7951.4
Model 8			
Vitamin C	1.13 (0.91, 1.39)	0.268	
TRAP	0.76 (0.63, 0.92)	0.005	7954.6
Model 9			
Provitamin A[3]	0.97 (0.83, 1.13)	0.658	
Lycopene	0.94 (0.90, 0.99)	0.018	
Vitamin C	1.19 (0.95, 1.50)	0.138	
TRAP	0.78 (0.65, 0.93)	0.006	7953.2

[1] EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; AIC, Akaike's information criterion; TRAP, total radical–trapping antioxidant parameter.

[2] HR for the continuous variable ($\log_2$) by Cox regression stratified by center after adjustment for age (time axis), sex, total energy intake, education, BMI, physical activity, cigarette smoking, and alcohol consumption. Mutually adjusted for the variables included in each model.

[3] As β-carotene equivalents: β-carotene + 0.5 α-carotene + 0.5 β-cryptoxanthin.

conditions are already present, although not clinically apparent, at the time at recruitment, so that the reported dietary habits are actually determined by the disease. We carried out our analyses by excluding the deaths that occurred during the initial period of follow-up, and the pattern of associations remained unchanged. For instance, the HRs for the $\log_2$-transformed intakes of lycopene and TRAP after exclusion of deaths during the first year of follow-up were 0.95 (95% CI: 0.90, 0.998) and 0.84 (0.76, 0.92), respectively; the corresponding figures after exclusion of deaths during the first 2 y of follow-up were 0.94 (0.89, 0.996) and 0.82 (0.74, 0.91).

Some limitations of our research must also be considered. The EPIC-Spain cohort cannot be considered a representative sample of the general Spanish population. However, the number of subjects was very large, subjects came from different social classes, and the pattern of dietary intake was similar to that observed in population-based surveys; furthermore, the main conclusions of our study are derived from within-cohort comparisons, so that internal rather than external validity is the primary issue here. Another limitation refer to antioxidants from plant-based foods; we were able to estimate the intakes of some micronutrients (vitamins C and E and carotenoids), but fruit and vegetables may contain many other compounds with potential antioxidant capacity, among them flavonoids and other polyphenols (29). Indeed, phenolic compounds and vitamin C, rather than carotenoids, are well correlated with indicators of TAC (30, 31). Furthermore, the assessment of TAC from plant food intake was based on in vitro measurements (23, 24). A substantial drawback of this approach is that some components that contribute to antioxidant activity in vitro may be poorly absorbed in vivo. Finally, part of the contribution to the total intake of some micronutrients may come from supplements; nevertheless, in our population, only a small proportion of subjects (3.8%) reported consumption of vitamins or mineral supplements of any type (32).

There is consistency between groups of fruit and vegetables and antioxidant nutrients associated with reduced mortality: we already showed (16) that, in our population, fresh fruit accounted for ≈51% of total vitamin C intake; provitamin A carotenoids were largely (70%) consumed from root, fruiting, and green leafy vegetables; and 72% of lycopene was provided by fruiting vegetables, mainly tomatoes. On the other hand, both plasma carotenoids and ascorbic acid are elevated in subjects with higher fruit and vegetable intakes, although ascorbic acid had the strongest correlation (33).

Except for lycopene, the relation between intake and mortality was not linear: relative to the lowest quartile of consumption, the risk of death was markedly lower for the second and third quartiles, but it remained stable or even tended to be higher in the fourth quartile. This phenomenon was observed both for the main food groups, vitamin C and provitamin A, and for all the indicators of TAC. It is also related to the fact that log transformation of the intake usually had a better fit to the continuous variable in natural units. One potential explanation may be related to the dose; for instance, for vitamin C, a steady state plasma concentration is achieved at doses of 200 mg/d, and thus additional intake may produce plasma and body saturation without any biological effect (34). On the other hand, for other compounds, such as carotene, a dual role is proposed: they may serve as an antioxidant or a prooxidant, depending on the redox potential of the biological environment where they act (35). Both issues also could be related to the conflicting results between observational and intervention studies, in which supplementation with high doses of vitamin failed to show any beneficial effect or even proved to be harmful (3, 36).

Lycopene, a nonprovitamin A carotenoid, is one of the major carotenoids in Western diets and the most predominant carotenoid in plasma. It is often assumed that these effects are associated with the antioxidant activity of lycopene, but it may also have other biological effects, such as decreasing insulin-like growth factor-I expression and down-regulating inflammatory signals (37). We found that, at least in part, the association of lycopene intake with reduced mortality seems not to be explained by its TAC. Nevertheless, it is assumed that tomato products are the main source of lycopene; however, in a European study based on EPIC, the average plasma lycopene was low in Spain, where the diet is rich in tomatoes; this finding may be explained in part by the fact that, whereas lycopene availability is higher from

TABLE 6
Multivariate association between mortality and the consumption of fruit and vegetables or nutrients and the total antioxidant capacity (TAC) of fruit and vegetables in the EPIC-Spain cohort[1]

	HR (95% CI) by quartile[2]				
	Q2	Q3	Q4	*P* for trend	HR (95% CI) continuous[2] ($\log_2$)
Food groups					
Fruiting vegetables	0.97 (0.77, 1.21)	0.82 (0.65, 1.05)	0.83 (0.65, 1.07)	0.079	0.94 (0.88, 1.00)
Root vegetables	0.83 (0.66, 1.05)	0.82 (0.65, 1.03)	0.76 (0.59, 0.96)	0.021	0.96 (0.90, 1.01)
Fresh fruit	0.89 (0.70, 1.12)	0.79 (0.62, 1.01)	0.82 (0.64, 1.04)	0.075	0.97 (0.93, 1.01)
Nutrients and TAC					
Lycopene	0.82 (0.65, 1.03)	0.81 (0.64, 1.02)	0.70 (0.54, 0.91)	0.005	0.95 (0.90, 0.99)
TRAP	0.73 (0.57, 0.92)	0.66 (0.51, 0.84)	0.85 (0.66, 1.09)	0.139	0.87 (0.79, 0.95)

[1] EPIC, European Prospective Investigation into Cancer and Nutrition; HR, hazard ratio; TRAP, total radical–trapping antioxidant parameter.
[2] HR (95% CI) by Cox regression stratified by center after adjustment for age (time axis), sex, total energy intake, education, BMI, physical activity, cigarette smoking, and alcohol consumption; the 3 food groups and lycopene plus TRAP also are mutually adjusted, although models for foods and nutrients (with TAC) are computed separately. The lowest quartile (Q1) was used as the reference category (HR=1).

sauce and cooked or processed tomatoes, in Spain, tomatoes are mainly consumed in the raw state (38). Furthermore, a weak correlation between dietary intake and plasma concentrations of lycopene was observed in most Mediterranean countries.

In conclusion, we found that high intakes of fresh fruit and root and fruiting vegetables are associated with reduced mortality in the adult population in Spain, probably because of the high content of vitamin C, provitamin A carotenoids, and lycopene in such foods. Antioxidant capacity could explain to some extent the potential effect of ascorbic acid and provitamin A but not that of lycopene. In contrast, although the most important confounders were considered, residual confounding by unknown factors cannot be totally ruled out. In any case, the results of the present study suggest that a diet rich in fruit and vegetables—mainly those with high content of vitamin C, provitamin A, and lycopene—is associated with improved survival, although this effect cannot be clearly attributed to a specific compound or mechanism.

The authors' responsibilities were as follows—AA and LC generated the idea for this study, carried out the data analysis, and wrote the draft of the manuscript. TB and PJ carried out the data management and the implementation of the databases of antioxidants, and contributed to the statistical analysis. CAG, AA, PA, EA, AB, MDC, MD, NL, CM, CN, JRQ, MJS, and MJT contributed to the design of the study, data collection, and quality control and analysis. CAG supervised and contributed to the interpretation of the results. All the contributors reviewed the manuscript draft, provided comments, and approved the final version of the manuscript. None of the authors had a personal or financial conflict of interest.

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