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Original Contribution

Healthy Aging 5 Years After a Period of Daily Supplementation With Antioxidant Nutrients: A Post Hoc Analysis of the French Randomized Trial SU.VI.MAX

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This study's objective was to investigate healthy aging in older French adults 5 years after a period of daily nutritional-dose supplementation with antioxidant nutrients. The study was based on the double-blind, randomized trial, Supplementation with Antioxidant Vitamins and Minerals (SU.VI.MAX) Study (1994–2002) and the SU.VI.MAX 2 Follow-up Study (2007–2009). During 1994–2002, participants received a daily combination of vitamin C (120 mg), β-carotene (6 mg), vitamin E (30 mg), selenium (100 μg), and zinc (20 mg) or placebo. Healthy aging was assessed in 2007–2009 by using multiple criteria, including the absence of major chronic disease and good physical and cognitive functioning. Data from a subsample of the SU.VI.MAX 2 cohort, initially free of major chronic disease, with a mean age of 65.3 years in 2007–2009 ($n = 3{,}966$), were used to calculate relative risks. Supplementation was associated with a greater healthy aging probability among men (relative risk = 1.16, 95% confidence interval: 1.04, 1.29) but not among women (relative risk = 0.98, 95% confidence interval: 0.86, 1.11) or all participants (relative risk = 1.07, 95% confidence interval: 0.99, 1.16). Moreover, exploratory subgroup analyses indicated effect modification by initial serum concentrations of zinc and vitamin C. In conclusion, an adequate supply of antioxidant nutrients (equivalent to quantities provided by a balanced diet rich in fruits and vegetables) may have a beneficial role for healthy aging.

aging; antioxidants; dietary supplements; minerals; randomized controlled trial; vitamins

Abbreviation: SU.VI.MAX, Supplementation with Antioxidant Vitamins and Minerals.

A United Nations report highlighted that, by the year 2050, more than a third of the population in "more developed" world regions will be 60 years of age or older (1). In this context, identifying modifiable factors that can help preserve overall health and quality of life is of major concern. As aging is a multifaceted process that affects various functions and organ systems, there is a clear need for holistic approaches in geriatric research. Rowe and Kahn (2, 3) suggested a construct named "successful aging," defined as the absence of disease and disability, the maintenance of high physical and cognitive function, and sustained engagement in social and productive activities. As the terminology "successful"/"nonsuccessful" has been criticized because of potential stigmatization of individuals with health problems (4, 5), alternative denotations such as "healthy aging" have been proposed. We follow this logic and thus use "healthy aging" throughout this paper.

In the context of aging, oxidative stress has long been the focus of underlying biological mechanisms of health decline. Yet, randomized supplementation trials that have tested the effect of antioxidants on mortality risk and chronic disease do not consistently suggest beneficial impacts (6–8). It has been underlined that the efficacy of such a supplementation may strongly depend on the nutritional status of an individual (9). Moreover, in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, age, smoking, physical exercise, and dietary vitamin C intake have been shown to modify the effect of vitamin E supplementation on health outcomes (10–12). Accordingly, investigating the effects of antioxidant supplementation within specific subpopulations appears to be of major interest.

To this day, very few prospective studies have examined the link between nutritional factors and healthy aging (13–16), and to the best of our knowledge, no study has yet investigated the role of antioxidant nutrients. We thus conducted a post hoc analysis of the Supplementation with Antioxidant Vitamins and Minerals (SU.VI.MAX) trial, including middle-aged adults initially free of any major chronic disease, in order to investigate the long-term associations of antioxidant nutrient supplementation with the probability of healthy aging. We hypothesized that the intervention would be more effective in individuals with initially low levels of the tested antioxidants and in those with a lower consumption of foods that are rich in antioxidants (fruits and vegetables).

METHODS

Study design and participants

The French SU.VI.MAX Study (1994–2002, registered at www.clinicaltrials.gov under NCT00272428) was a randomized, double-blind, placebo-controlled, primary prevention trial. It was designed to test the potential association between daily supplementation, over a period of 8 years, with antioxidant vitamins and minerals at nutritional doses (ascorbic acid (120 mg), vitamin E (30 mg), β-carotene (6 mg), selenium (100 μg), and zinc (20 mg)) and the incidence of cancer, ischemic heart disease, and overall mortality (17). Details about the cohort are available elsewhere (17, 18). Briefly, after a national recruitment campaign with a call for volunteers living in France (women aged 35–60 years and men aged 45–60 years), 12,741 subjects met all eligibility criteria (17), provided informed consent and all other necessary information, and were randomized and included in the final study sample.

Following the trial phase, participants were asked if they would be willing to participate in an additional follow-up, including further questionnaires and examinations. This additional follow-up was conducted in 2007–2009 and was named "SU.VI.MAX 2" (19). A total of 6,850 individuals were included in the SU.VI.MAX 2 cohort.

The SU.VI.MAX and SU.VI.MAX 2 studies were conducted according to the guidelines laid down in the Declaration of Helsinki and were approved by the Ethics Committee for Studies with Human Subjects of the Paris-Cochin Hospital (nos. 706 and 2,364, respectively) and the Comission Nationale de l'Informatique et des Libertés (nos. 334,641 and 907,094, respectively). Written, informed consent to participate in the studies was obtained from each subject.

The target population for the present study comprised all participants of the SU.VI.MAX 2 cohort that were aged 45–60 years at baseline (1994–1995) ($n = 5,583$) and who had no prevalent major chronic disease (diabetes, ischemic cardiovascular disease, cancer) at baseline (1994–1995) ($n = 5,243$). After exclusion of participants with missing data on healthy aging indicators, our final study sample consisted of 3,966 individuals (Figure 1). Accordingly, our study sample is a subsample of the SU.VI.MAX 2 cohort. Restricting our analyses to subjects aged 45–60 years at baseline allowed us to obtain a sample of relatively old individuals at follow-up, with similar age ranges for men and women.

Definition of "healthy aging"

We developed a healthy aging definition based on the Rowe and Kahn model (3). As this concept has been criticized for an insufficient consideration of older individuals' subjective perceptions (20) and mental health (21), we chose to add these aspects to our healthy aging definition (in line with many other authors (13–16, 22–26)). Thus, we defined healthy aging as follows: remaining free of cancer, cardiovascular disease, or diabetes during follow-up, while also presenting (at follow-up) with good physical and cognitive functioning, no limitations in instrumental activities of daily living, no depressive symptoms, no health-related limitations in social life, good overall self-perceived health, and no function-limiting pain (Table 1). Only those participants who fulfilled all of these criteria were considered to be aging healthily and, thus, healthy aging was coded as a binary variable.

Blood sampling and baseline (1994–1995) antioxidant status assessment

The treatment of baseline (1994–1995) fasting blood samples and the measurement of serum concentrations of the tested antioxidants have been described previously (19).

Assessment of chronic disease incidence

Ascertainment of cancer and cardiovascular disease incidence has been extensively described (17, 27). Event validation was performed by an expert committee of specialized physicians, blinded to group assignment. Cardiovascular disease was defined by *International Classification of Diseases, 10th Revision, Clinical Modification* (28), codes 120–125, 163, 165, 166, 170, 171, and 174, and cancer was defined as cancer of any kind, except for basal cell carcinoma of the skin. Diabetes was defined as having fasting blood glucose ≥7 mmol/L (≥126 mg/dL), antidiabetic medication use, or self-reported diabetes at the end of follow-up.

Assessment of healthy aging criteria at follow-up

The remaining healthy aging indicators were assessed by clinical and neuropsychological examinations and questionnaires completed in 2007–2009. Good physical functioning was defined as having a score of ≥11 of 12 points (29–32) on the short physical performance battery described by Guralnik et al. (33).

To be considered as having good cognitive function, participants had to have ≥27 points (34) on the Mini-Mental State Examination (35). Next, we applied 2 additional criteria to obtain a more sensitive overall indicator of cognitive function: first, a score ≥19 of 48 points (36) on the delayed, cued-recall score of the RI-48 (rappel indicé-48 items) test (36), measuring episodic memory and used for the detection of early Alzheimer disease (36); and second, a scaled score of ≥5.5 points on the number-letter switching task of the Delis-Kaplan Trail-Making Test (37), assessing mental flexibility. This cutoff represents the mean minus 1.29 standard deviations in the reference population aged 50–89 years (38).

Limitations in instrumental activities of daily living were measured by a validated questionnaire (39). Participants who

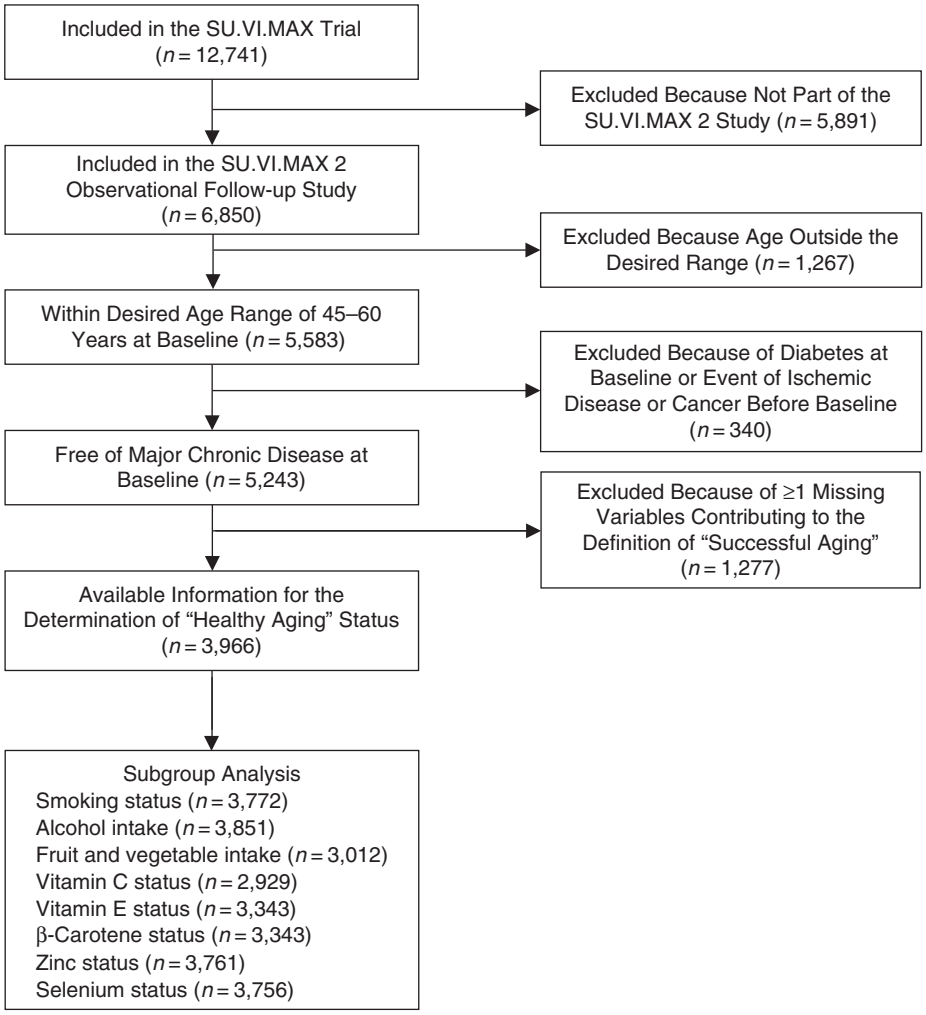

Figure 1. Selection of participants for the present analyses from the Supplementation with Antioxidant Vitamins and Minerals (SU.VI.MAX) and SU.VI.MAX 2 studies, France, 1994–2009. Subgroup analyses were carried out only in those participants for whom the stratification variable was not missing. Information on fruit and vegetable consumption was available for all participants who had completed 3 or more dietary records.

did not report any limitation fulfilled the respective criterion for healthy aging. Next, the absence of depressive symptoms was assessed by the French version of the Center for Epidemiologic Studies Depression Scale (40), using the internationally applied cutoff of <16 of 60 points (41).

To evaluate the remaining criteria of our healthy aging definition, we used selected items of the French version of the Medical Outcomes Study Short Form-36 Health Survey (42). Participants were considered to be free of limitations in social life if they reported that health problems only slightly or not at all interfered with their social life (item 6) and that such limitations did not occur more often than "some of the time" (item 10). They were considered to have good overall self-perceived health if they declared that their health was generally "good" to "excellent" (item 1). Moreover, participants were considered to have no function-limiting pain if they reported experiencing no more than "mild" physical pain during the previous month (item 7) and if such pain had only limited or no impact on their daily activities (item 8).

Fruit and vegetable consumption at baseline (1994–1995)

The collection and treatment of data on food group consumption have been extensively described previously (17). For this analysis, we averaged data from all eligible 24-hour dietary records provided during the first 26 months of participation in the study. Daily consumption of fruits and vegetables was calculated for participants having completed at least 3 dietary records during this period ($n = 8,111$).

Other variables collected at the beginning of the study (1994–1995 or 1995–1996)

Data on sex, date of birth, education (primary, secondary, university level), occupational status (4 categories), smoking

Table 1. Criteria Used to Define "Healthy Aging," SU.VI.MAX and SU.VI.MAX 2 Studies, France, 1994–2009

Criteria[a]	Definition	Corresponding Rowe and Kahn Criterion[b]
Good physical functioning	SPPB ≥11 of 12	Maintenance of high physical and cognitive function
Good cognitive functioning	MMSE ≥27, RI-48 ≥19 of 48, and DK-TMT ≥5.5	Maintenance of high physical and cognitive function
No limitations in IADL	<1 limitation	Avoiding disease and disability
No depressive symptoms	CES-D <16 of 60	
No health-related limitations in social life	SF-36 responses: 1–2 for item 6 and 3–5 for item 10	Sustained engagement in social and productive activities
Good overall self-perceived health	SF-36 responses: 1–3 for item 1	
No function-limiting pain	SF-36 responses: 1–3 for item 7 and 1–2 for item 8	Avoiding disease and disability
No incident major chronic disease	No incident diabetes, cancer, or cardiovascular disease during follow-up	Avoiding disease and disability

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale (40); DK-TMT, Delis-Kaplan version of the Trail-Making Test (37); IADL, instrumental activities of daily living (39); MMSE, Mini-Mental State Examination (35); RI-48, rappel indicé-48 items (36); SF-36, Medical Outcomes Study Short Form-36 Health Survey (42); SPPB, short physical performance battery (33); SU.VI.MAX, Supplementation with Antioxidant Vitamins and Minerals.

[a] All criteria were assessed at follow-up (2007–2009), except the incidence of major chronic disease, which was assessed from study inclusion through follow-up (1994–2009). All subjects were free of major chronic disease at inclusion.

[b] Rowe and Kahn (3).

status (never smoked, former smoker, current smoker), and physical activity (irregular, <1 hour of walking equivalents/day, ≥1 hour of walking equivalents/day) were collected at baseline (1994–1995) through self-administered questionnaires. The 4 occupational categories referred to homemakers, manual workers, intermediate professions, and managerial staff/intellectual professions. Categories for retired and unemployed people were determined according to the last job held.

Anthropometric and clinical measurements were performed at the initial clinical examination (1995–1996), as previously described (17, 43). Body mass index was calculated as weight (kg)/height $(m)^2$ and categorized as <25 kg/m^2, 25–29 kg/m^2, and ≥30 kg/m^2. Systolic and diastolic blood pressures (mm Hg) were measured with a standard mercury sphygmomanometer after the participants had been lying down for 10 minutes.

Alcohol intake (g/day) was estimated by using a short, validated, semiquantitative dietary questionnaire (44) administered at baseline (1994–1995).

Descriptive statistics

Participant characteristics were tabulated for the entire study sample and stratified by study group. Moreover, using Mann-Whitney U tests and χ^2 tests, we compared participants included in our analyses with those participants of the original SU.VI.MAX trial who were aged 45–60 years at baseline but not included in our analyses.

Main statistical analyses

To test the effect of antioxidant supplementation on healthy aging, we calculated unadjusted relative risks by dividing the healthy aging proportion in the supplemented group by the respective proportion in the placebo group. As the original results of the SU.VI.MAX trial concerning chronic disease incidence and mortality substantially differed between men and women (17), we computed global and sex-stratified models.

Exploratory subgroup analyses

Effect modification by baseline (1995–1995) status of the tested antioxidant nutrients (<25th or ≥25th percentile) and by consumption of fruits and vegetables, which contain a larger mixture of antioxidants than those tested in this study (<400 g/day vs. ≥400 g/day), was examined via interaction terms and stratified models. The 25th percentile cutoff was chosen to obtain a sufficient number of participants in the "low" group and, at the same time, "low" groups with sufficiently small antioxidant concentrations (as we hypothesized the presence of thresholds above which adding more antioxidants by supplementation would no longer improve health during aging). The 400-g cutoff was chosen because consuming at least 400 g (5 portions) per day is one of the official French nutritional recommendations (45, 46), and it has been recommended by the World Health Organization for the prevention of chronic diseases (47).

We also investigated effect modification by age at follow-up (categories: <60 years, 60–64 years, 65–69 years, ≥70 years) and by 2 factors known to influence antioxidant status and metabolism (48): smoking status (nonsmoker/former smoker vs. current smoker) and alcohol consumption (<10 g/day vs. ≥10 g/day).

Second-level interactions (interactions of the above-listed variables with antioxidant supplementation, stratified by sex) were also investigated. Here, we applied the same cutoffs as for the other analyses (no sex-specific percentiles were calculated).

Sensitivity analyses

As there were no pronounced differences between study groups in terms of the investigated baseline variables, we chose to calculate relative risks as our main result. To verify that adjustment would not substantially change our results, we also ran logistic regression models to calculate crude odds ratios as well as odds ratios adjusted for age at follow-up, sex, educational level, occupational status, smoking, alcohol

Table 2. Participant Characteristics ($n = 3,966$), SU.VI.MAX and SU.VI.MAX 2 Studies, France, 1994–2009

Characteristics	No.	Percentile		%	Mean (SD)
		50	25–75		
Age at follow-up in 2007–2009, years[a]	3,966	64.7	61.6–69.0		65.3 (4.5)
<60				11.7	
60–64				39.9	
65–69				28.4	
≥70				20.0	
Assigned study group					
Total	3,966				
Antioxidant supplementation group				53.5	
Sex					
Total	3,966				
Men				51.1	
Educational level	3,966				
Primary education only				21.5	
Secondary education				39.7	
University level				38.8	
Occupational status	3,837				
Homemaker				7.6	
Manual worker				5.5	
Employee				56.1	
Managerial staff[b]				30.8	
Smoking habits	3,772				
Never smoker				51.0	
Former smoker				37.9	
Current smoker				11.1	
Physical activity level	3,852				
Irregular or none				22.1	
<1 hour/day				31.0	
≥1 hour/day				46.8	
Alcohol consumption, g/day	3,851	13.6	0.0–28.3		16.8 (17.5)
Fruit/vegetable intake, g/day	3,012	366.6	270.3–481.9		387.6 (169.2)
Body mass index[c]	3,246	24.0	22.0–26.3		24.4 (3.4
Systolic blood pressure, mm Hg	3,295	120.0	115.0–135.0		124.8 (13.8)
Diastolic blood pressure, mm Hg	3,295	80.0	75.0–90.0		80.4 (8.8)
Fasting blood glucose, mmol/L	3,845	5.61	5.27–6.00		5.65 (0.54)
Selenium, μmol/L[d]	3,756	1.10	0.99–1.23		1.12 (0.19)
Zinc, μmol/L[d]	3,761	13.1	11.9–14.3		13.2 (1.9)
Vitamin C, μmol/L[d]	2,909	55.4	42.2–67.5		56.0 (27.2)
Vitamin E, μmol/L[d]	3,343	31.2	26.7–36.1		32.0 (7.9)
β-Carotene, μmol/L[d]	3,343	0.51	0.33–0.77		0.61 (0.42)

Abbreviations: SD, standard deviation; SU.VI.MAX, Supplementation with Antioxidant Vitamins and Minerals.
[a] All indicators are baseline (1994–1995) variables, except age.
[b] Or intellectual profession.
[c] Body mass index expressed as weight (kg)/height $(m)^2$.
[d] Blood serum concentrations.

intake (quintiles), body mass index status, and physical activity. Missing data on physical activity ($n = 34$), body mass index ($n = 82$), alcohol intake ($n = 115$), occupational status ($n = 129$), and smoking status ($n = 194$) were dealt with by multiple imputation (SAS proc mi/proc mianalyze; SAS Institute, Inc., Cary, North Carolina).

Table 3. Antioxidant Supplementation as a Predictor of Healthy Aging, SU.VI.MAX and SU.VI.MAX 2 Studies, France, 1994–2009[a]

Stratification Variable	Total No.	Healthy Aging by Study Group				RR[b]	95% CI	*P* Value[c]
		Supplementation		Placebo				
		No.	%	No.	%			
All participants	3,966	809	38.1	657	35.6	1.07	0.99, 1.16	
Sex								0.03
Men	2,027	454	42.4	350	36.6	1.16	1.04, 1.29	
Women	1,939	355	33.8	307	34.6	0.98	0.86, 1.11	
Vitamin C status, percentile[d]								0.06
<25th	727	161	41.4	109	32.3	1.28	1.06, 1.56	
≥25th	2,182	428	37.1	369	35.9	1.03	0.92, 1.15	
Vitamin E status, percentile[e]								0.31
<25th	835	182	39.3	124	33.3	1.18	0.98, 1.42	
≥25th	2,508	510	38.1	420	36.0	1.06	0.96, 1.17	
β-Carotene status, percentile[f]								0.93
<25th	834	173	38.7	137	35.4	1.09	0.91, 1.31	
≥25th	2,509	519	38.3	407	35.3	1.08	0.98, 1.20	
Zinc status, percentile[g]								0.05
<25th	953	206	40.7	145	32.4	1.26	1.06, 1.49	
≥25th	2,808	570	37.7	473	36.6	1.03	0.94, 1.13	
Selenium status, percentile[h]								0.73
<25th	918	175	36.2	149	34.3	1.05	0.88, 1.26	
≥25th	2,838	597	39.1	470	35.9	1.09	0.99, 1.20	
Fruit and vegetable consumption, g (5 portions)/day								0.22
<400	1,757	372	40.3	288	34.5	1.17	1.03, 1.32	
≥400	1,255	269	40.0	225	38.6	1.04	0.90, 1.19	
Age at follow-up examination, years								0.69
<60	463	93	39.4	91	40.1	0.98	0.79, 1.23	
60–64	1,583	365	43.4	292	39.4	1.10	0.98, 1.24	
65–69	1,125	231	36.5	162	32.9	1.11	0.94, 1.30	
≥70	795	120	29.2	112	29.2	1.00	0.81, 1.24	
Smoking status								0.20
Nonsmoker	3,352	702	39.2	559	35.9	1.09	1.00, 1.19	
Smoker	420	68	29.7	62	32.5	0.91	0.69, 1.22	
Alcohol intake, g/day								0.41
<10	1,670	350	38.6	262	34.4	1.12	0.99, 1.27	
≥10	2,181	439	38.3	380	36.7	1.04	0.94, 1.16	

Abbreviations: CI, confidence interval; RR, relative risk; SU.VI.MAX, Supplementation with Antioxidant Vitamins and Minerals.

[a] In SU.VI.MAX (antioxidant supplementation trial, 1994–2002), all stratification variables (except age) were ascertained in 1994–1995. In SU.VI.MAX 2, follow-up questionnaires and examinations served to determine healthy aging status (2007–2009).

[b] Unadjusted relative risk for the healthy aging proportion in the supplemented group in relation to the respective proportion in the placebo group.

[c] *P* for interaction, calculated via interaction terms in unadjusted logistic regression models.

[d] 42.19 μmol/L.

[e] 26.68 μmol/L.

[f] 0.33 μmol/L.

[g] 11.90 μmol/L.

[h] 0.99 μmol/L.

All analyses were conducted with the Statistical Analysis Systems, version 9.3, statistical software package (SAS Institute, Inc.), and statistical tests were 2 tailed.

RESULTS

Descriptive statistics

Of the 12,741 participants of the original SU.VI.MAX cohort, 10,092 participants were 45–60 years of age at inclusion. Of these, 6,126 were not part of the SU.VI.MAX 2 cohort or did not meet other inclusion criteria. Compared with these excluded participants, the 3,966 included participants belonged more often to the supplementation study group, were older, were more educated, had a healthier lifestyle (in terms of smoking, physical activity, alcohol intake, and fruit and vegetable consumption), had more favorable health markers (in terms of body mass index, blood pressure, and blood glucose), and had higher vitamin C and β-carotene concentrations (Web Table 1, available at http://aje.oxfordjournals.org/).

Participant characteristics of the 2,017 men and 1,939 women included in our study sample are presented in Table 2. The mean age at follow-up (2007–2009) was 65.3 (standard deviation, 4.5) years, and the mean follow-up time was 13.4 (standard deviation, 0.5) years. Web Table 2 shows participant characteristics stratified by study group. There were no substantial differences between groups.

Main results

Based on data from 2007 to 2009, 804 men (39.7%) and 662 women (34.1%) were identified as meeting our criteria for healthy aging. Relative risk values for antioxidant supplementation as a predictor of healthy aging are presented in Table 3, stratified by sex, categories of age at follow-up, baseline antioxidant levels, fruit and vegetable consumption, tobacco smoking, and alcohol intake. No overall association of antioxidant supplementation with healthy aging was detected. In sex-stratified analyses, a significant beneficial association with healthy aging was present only among men (for supplementation vs. placebo group, relative risk = 1.16, 95% confidence interval: 1.04, 1.29).

Exploratory subgroup analyses

No significant interactions were seen for any of the stratification variables examined (all P's ≥ 0.05). Yet, there was a significant beneficial association of supplementation among individuals who consumed <5 portions of fruits and vegetables per day at baseline but not among individuals who consumed ≥5 portions. In terms of baseline serum levels of the tested antioxidants (<25th or ≥25th percentile), a beneficial association of the administered supplements was seen in participants with low baseline zinc concentrations but not in their counterparts with higher levels. A similar observation was made concerning participants with low versus high baseline vitamin C concentrations.

Table 4 presents results obtained by double stratification according to 1) sex and 2) vitamin C status, zinc status, and fruit and vegetable consumption. No significant association of supplementation was observed among men or women with low vitamin C concentrations, although the relative risk among women was quite elevated (relative risk = 1.35). On the other hand, a significant association of supplementation was seen among men, but not among women with low zinc concentrations or fruit and vegetable consumption.

Table 4. Antioxidant Supplementation as a Predictor of Healthy Aging by Investigation of Second-Level Interactions, SU.VI.MAX and SU.VI.MAX 2 Studies, France, 1994–2009[a]

Stratification Variable	Men (n = 2,027)			Women (n = 1,939)		
	No.	RR[b]	95% CI	No.	RR[b]	95% CI
Vitamin C status, percentile[c]						
<25th	499	1.25	1.00, 1.58	228	1.35	0.94, 1.94
≥25th	991	1.15	0.99, 1.34	1,191	0.93	0.80, 1.09
Zinc status, percentile[d]						
<25th	376	1.35	1.03, 1.77	577	1.20	0.96, 1.49
≥25th	1,564	1.14	1.01, 1.28	1,244	0.89	0.76, 1.04
Fruit and vegetable consumption, g (5 portions)/day						
<400	875	1.21	1.02, 1.43	882	1.12	0.93, 1.33
≥400	703	1.15	0.97, 1.38	552	0.90	0.72, 1.13

Abbreviations: CI, confidence interval; RR, relative risk; SU.VI.MAX, Supplementation with Antioxidant Vitamins and Minerals.

[a] In SU.VI.MAX (antioxidant supplementation trial, 1994–2002), all stratification variables were ascertained in 1994–1995. In SU.VI.MAX 2, follow-up questionnaires and examinations served to determine healthy aging status (2007–2009).

[b] Unadjusted relative risk for the healthy aging proportion in the supplemented group in relation to the respective proportion in the placebo group.

[c] 42.19 μmol/L.

[d] 11.90 μmol/L.

Supplemental analyses

To investigate effect modification by vitamin C and zinc status in more depth, we also examined whether or not the association of supplementation would gradually decrease across quartiles. Web Table 3 shows that there was no pronounced linear decline of relative risk across quartiles. As for fruit and vegetable intake, the relative risk gradually declined across quartiles, but all within-quartile relative risk values were nonsignificant.

Sensitivity analyses

Unadjusted models and fully adjusted logistic regression models yielded similar results (refer to Web Table 4).

DISCUSSION

In this post hoc analysis of the SU.VI.MAX trial, we investigated the effect of daily supplementation with nutritional-dose antioxidants on healthy aging 5 years after the end of the trial. In analyses with the entire study sample and in analyses restricted to women, no significant effects were observed. On the other hand, antioxidant supplementation was linked to a higher probability of healthy aging among men. Next, consistent with our hypothesis, the effect of antioxidant supplementation on healthy aging varied according to baseline antioxidant status and consumption of fruits and vegetables. Significant beneficial effects of the supplementation were observed in 3 specific subgroups of participants: those with low baseline vitamin C levels, those with low baseline zinc levels, and those consuming <5 portions of fruits and vegetables per day at baseline.

To better understand the sex specificity of our findings, we compared the modifying effect of vitamin C and zinc concentrations and of fruit and vegetable consumption between sexes (Table 4). Men, but not women, with low zinc concentrations and with a low fruit and vegetable consumption appeared to benefit from antioxidant supplementation. On the other hand, the effect of supplementation appeared to be stronger among women with low vitamin C concentrations than among men with low serum vitamin C. Yet, as only few women had vitamin C concentrations below the 25th percentile, statistical power was low, and no significant results were observed. It is possible that the sex specificity of our findings is partly explained by sex differences in the prevalence of low baseline vitamin C concentrations in our sample; that is, if as many women as men in our sample would have had low vitamin C concentrations at baseline, there may have been a more pronounced overall effect of supplementation among women. However, there may be additional underlying factors.

To the best of our knowledge, our study is the first to investigate the relationship between antioxidant supplements and a multidimensional measure of healthy aging. Thus, existing analyses of antioxidant trials cannot directly be compared with our study but can contribute to its interpretation. A recent literature review concluded that there was no evidence of a protective effect of an antioxidant nutrient supplementation on overall mortality. On the contrary, β-carotene and vitamin E appeared to slightly increase mortality risk (6). In a meta-analysis of the association of various vitamin and antioxidant supplements with cardiovascular disease, vitamin E was associated with specific favorable outcomes only when the analysis was restricted to high-quality trials (8). Concerning cancer prevention, results from primary and secondary prevention trials do not support a favorable effect of antioxidant supplements, according to a recent meta-analysis (7, 49).

The potential role of an adequate antioxidant status has also been investigated with regard to physical, cognitive, and mental health—with mixed results. A beneficial outcome of antioxidant use on cognitive health has been suggested by some observational studies (50) but has not been confirmed by randomized trials (51, 52). Next, better physical functioning has been related to a higher total antioxidant capacity in a recent observational study (53). Moreover, concerning mental health, some observational (54, 55) and intervention (56) studies suggest a beneficial role of antioxidants.

One possible reason for the lack of evidence of a beneficial association of antioxidants with different health outcomes is the relatively short treatment and follow-up durations in many intervention trials (57, 58). In addition, the effect of supplementation may depend on baseline antioxidant levels (as in our study), as well as other factors such as smoking status and exercise (10, 11). Finally, in our study, a combination of 5 different antioxidant agents was used, and synergistic actions of these different agents (57) may have increased the magnitude of the observed effect.

Some limitations of our study should be noted. Most variables comprising our healthy aging definition were available only at follow-up. Thus, we were not able to formally investigate health decline in the course of aging. Yet, as our study sample was initially middle aged and free of any disease likely to hinder study participation, subjects were considered as generally healthy. Moreover, our study sample was only a fraction of the original SU.VI.MAX cohort, and it differed in multiple aspects from excluded participants. To investigate potential bias related to this issue, we reanalyzed our data using inverse probability weighting (59, 60). We estimated the probability to be included in our study sample as a function of baseline sociodemographic, lifestyle, and health variables for each subject of the "source population" (10,092 SU.VI.MAX participants initially aged 45–60 years) using logistic regression. Next, we recalculated relative risks using the inverse of the probability to be included (multiplied by the sampling proportion, $\text{number}_{\text{included}}/\text{number}_{\text{total}}$) as weights. These results did not substantially differ from those of our main analyses (data not shown).

Important strengths of our study are its initial randomized controlled design and, as previously reported, the high compliance of the SU.VI.MAX participants with the allocated treatment (17, 27). Next, baseline measurements of serum concentrations of the tested antioxidants were available, which allowed us to conduct stratified analyses.

In conclusion, our stratified analyses indicate that, while an overall beneficial association of a supplementation with combined antioxidant vitamins and minerals at moderate doses may not exist, specific subpopulations could benefit from antioxidant treatment. Yet, our subgroup analyses were of exploratory nature and thus have to be interpreted with caution. To verify our findings, further randomized controlled trials

targeting populations at risk with a low baseline antioxidant status would be needed. According to our data, men may be such an "at risk" group.

Altogether, our results support the importance of a well-balanced intake of antioxidant nutrients at nutritional doses (as can be supplied by a diversified and adequate fruit and vegetable intake) for preserving overall health in the course of aging.

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