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ORIGINAL CONTRIBUTION

Dietary antioxidant capacity and all-cause and cause-specific mortality in the E3N/EPIC cohort study

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Abstract
Purpose The cellular oxidative stress (balance between pro-oxidant and antioxidant) may be a major risk factor for chronic diseases. Antioxidant capacity of human diet can be globally assessed through the dietary non-enzymatic antioxidant capacity (NEAC). Our aim was to investigate the relationship between the NEAC and all-cause and cause-specific mortality, and to test potential interactions with smoking status, a well-known pro-oxidant factor.
Methods Among the French women of the E3N prospective cohort study initiated in 1990, including 4619 deaths among 1,199,011 persons-years of follow-up. A validated dietary history questionnaire assessed usual food intake; NEAC intake was estimated using a food composition table from two different methods: ferric ion reducing antioxidant power (FRAP) and total radical-trapping antioxidant parameter (TRAP). Hazard ratio (HR) estimates and 95 % confidence intervals (CI) were derived from Cox proportional hazards regression models.
Results In multivariate analyses, FRAP dietary equivalent intake was inversely associated with mortality from all-causes (HR for the fourth vs. the first quartile: $HR_4 = 0.75$, 95 % CI 0.67, 0.83, $p_{trend} < 0.0001$), cancer, and cardiovascular diseases. Similar results were obtained with TRAP. There was an interaction between NEAC dietary equivalent intake and smoking status for all-cause and cardiovascular disease mortality, but not cancer mortality (respectively, for FRAP, $p_{inter} = 0.002$; 0.013; 0.113, results were similar with TRAP), and the association was the strongest among current smokers.
Conclusion This prospective cohort study highlights the importance of antioxidant consumption for mortality prevention, especially among current smokers.

Keywords Non-enzymatic antioxidant capacity · FRAP · TRAP · All-cause and cause-specific mortality · E3N study

Abbreviations

NEAC	Non-enzymatic antioxidant capacity
FRAP	Ferric ion reducing antioxidant power
HAT	Hydrogen atom transfer
SET	Single electron transfer
TRAP	Total radical-trapping antioxidant parameter

Introduction

Human diet represents a source of many different compounds endowed with antioxidant activity, mainly polyphenols and vitamins [1]. Fruits and vegetables are one of the main sources of antioxidant compounds, and several studies have reported an inverse association between fruit and vegetable consumption and mortality [2]. Fruit and vegetables are not the only source of antioxidants in the diet and other foods like wine, tea, or chocolate also provide an important contribution to antioxidant levels [3, 4]. Given the diversity in the sources of antioxidants and potential interactions between them, it is important to use an indicator that adequately reflects the daily exposure to antioxidants and takes into account the synergistic effect of

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all the antioxidant substances present in the diet [5]. The non-enzymatic total dietary antioxidant capacity (NEAC) measures the antioxidant potential of foods and beverages, including synergistic interactions of the redox molecules present in complex matrixes [5]. The index assesses all antioxidants, even those that are not well characterized or measured, and allows avoiding multiple testing of individual nutrients, which is of particular interest for epidemiological studies [6, 7].

Several methods exist to measure NEAC in food samples [8, 9]. They are based on the two major reaction mechanisms to deactivate radicals, which almost always occur together: SET (single electron transfer) and HAT (hydrogen electron transfer). SET-based methods, such as FRAP (ferric ion reducing antioxidant power), detect the ability of a potential antioxidant to transfer one electron to reduce any compound. HAT-based methods like TRAP (Total radical-trapping antioxidant parameter) measure the classical ability of an antioxidant to quench free radicals by hydrogen donation [8]. In consequence, FRAP and TRAP are two complementary methods to measure dietary NEAC.

The total dietary antioxidant capacity has been inversely associated with the risk of cancer [10–16], stroke [17, 18], myocardial infarction [19], and heart failure [20]. Only two cohort studies have addressed the relationship between dietary NEAC and all-cause mortality, with an inverse association in the EPIC-Spain study [21], but no association in the PREDIMED study [22].

The aim of the present study was to investigate the relationship between dietary NEAC and all-cause and cause-specific mortality in the large prospective cohort of middle-aged French women, using FRAP and TRAP, i.e., two complementary measures of NEAC. We also tested for potential interactions with smoking status, a major pro-oxidant factor [23, 24].

Methods

The E3N cohort study

The E3N (*Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale*) prospective cohort was initiated in France in 1990, in order to study the main risk factors for cancer and severe chronic conditions in women [25]. It includes 98,995 French women born between 1925 and 1950 and covered by the MGEN (*Mutuelle Générale de l'Education Nationale*), a national teacher's health insurance plan. All women signed an informed consent form, in compliance with the rules of the French National Commission for Data Protection and Privacy (*Commission nationale de l'informatique et des libertés*) from which approval was obtained.

Data collection

Women declare all medicals events, including cancer occurrence in self-administered questionnaires. Questionnaires are completed every 2–3 years, and record information such as lifetime use of hormonal treatments, occurrence of diseases, height and weight, and smoking status.

Dietary data

Dietary data were collected between June 1993 and July 1995. The diet history questionnaire was sent to 95,644 women (with two reminders for non-answering women). It was made of two parts: (1) questions about intake (quantity and frequency) of food groups and (2) qualitative data in order to detail food groups into individual foods. The questionnaire was sent with a booklet of pictures to estimate portion sizes [26]. This provided data on the intake of 208 foods and drinks. It was validated with twelve 24-h recalls, and reproducibility was evaluated within 1 year [27]. In all, 77,613 questionnaires were collected, with a response rate of 81.1 %. Among them, 985 questionnaires were excluded because women did not agree to a follow-up by the MGEN in case they left the study and 2120 because of miscoded or double answers, leaving 74,508 available questionnaires for the analysis of dietary factors. Mean daily intake in nutrients was evaluated using a food composition table derived from the French food composition table of the French Information Center on Food Quality (CIQUAL: *Centre d'information sur la qualité des aliments*). Dietary NEAC was evaluated using two complementary methods: FRAP and TRAP. The contributions of foods to these two measures of antioxidant capacity were calculated using a database created by Pellegrini et al. [3, 4]. For four food items (apple, melon, beer, and vinegar), two values were available, and we used an average value. If there was no exactly matching food item in the database, we used the value of a similar item, based on similarity in botanical group and similar vitamin E, vitamin C, and polyphenol content. The antioxidant capacity from coffee was taken into account only in analysis by categories of dietary antioxidant capacity, but not in the main analysis in the present study, due to (1) uncertainty about the in vivo absorption of its main antioxidant compounds and (2) the fact that coffee could act as an important confounder considering its associations with multiple lifestyle factors [28]. Information on dietary antioxidant (vitamin E, vitamin C, or beta-carotene) supplement intake was provided in two questionnaires, sent, respectively, in 1994 and 2000.

Identification of mortality cases

Information on vital status and dates of death were obtained from the health insurance database, postal

service, physician, hospital, municipal registries, and next of kin. Complementary information on causes of death was retrieved from Inserm-CépiDc (French centre of epidemiology on medical causes of death). Causes of death were coded by CepiDc according to the 9th and the 10th revisions of the international classification of diseases (ICD-9 and ICD-10), and the underlying cause of mortality was extracted, i.e., according to the WHO, the disease or injury which initiated the train of morbid events directly leading to death, or the circumstances of the accident or violence which produced the fatal injury. In our population, we identified and coded 99.3 % of death occurring before 2010. Cause-specific mortality was defined as follows: cancer: 140-210, C00-C99; cardiovascular diseases: 390-459, I00-I99; diseases of the nervous system: 320-359, G00-G99; external causes: 800-999, V00-V99, W00-W99, X00-X99, Y00-Y99; other diseases.

Population and follow-up

Baseline was defined as the date of response to the dietary questionnaire (1993–1995). Participants contributed person-years of follow-up until the date of death (for cases), the date the last completed questionnaire was returned (for non-cases), or the date the last available questionnaire was mailed (November 2011), whichever occurred first.

From the initial 74,508 women who answered the 1993 dietary questionnaire, we excluded 520 women lost to follow-up after the baseline questionnaire and 1476 with extreme values of energy intake (individuals in the top and bottom 1 % of the ratio of energy intake to basal metabolic rate computed on the basis of age, height, and weight [29]). Thus, 72,512 women were eligible for the study of overall mortality. For cause-specific mortality, we further excluded women with unknown causes of death ($N = 177$).

Statistical methods

Hazard ratio (HR) estimates and their 95 % confidence intervals (CI) were derived from Cox proportional hazards regression models with age as the time scale. HRs were determined considering the lowest quartile of antioxidant consumption as the reference category. Linear trends across categories were tested by assigning the median value for each exposure category and modeling exposure as a semi-continuous variable. In multivariate analyses, models were stratified by 5-year interval birth cohorts and simultaneously adjusted for personal and family history of cancer (yes or no), personal history of cardiovascular diseases, and diabetes (yes or no), body mass index (<22.4; 22.4 to <25; ≥25, kg/m^2), educational level (less or more than 12 years schooling), smoking status (never, former, current), physical activity (quartiles, METs), total energy without alcohol (continuous, kcal/day), alcohol (continuous, ml/day), and dietary fiber (continuous, g/day) intake. Additional adjustments for coffee or saturated fatty acids did not appreciably change the observed associations and were not included in the main model. Since missing values in all adjustment variables represented <5 % of observations, they were imputed to the modal category for categorical variables and to the median value for quantitative variables.

HRs according to cause-specific mortality were estimated by using competing risk models where deaths of other causes than those under study were censored at the date of death [30]. We additionally investigated associations between all-cause mortality and NEAC dietary equivalent intake. NEAC was included continuously as restricted cubic splines based on three knots as adjustment variables in the Cox regression model. The knots were located at the 25th (reference value), 50th, and 75th percentiles. Estimates of all-cause mortality risk associated with NEAC dietary equivalent intake were extracted from the model.

To evaluate the combined effect of NEAC dietary equivalent intake and smoking status on all-cause and cause-specific mortality, indicator variables were included in the regression model representing quartiles of NEAC dietary equivalent intake by smoking status (non-smoker, passive smoking only, former smoker, and current smoker), using the highest quartile of NEAC dietary equivalent intake, and women who never smoked and were not exposed to passive smoking as the reference category. We then tested for potential interactions between smoking status (non-smoker, passive smoking only, former smoker, and current smoker) and NEAC dietary equivalent intake (continuous).

We additionally performed three sensitivity analyses: [1] censoring women using antioxidant supplements (vitamin E, vitamin C, or beta-carotene) at the date they declared supplement intake in the 1994 and 2000 questionnaires ($N = 72,501$); [2] restricting analyses to women who did not report any prevalent cancer before baseline ($N = 68,195$), and [3] excluding the first 2 years of follow-up to investigate potential reverse causation bias ($N = 72,282$).

All p values were two-tailed, and statistical significance was set at the 0.05 level. All analyses were performed using the SAS software, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

Results

During 16.5 years of follow-up (11.1 ± 4.9 years for cases, and 16.9 ± 3.0 years for non-cases), 4619 deaths were recorded among 1,199,011 person-years, including 2726 from cancer, 584 from cardiovascular diseases, 265 from nervous system diseases, 296 from external causes, and 571

from other diseases. Major contributors to dietary FRAP and TRAP in our cohort were: fruit and vegetables (29 and 42 %, respectively), wine (16 and 22 %), tea (14 and 18 %), chocolate (9 and 12 %), and nuts (7 and 1.3 %). Characteristics of participants according to quartiles of FRAP and TRAP dietary equivalent intake are listed in Table 1. Women with a higher NEAC dietary equivalent intake consumed more foods high in antioxidants, including some alcoholic beverages. Such women were more likely to have a family and personal history of cancer, a higher level of education, high energy and dietary intakes, to be more physically active, and to be past or current smoker. They were less likely to have a personal history of cardiovascular disease.

Associations between NEAC dietary equivalent intake and all-cause and cause-specific mortality are presented in Table 2. In the multivariate adjusted model, FRAP and TRAP dietary equivalent intake were inversely associated with all-cause, cancer, and cardiovascular mortality, and mortality from other diseases, but not with mortality from external causes and diseases of the nervous system. The spline regression curves for the association between all-cause mortality and NEAC dietary equivalent intake (Fig. 1) demonstrated a regular decrease in mortality with increasing NEAC dietary equivalent intake.

Associations between NEAC dietary antioxidant intake and all-cause mortality by food group specific NEAC dietary antioxidant intake are presented in Table 3. FRAP from fruits and vegetables, wine, and tea were inversely associated with all-cause mortality, by not FRAP from coffee. Results were similar for TRAP.

The potential effect modification by smoking status of the association between NEAC dietary equivalent intake and all-cause, cancer, and cardiovascular disease mortality was modeled using combined variables of NEAC intake and smoking categories (non-smoker, passive smoking only, former smoker, and current smoker; Table 4). The category meant to be associated with the lowest risk (fourth quartile of NEAC dietary equivalent intake in non-smokers) was used as the reference category. For all-cause, cancer, and cardiovascular diseases mortality, the highest risk was observed in current smokers in the first quartile of NEAC dietary equivalent intake. The increase in risk associated with the first quartile of NEAC dietary antioxidant intake was not amplified by passive smoking neither the fact to be former smoker (Table 4). The interaction was statistically significant for all-cause and cardiovascular disease mortality, but not for cancer mortality. Results were very similar for TRAP.

In the sensitivity analyses restricted to women who did not report any antioxidant (vitamin E, vitamin C, or beta-carotene) supplementation during follow-up (1,008,661 person-years, 3759 cases), who did not report any prevalent cancer at baseline (1,134,082 person-years, 3714 cases), or when excluding cases that occurred during the first 2 years of follow-up (1,198,750 person-years, 4389 cases), results were not modified (data not tabulated).

Discussion

In this large prospective study of middle age women, NEAC dietary equivalent intake was inversely associated with all-cause, cancer, cardiovascular disease, and other disease mortality, but not with mortality from nervous system diseases or external causes. Modeled using spline regression curves there is a regular dose–effect inverse association between all-cause mortality and NEAC dietary equivalent intake. The inverse association was similar in non-smokers, passive smokers, and former active smokers, while it was much stronger in current smokers, with a statistically significant interaction for all-cause and cardiovascular mortality.

The inverse association of NEAC dietary equivalent intake and all-cause mortality is in line with results from EPIC-Spain study [21]. Recent studies have shown an inverse association between NEAC dietary equivalent intake and risk of stroke, heart failure, and myocardial infarction [17–20], but this is the first study that shows an inverse association between NEAC dietary equivalent intake and overall cardiovascular disease mortality. The total dietary antioxidant capacity has been inversely associated with breast [10], gastric [11, 12, 16], colorectal [13, 14], and liver cancer risks [15] in several cohort studies. But, to our knowledge, none have studied the relationship between NEAC dietary equivalent intake and overall cancer mortality. We have found no association between NEAC dietary equivalent intake and mortality from diseases of the nervous system, a heterogeneous group of diseases, which does not exclude a potential association with a specific condition. However, this result is consistent with previous studies showing no association between dietary antioxidant capacity and neurological diseases [31, 32].

Looking results by food groups specific NEAC, dietary antioxidant intake from fruits and vegetables, wine and tea was inversely associated with all-cause mortality, while the was no association with dietary antioxidant mortality from coffee. This is an issue. Indeed, coffee is one of the main providers of antioxidants, not through vitamins but through phenolic substances; thus, considering separately FRAP from coffee and FRAP from other sources can be questioned. The main contributors to the dietary antioxidant capacity from coffee are end products from the Maillard reaction, which occurs during coffee roasting [33]. These polyphenols are mostly too large to be absorbed through the intestinal mucosa, so that their role in the cell

Table 1 Population characteristics according to quartiles of NEAC dietary equivalent intake in the E3N study

Baseline characteristics	Total	FRAP (mmol/day)[a]				TRAP (mmol/day)[b]			
		*Q*1	*Q*2	*Q*3	*Q*4	*Q*1	*Q*2	*Q*3	*Q*4
Person-years	1,199,011	297,420	300,546	300,875	300,171	297,691	300,676	300,608	300,036
Age (y)[c]	52.9 ± 6.7	52.9 ± 6.8	53.1 ± 6.7	53.1 ± 6.7	52.7 ± 6.6	52.7 ± 6.7	53.1 ± 6.7	53.1 ± 6.7	52.9 ± 6.6
Dietary intake[c]									
Energy without alcohol (kcal/day)	2129 ± 544	1838 ± 440	2053 ± 470	2198 ± 508	2429 ± 572	1898 ± 465	2079 ± 498	2191 ± 525	2350 ± 580
Fruit and vegetables (g/day)	529.6 ± 241.2	399.8 ± 166.7	511.3 ± 199.2	565.2 ± 231.0	642.1 ± 284.3	407.0 ± 167.9	521.0 ± 207.6	565.3 ± 238.0	625.2 ± 281.6
Dietary fiber (g/day)	52.7 ± 20.9	45.7 ± 18.9	51.7 ± 19.8	54.4 ± 20.1	59.0 ± 22.4	47.2 ± 19.4	52.2 ± 20.2	54.2 ± 20.3	57.2 ± 22.4
Tea (ml/day)	187.0 ± 280.5	39.6 ± 85.7	111.4 ± 159.2	203.1 ± 231.1	393.7 ± 397.8	28.6 ± 65.0	99.1 ± 140.2	202.5 ± 217.2	417.6 ± 397.8
Chocolate (g/day)	8.0 ± 14.6	2.5 ± 4.9	5.1 ± 8.0	8.4 ± 11.8	16.0 ± 22.8	2.2 ± 4.1	5.0 ± 7.4	8.5 ± 11.4	16.4 ± 23.1
Alcohol (g/day)	11.6 ± 13.9	4.3 ± 5.7	8.3 ± 8.5	12.6 ± 11.7	21.2 ± 19.4	4.2 ± 5.7	8.1 ± 8.0	12.5 ± 11.2	21.6 ± 19.6
Physical activity (METs-h/w)	49.4 ± 50.4	45.3 ± 50.1	48.4 ± 47.4	50.4 ± 49.1	53.6 ± 54.6	45.6 ± 51.3	48.4 ± 47.1	50.5 ± 50.0	53.2 ± 52.9
BMI (kg/m^2)	23.0 ± 3.3	23.0 ± 3.5	23.0 ± 3.3	22.9 ± 3.2	23.0 ± 3.2	23.0 ± 3.5	23.0 ± 3.3	23.0 ± 3.2	22.9 ± 3.2
Smoking status[d]									
Never smoker	20,978 (28.9)	6278 (34.6)	5614 (31.0)	4998 (27.6)	4088 (22.6)	6169 (34.0)	5657 (31.2)	5070 (28.0)	4082 (22.5)
Passive smoking only	17,844 (26.6)	4710 (26.0)	4452 (24.9)	4487 (24.7)	4130 (22.8)	4805 (26.5)	4496 (24.8)	4444 (24.5)	4099 (22.6)
Former smoker	23,814 (32.8)	5063 (27.9)	5743 (31.7)	6183 (34.1)	6825 (37.7)	5057 (27.9)	5753 (31.7)	6145 (33.9)	6859 (37.8)
Current smoker	9876 (13.6)	2077 (11.5)	2251 (12.4)	2463 (13.6)	3085 (17.0)	2097 (11.6)	2222 (12.3)	2469 (13.6)	3088 (17.0)
Number of schooling years[d]									
<12 years	46,669 (64.4)	12,729 (70.2)	12,010 (66.3)	11,445 (63.2)	10,481 (57.8)	12,776 (70.5)	12,118 (66.8)	11,421 (63.0)	10,354 (57.1)
>12 years	25,843 (35.6)	5399 (29.8)	6118 (33.7)	6679 (36.8)	7647 (42.2)	5352 (29.5)	6010 (33.2)	6707 (37.0)	7774 (42.9)
Personal and family history of disease[d]									
Personal history of cancer	No	68,195 (94.1)	17,073 (94.2)	17,068 (94.2)	17,055 (94.1)		17,096 (94.3)	17,054 (94.1)	17,050 (94.1)
	Yes	4317 (5.9)	1055 (5.8)	1060 (5.8)	1073 (5.9)		1032 (5.7)	1074 (5.9)	1078 (5.9)
Personal history of cardiovascular diseases	No	43,702 (60.3)	10,687 (58.9)	10,951 (60.4)	10,961 (60.5)		10,743 (59.3)	10,920 (60.2)	10,923 (60.3)
	Yes	28,810 (39.7)	7441 (41.1)	7177 (39.6)	7167 (39.5)		7395 (40.7)	7208 (39.8)	7205 (39.7)
Personal history of T2 diabetes	No	71,573 (98.7)	17,838 (98.4)	17,913 (98.8)	17,904 (98.8)		17,852 (98.5)	17,892 (98.7)	17,916 (98.8)
	Yes	939 (1.3)	290 (1.6)	215 (1.2)	224 (1.2)		276 (1.5)	236 (1.3)	212 (1.2)
Family history of cancer	No	34,235 (47.2)	8715 (48.1)	8530 (47.1)	8524 (47.0)		8693 (47.9)	8527 (47.0)	8617 (47.5)
	Yes	38,277 (52.8)	9413 (51.9)	9598 (52.9)	9604 (53.0)		9435 (52.1)	9601 (53.0)	9511 (55.5)

Q quartiles, *MET* metabolic equivalent task, *BMI* body mass index, *FRAP* ferric ion reducing antioxidant power, *TRAP* total radical-trapping antioxidant parameter, *y* years, *w* week, *d* day

[a] $Q1$: <9.4 mmol/day, $9.4 \leq Q2 < 12.6$, $12.6 \leq Q3 < 16.5$ $Q2 \geq 16.5$

[b] $Q1$: <3.2 mmol/day, $3.2 \leq Q2 < 4.5$, $4.5 \leq Q3 < 6.2$ $Q2 \geq 6.2$

[c] Means ± Standard Deviation

[d] *n* (%)

antioxidant defense has been questioned [34]. Therefore, several authors have made the choice to exclude coffee from the NEAC antioxidant capacity [12, 35]. Others have estimated an absorption score for coffee, which minimizes the impact of coffee in the dietary antioxidant capacity [7]. In addition, coffee also has other effects especially through caffeine which has been negatively associated with the cardiovascular system. Finally, coffee drinking is also often associated with unhealthy behaviors such as smoking or heavy alcohol drinking, which may result in some residual confounding. When considering a model that included FRAP from coffee, FRAP from fruit and vegetables, and FRAP from other sources (or when considering an even more detailed partition of FRAP), there was no association with FRAP from coffee while there was an inverse association of mortality with FRAP from fruit and vegetables,

Table 2 Multivariable hazard ratio of all-cause and cause-specific mortality by quartiles of NEAC dietary equivalent intake

Mortality	FRAP (mmol/day)[a]					TRAP (mmol/day)[b]				
	*Q*1	*Q*2	*Q*3	*Q*4	*p* trend	*Q*1	*Q*2	*Q*3	*Q*4	*p* trend
All-cause										
Cases ($N = 4619$)	1298	1145	1090	1086		1248	1154	1103	1114	
HR (95 %CI)[c]	1.00	0.86 [0.79, 0.93]	0.82 [0.76, 0.89]	0.85 [0.79, 0.92]	<0.001	1.00	0.88 [0.81, 0.95]	0.83 [0.77, 0.90]	0.87 [0.80, 0.94]	0.001
HR (95 %CI)[d]	1.00	0.85 [0.78, 0.92]	0.78 [0.72, 0.85]	0.75 [0.68, 0.83]	<0.001	1.00	0.87 [0.80, 0.94]	0.80 [0.73, 0.87]	0.78 [0.70, 0.86]	<0.001
Cause-specific										
Cancer										
Cases ($N = 2726$)	733	666	650	677		705	674	661	686	
HR (95 %CI)[d]	1.00	0.87 [0.78, 0.97]	0.82 [0.73, 0.91]	0.79 [0.70, 0.90]	<0.001	1.00	0.90 [0.81, 1.00]	0.84 [0.75, 0.95]	0.82 [0.72, 0.93]	0.003
Cardiovascular diseases										
Cases ($N = 584$)	173	160	123	128		170	152	134	128	
HR (95 %CI)[d]	1.00	0.90 [0.72, 1.12]	0.67 [0.52, 0.86]	0.70 [0.52, 0.93]	0.005	1.00	0.83 [0.66, 1.04]	0.69 [0.54, 0.88]	0.66 [0.50, 0.87]	0.003
Diseases of the nervous system										
Cases ($N = 265$)	84	58	59	64		76	66	52	71	
HR (95 %CI)[d]	1.00	0.71 [0.51, 1.00]	0.77 [0.54, 1.11]	1.01 [0.68, 1.50]	0.819	1.00	0.87 [0.62, 1.22]	0.74 [0.51, 1.07]	1.22 [0.83, 1.79]	0.304
Other diseases										
Cases ($N = 571$)	164	147	141	119		162	142	146	121	
HR (95 %CI)[d]	1.00	0.84 [0.67, 1.06]	0.75 [0.59, 0.96]	0.59 [0.44, 0.79]	<0.001	1.00	0.79 [0.63, 0.99]	0.75 [0.59, 0.96]	0.57 [0.43, 0.77]	<0.001
External causes										
Cases ($N = 296$)	88	73	75	60		88	67	76	65	
HR (95 %CI)[d]	1.00	0.84 [0.61, 1.15]	0.86 [0.61, 1.19]	0.70 [0.46, 1.04]	0.103	1.00	0.76 [0.55, 1.05]	0.85 [0.61, 1.19]	0.74 [0.51, 1.09]	0.216

[a] $Q1$: <9.4 mmol/day, $9.4 \leq Q2 < 12.6$, $12.6 \leq Q3 < 16.5$ $Q2 \geq 16.5$

[b] $Q1$: <3.2 mmol/day, $3.2 \leq Q2 < 4.5$, $4.5 \leq Q3 < 6.2$ $Q2 \geq 6.2$

[c] Cox's proportional hazards model with individuals' age as the time scale

[d] Cox's proportional hazards model stratified by 5-year interval birth cohorts with individuals' age as the time scale, adjusted on personal and family history of cancer, personal history of cardiovascular diseases and diabetes, body mass index, educational level, smoking status, physical activity, total energy without alcohol, and intake of alcohol and fibers

and with FRAP from other source. These results suggest that the antioxidant capacity of various sources is inversely associated with mortality, but not that of coffee.

There is a dose–effect inverse association between all-cause mortality and NEAC dietary equivalent intake, modeled using spline regression curves. One of the major sources of NEAC is fruit and vegetables. It is noteworthy that 68 % of women of the cohort eat 400 g/day of fruits and vegetables or more, which is the amount recommended by the French national food safety agency (ANSES).

Mechanisms of action of dietary antioxidant capacity had been explored in a crossover intervention study, showing a significant beneficial effect on systemic inflammation and liver dysfunction [36]. Although it is difficult to dissociate the TAC from food groups from the food groups themselves, findings from the intervention study that compared a high TAC with a low TAC diet without changing the quantities within food groups [36] suggest a role for the TAC per se in some aspects of health such as inflammation. In our study, our findings that not only the FRAP

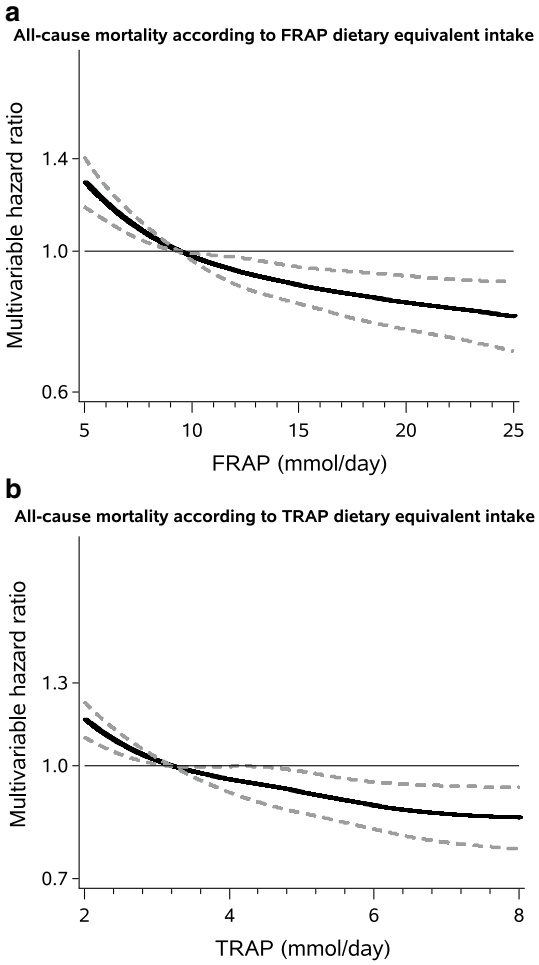

Fig. 1 All-cause mortality according to NEAC dietary equivalent intake: **a** FRAP; **b** TRAP Hazards ratios were calculated from Cox's proportional hazards models based on restricted cubic splines stratified by 5-year interval birth cohorts with individuals' age as the time scale and adjusted on personal and family history of cancer, personal history of cardiovascular diseases and diabetes, body mass index, educational level, smoking status, physical activity, total energy without alcohol, and intake of alcohol and fibers. The knots were located at the 25th, 50th, and 75th percentiles, corresponding to 9.4, 12.5, and 16.5 mmol/day, respectively, for FRAP, and to 3.2, 4.5, and 6.2 mmol/day, respectively, for TRAP. The 25th percentile was used as the reference value. *Hatched lines* represent the 95 % confidence intervals for the adjusted estimate (*solid line*). The vertical axis is on a log-scale

Table 3 Multivariable hazard ratio of all-cause mortality by quartiles of food group specific NEAC dietary equivalent intake

All-cause mortality	Cases ($N = 4619$)	HR[a]
FRAP—fruit and vegetable		
*Q*1: <3.0	1192 (25.81)	1.00
*Q*2: [3.0, 4.2)	1076 (23.30)	0.86 [0.79, 0.93]
*Q*3: [4.2, 5.6)	1137 (24.62)	0.85 [0.78, 0.93]
*Q*4: ≥5.6	1214 (26.28)	0.84 [0.78, 0.92]
p trend		<0.001
FRAP—coffee		
*Q*1: <7.8	1203 (26.04)	1.00
*Q*2: [7.8, 26.6)	1159 (25.09)	0.96 [0.89, 1.04]
*Q*3: [26.6, 46.2)	1154 (24.98)	0.97 [0.90, 1.06]
*Q*4: ≥46.2	1103 (23.88)	1.03 [0.94, 1.12]
p trend		0.451
FRAP—wine		
*Q*1: <0.04	1272 (27.54)	1.00
*Q*2: [0.04, 0.8)	1027 (22.23)	0.83 [0.76, 0.90]
*Q*3: [0.8, 2.7)	1077 (23.32)	0.81 [0.74, 0.88]
*Q*4: ≥2.7	1243 (26.91)	0.76 [0.67, 0.85]
p trend		<0.001
FRAP—chocolate		
*Q*1 + *Q*2: < 0.2	2320 (50.23)	1.00
*Q*3: [0.2, 1.6)	1157 (25.05)	0.91 [0.85, 0.98]
*Q*4: ≥1.6	1142 (24.72)	0.87 [0.80, 0.93]
p trend		<0.001
FRAP—tea		
*Q*1 + *Q*2: <0.3	1973 (42.71)	1.00
*Q*3: [0.3, 3.0)	1370 (29.66)	0.98 [0.91, 1.05]
*Q*4: ≥3.0	1276 (27.63)	0.91 [0.84, 0.98]
p trend		0.012
FRAP—others		
*Q*1: <2.4	1315 (28.47)	1.00
*Q*2: [2.4, 3.4)	1161 (25.14)	0.99 [0.91, 1.07]
*Q*3: [3.4, 4.8)	1115 (24.14)	1.00 [0.92, 1.10]
*Q*4: ≥4.8	1028 (22.26)	0.97 [0.88, 1.07]
p trend		0.209

[a] Cox's proportional hazards model stratified by 5-year interval birth cohorts with individuals' age as the time scale, adjusted on personal and family history of cancer, personal history of cardiovascular diseases and diabetes, body mass index, educational level, smoking status, physical activity, total energy without alcohol, and intake of alcohol and fibers

from fruit and vegetables but also that from other sources was inversely associated with mortality suggest a benefit though the complementarities of various antioxidants. Our results thus suggest benefiting from the complementarities of antioxidants from various food sources rather than from a limited range of antioxidants from dietary supplements.

Smoking is a major pro-oxidant factor [24]. Experimental and epidemiological data suggest the importance of the antioxidant/pro-oxidant balance on several diseases [37–39]. We demonstrated a significant interaction between NEAC dietary equivalent intake and the smoking status for all-cause and cardiovascular disease mortality, but not cancer mortality. Indeed, cigarette smoking is one of the major causes of cardiovascular diseases and related mortality and morbidity [23, 40]. A recent randomized-controlled trial demonstrated that blueberry modulates peripheral arterial dysfunction induced by acute cigarette smoking in young

Table 4 Multivariable hazard ratio mortality by quartiles of NEAC dietary equivalent intake according to smoking status

FRAP (mmol/day)[a]	All-cause mortality			Cancer mortality			Cardiovascular disease mortality		
	Cases	HR (95 %CI)[c]	Abs. risk[d]	Cases	HR (95 %CI)[c]	Abs. risk[d]	Cases	HR (95 %CI)[c]	Abs. risk[d]
Non-smoker									
*Q*4	279	1.00	10.86	167	1.00	10.30	36	1.00	10.47
*Q*3	351	1.02 [0.87, 1.20]	11.07	184	0.92 [0.74, 1.14]	9.46		52	1.23 [0.78, 1.92]
*Q*2	415	1.16 [0.99, 1.35]	12.61	216	1.04 [0.84, 1.28]	10.68	68	1.58 [1.02, 2.45]	16.57
*Q*1	515	1.32 [1.13, 1.54]	14.31	270	1.19 [0.97, 1.46]	12.24	79	1.59 [1.02, 2.49]	16.66
p tend[e]		0.004			0.116			0.179	
Passive smoking									
*Q*4	231	1.08 [0.90, 1.28]	11.68	146	1.04 [0.83, 1.30]	10.69	31	1.61 [0.98, 2.64]	16.85
*Q*3	236	1.05 [0.88, 1.25]	11.41	151	1.05 [0.84, 1.31]	10.80	17	0.81 [0.45, 1.46]	8.45
*Q*2	227	1.01 [0.85, 1.21]	10.99	145	1.03 [0.82, 1.29]	10.61	30	1.35 [0.81, 2.24]	14.08
*Q*1	272	1.25 [1.05, 1.50]	13.62	166	1.19 [0.95, 1.50]	12.28	27	1.34 [0.78, 2.29]	14.01
p tend[e]		0.820			0.847			0.932	
Former smoker									
*Q*4	378	0.97 [0.83-1.14]	10.53	240	0.96 [0.78, 1.17]	9.85	42	1.13 [0.71, 1.79]	11.77
*Q*3	353	1.07 [0.91, 1.25]	11.57	219	1.04 [0.85, 1.28]	10.75	42	1.31 [0.82, 2.09]	13.69
*Q*2	338	1.14 [0.97, 1.34]	12.33	200	1.06 [0.86, 1.31]	10.91	42	1.49 [0.93, 2.39]	15.58
*Q*1	309	1.22 [1.03, 1.45]	13.23	188	1.18 [0.94, 1.47]	12.14	35	1.40 [0.84, 2.33]	14.67
p tend[e]		0.004			0.179			0.149	
Current smoker									
*Q*4	198	1.24 [1.03-1.50]	13.49	124	1.16 [0.91, 1.46]	11.90	23	1.74 [1.01, 3.00]	18.18
*Q*3	150	1.31 [1.07, 1.61]	14.26	96	1.29 [1.00, 1.66]	13.25	13	1.31 [0.68, 2.50]	13.66
*Q*2	165	1.64 [1.35, 2.00]	17.82	105	1.55 [1.21, 1.99]	15.99	20	2.42 [1.36, 4.28]	25.28
*Q*1	202	2.33 [1.93, 2.82]	25.35	109	1.94 [1.51, 2.50]	19.98	37	4.94 [2.99, 8.15]	51.67
p tend[e]		<0.001			<0.001			0.004	
p inter[f]	0.002			0.113				0.013	

[a] $Q1$: <9.4 mmol/day, $9.4 \leq Q2 < 12.6$, $12.6 \leq Q3 < 16.5$ $Q2 \geq 16.5$

[b] $Q1$: <3.2 mmol/day, $3.2 \leq Q2 < 4.5$, $4.5 \leq Q3 < 6.2$ $Q2 \geq 6.2$

[c] Cox's proportional hazards model stratified by 5-year interval birth cohorts with individuals' age as the time scale, adjusted on personal and family history of cancer, personal history of cardiovascular diseases and diabetes, body mass index, educational level, physical activity, total energy without alcohol, and intake of alcohol and fibers

[d] Absolute risk during follow-up, per 100,000 women

[e] Linear trends across categories were tested by assigning the median values for each exposure category and modeling as a continuous variable in the stratified model, using the fourth quartile as reference

[f] The presence of effect modification was tested using the interaction term of the continuous NEAC and smoking status categories

male volunteers [41]. Another trial in healthy volunteers observed that endothelial dysfunction following smoking of one cigarette was counterbalanced by consumption of either red wine or de-alcoholized red wine in healthy smokers [42]. Here, we show for the first time in a large cohort study a significant interaction between smoking status and NEAC antioxidant consumption, which is another argument for the importance of antioxidant consumption, especially in active smokers. Indeed, smokers with a high NEAC dietary equivalent intake have a decreased risk of overall mortality by 89 % for FRAP and 66 % for TRAP, compared to smokers with a low NEAC dietary equivalent intake. However, smokers with a high NEAC intake have a higher risk of overall mortality by 22 % for FRAP and 24 % for TRAP than non-smokers with high NEAC intake.

Strengths of the present study include its prospective design, extensive follow-up, and adjustment for potential confounders. Causes of death were obtained from a National service, Inserm-CépiDc (French centre of epidemiology on medical causes of death). We obtained similar results with FRAP and TRAP, the two usual methods for in vitro determination of NEAC in foods. These complementary methods cover the two major reaction mechanisms to deactivate radicals, single electron transfer (SET), and hydrogen electron transfer (HAT), which almost always occur together in all samples [8]. They allow assessing

intakes of all antioxidants present in the diet, even those that are not well characterized or measured, and therefore capture synergistic and cumulative interactions among antioxidant nutrients in the food matrix [6].

Our study also has limitations. First, our population is composed of mostly educated women, who exercise, and have regular medical screening. Like most cohorts of volunteers, they are likely to be more concerned about their health than the general French population. We can thus assume that the observed strong inverse association between NEAC dietary equivalent intake and mortality would be even stronger in a population with a wider spectrum of NEAC intake. Second, there was no repetition of dietary measurement during follow-up; therefore, some misclassification of dietary variables due to changes in dietary habits may have occurred. Since misclassification is unlikely to be differential in prospective studies, it should reduce the relative risks toward unity and thus may result in missed or reduced observed associations. In addition, measurement error occurs easily in dietary assessment, but the validation of our self-administered dietary history questionnaire has shown a good reproducibility and validity [27]. Measurement error occurs easily in dietary assessment, but the validation of our self-administered dietary history questionnaire has shown a good reproducibility and validity [27]. Since there was no available database on the NEAC content of foods for French foods, we used a database developed in Italy, where most food items are shared with France. To the best of our knowledge there is only one other NEAC database available, developed by a Norwegian team, and restricted to FRAP [43]. Since there was a high correlation between the Italian and the Norwegian FRAP values in our study, we chose to only use the Italian database which provided values for both FRAP and TRAP. Further studies may develop more precise estimates of NEAC considering cooked foods and using non-water-based techniques, which would be of interest to compare with presently available NEAC values.

In conclusion, NEAC dietary equivalent intake was inversely associated with all-cause and cause-specific mortality in a cohort of French women, with an interaction between NEAC dietary equivalent intake and the smoking status for all-cause and cardiovascular disease mortality. This highlights the importance of healthy habits for preventing all-cause and cause-specific mortality, and especially the importance for smokers of consuming a healthy diet rich in a panel of antioxidants. However, these data only apply to antioxidants from foods, which are likely to be well balanced and complementary in their actions, and should not be extrapolated to antioxidant supplement intakes.

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Authors contribution N.B. and M.C.B.R. designed research; N.B., V.D., and M.C.B.R. conducted research; V.D., L.Da., and M.S. contributed to construction of dietary and medical data; N.B., V.D., L.Da., and M.C.B.R. analyzed data; N.B. and M.C.B.R. wrote the paper; M.C.B.R. had primary responsibility for final content; V.D., L.Da., L.Do., G.F., and M.S. revised the article critically. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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