# Prospective association between the Dietary Inflammatory Index and mortality: modulation by antioxidant supplementation in the SU.VI.MAX randomized controlled trial[1,2]

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## ABSTRACT

**Background:** Chronic inflammation is a central mechanism involved in cardiovascular diseases, cancer, diabetes, and chronic respiratory diseases, 4 leading causes of mortality. Diet is a major source of pro- and anti-inflammatory bioactive compounds. The Dietary Inflammatory Index (DII) was designed to estimate the overall inflammatory potential of the diet.

**Objective:** Our aim was to study the prospective association between the DII and mortality, as well as assess whether antioxidant supplementation could modulate this association.

**Design:** The Supplémentation en Vitamines et Minéraux Antioxydants study was a randomized, double-blind, placebo-controlled trial in which participants received low-dose antioxidants or a placebo from 1994 to 2002. In this observational prospective analysis, 8089 participants (mean ± SD age at baseline: 49.0 ± 6.3 y) were followed between 1994 and 2007 (median: 12.4 y). The DII was calculated from repeated 24-h dietary records; higher scores correspond to more proinflammatory diets. A total of 207 deaths occurred during follow-up, including 123 due to cancer and 41 due to cardiovascular events. Multivariate Cox proportional hazards models were computed.

**Results:** Sex-specific tertiles of the DII were positively associated with cardiovascular + cancer mortality (HR for tertile 3 compared with tertile 1 = 1.53; 95% CI: 1.01, 2.32; *P*-trend = 0.05) and specific cancer mortality (HR for tertile 3 compared with tertile 1 = 1.83; 95% CI: 1.12, 2.99; *P*-trend = 0.02). The corresponding *P* value was 0.07 for all-cause mortality. The DII was statistically significantly associated with increased all-cause mortality in the placebo group (HR for tertile 3 compared with tertile 1 = 2.10; 95% CI: 1.15, 3.84; *P*-trend = 0.02) but not in the antioxidant-supplemented group (*P*-trend = 0.8; *P*-interaction = 0.098).

**Conclusion:** These results suggest that a proinflammatory diet is associated with increased all-cause and cancer mortality and antioxidants may counteract some of the proinflammatory effects of the diet. This trial was registered at clinicaltrials.gov as NCT00272428. *Am J Clin Nutr* 2016;103:878–85.

**Keywords:** antioxidants, Dietary Inflammatory Index, inflammation, mortality, prospective study

## INTRODUCTION

Chronic inflammation has been broadly acknowledged as a central mechanism in metabolic disorders associated with morbidity and mortality (1). In a meta-analysis of 54 long-term prospective studies, Kaptoge et al. (2) showed that blood C-reactive protein (CRP)[8] concentration, a biomarker of systemic inflammation, was positively associated with vascular mortality and death from several cancers. Since then, several prospective studies showed positive associations between biomarkers of inflammation, such as C-reactive protein (3), IL-6 (3, 4), TNF-$\alpha$ receptor 1 (4), and chitinase 3–like protein 1 (5), and mortality.

The effect of diet on chronic inflammation has been widely investigated (6–8). Pro- or anti-inflammatory properties have been attributed to several bioactive components of the diet, based on experimental and epidemiologic studies (6–11). A

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[2] Supplemental Figure 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[8] Abbreviations used: CRP, C-reactive protein; CVD, cardiovascular disease; DII, Dietary Inflammatory Index; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants.

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literature-derived scoring system, the Dietary Inflammatory Index (DII), has been developed to estimate the pro- and anti-inflammatory potential of the overall diet and to investigate its possible relations with health outcomes (12).

Although several studies have been published regarding the associations between the DII and incidence of chronic diseases (13–29), only 2 studies, restricted to women, have investigated the relation between the pro- and anti-inflammatory potential of the diet measured with the DII and mortality (30, 31), and none has studied how this association is modulated by antioxidant supplementation.

Experimental studies have shown that chronic inflammation and oxidative stress are interrelated, and both contribute to the etiology of the main causes of death by chronic diseases, that is, cardiovascular diseases (CVDs), cancer, diabetes, and chronic respiratory diseases (1, 32, 33). Thus, we hypothesized that a proinflammatory diet could increase mortality risk and that the addition of antioxidants to the diet may counteract this association. Therefore, our objectives were *1*) to investigate the relation between the DII and mortality (all causes, CVD, and cancer) in a large French prospective cohort and *2*) to determine whether this relation is modulated by antioxidant supplementation.

## METHODS

### Study population

The Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study is a population-based, double-blind, placebo-controlled, randomized trial (registered at clinicaltrials.gov as NCT00272428) initially performed to evaluate the effect of a daily intake of antioxidant supplements on ischemic heart disease and cancer incidence. All participants took a daily capsule containing a combination of 120 mg ascorbic acid, 30 mg vitamin E, 6 mg $\beta$-carotene, 100 $\mu$g selenium, and 20 mg zinc or a placebo (34). These antioxidants corresponded to vitamins and minerals that were frequently consumed as part of a balanced diet rich in fruits and vegetables and for which a protective effect against the development of chronic diseases was suggested by experimental and/or epidemiologic literature available at this time (35, 36). Participants were advised against taking any self-prescribed dietary supplement during the trial. During the first year of the study (1994–1995), 13,017 subjects were enrolled (7876 women aged 35–60 y and 5141 men aged 45–60 y). The intervention study lasted until 2002, and health event monitoring was pursued until September 2007. At the end of the intervention phase, the 7.5-y antioxidant supplementation was associated with lower total cancer incidence and all-cause mortality in men but not in women. In total, 5.2% of all participants were lost to follow-up.

Subjects provided written informed consent. The study was conducted according to the Declaration of Helsinki guidelines and was approved by the Ethics Committee for Studies with Human Subjects at the Paris-Cochin Hospital (CCPPRB No. 706) and the "Commission Nationale de l'Informatique et des Libertés" (CNIL No. 334641).

### Baseline data collection

At enrollment, all participants completed questionnaires regarding sociodemographics, smoking status, physical activity, family history of CVD and cancer, and medication use. They also underwent a clinical examination and anthropometric measurements by study nurses and physicians. Age at menopause (natural or artificial) was self-reported by women during follow-up.

Dietary data were collected by using the Minitel Telematic Network (an Internet prototype), widely used in France as an adjunct to the telephone, at the beginning of the study. Participants were invited to provide a 24-h dietary record every 2 mo (randomly distributed over weekends and weekdays). To comply with the prospective design, we used dietary records from the first 2 y of follow-up. The participants had to select the foods consumed at breakfast, lunch, dinner, and/or any other occasion throughout the day among a predefined list of $\sim$1,000 items. Portion sizes were estimated by using a validated picture booklet distributed at enrollment (37). Participants were advised to declare all types of seasoning (such as garlic, ginger, pepper, or onion) when completing their 24-h records. In addition, the amounts of food or seasoning consumed from composite dishes were estimated by using French recipes validated by nutrition professionals. Energy, alcohol, and nutrient intakes were estimated by using a published French food composition table (38). The Phenol-Explorer database was used to estimate intake of total polyphenols, as well as intakes of the main groups and subgroups of polyphenols (www.phenol-explorer.eu) (39, 40).

### DII computation

The computation of the DII has been described in detail previously (12). Briefly, the DII is a score initially designed with 45 dietary variables determined from a literature review of 1943 articles published up to 2010. A literature-derived inflammatory effect score was assigned to every micronutrient, macronutrient, or food variable associated with an increase (+1), a decrease ($-1$), or no effect (0) on 6 inflammatory biomarkers: IL-1$\beta$, IL-4, IL-6, IL-10, TNF-$\alpha$, and CRP.

Mean intake of every food variable is transformed with standardized values from a world database into a $z$ score, then converted to a percentile and centered. Finally, the centered percentile score for each food variable was multiplied by its associated coefficient, and then these were summed across the 45 dietary variables, thus providing an individual DII score. In the present study, the DII was based on 36 dietary variables that were available in our database. The following variables were computed into the score as proinflammatory factors: total intakes of energy, protein, carbohydrate, total fat, SFAs, cholesterol, vitamin B-12, and iron, whereas intakes of MUFAs, PUFAs, n–3 fatty acids, n–6 fatty acids, alcohol, fiber, magnesium, niacin, thiamine, riboflavin, vitamin B-6, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, $\beta$-carotene, anthocyanidins, flavan-3-ol, flavonols, flavanones, flavones, isoflavones, garlic, ginger, pepper (seasoning), onion, and tea were entered as anti-inflammatory factors. Lower DII scores represented more anti-inflammatory diets, whereas higher DII scores represented more proinflammatory diets.

### Vital status and causes of death

Information about vital status and causes of death was received from relatives or physicians during follow-up. At the end of

follow-up, vital status of all subjects of the cohort and causes of death were verified with the national death registry (CépiDC). Causes of death from chronic diseases were classified by using the International Classification of Diseases, 10th Revision, Clinical Modification (41).

### Statistical analysis

Among the 13,017 participants of the SU.VI.MAX study, 8112 provided at least 3 valid 24-h dietary records within the first 2 y of follow-up. To perform our analysis in a prospective design, we excluded subjects for whom death occurred within the first 3 y of follow-up ($n$ = 23); leaving 8089 subjects for analysis (participants' flowchart, **Supplemental Figure 1**). Less than 5% of all covariate values were missing and were replaced by the modal value. Food and nutrient intakes were assessed by using mean intakes calculated from all dietary records provided during the first 2 y of follow-up for each participant.

Baseline characteristics of participants were compared between subjects who died during follow-up (all causes) and those who did not by using $\chi^2$ tests or Student's $t$ tests, as appropriate.

HRs and 95% CIs obtained from Cox proportional hazards models were used to estimate the association between the DII (continuous and sex-specific tertiles) and overall mortality, CVD + cancer mortality, and cancer-specific mortality. Statistical power was too limited to perform the analysis for CVD mortality separately (41 deaths due to CVD). Participants contributed person-time until the date of death, the date of the last completed questionnaire, or 30 September 2007, whichever occurred first. We confirmed that the proportional hazards assumption was satisfied through examination of the log-log (survival) compared with log-time plots. Tests for linear trend were performed by using the ordinal score of tertiles of the DII.

Multivariable models were adjusted for age (timescale in the Cox model), sex (male/female), antioxidant supplementation group of the initial SU.VI.MAX trial (antioxidant/placebo), number of dietary records (continuous), BMI (in kg/m$^2$; $<$25, $\geq$25 to $<$30, or $\geq$30), physical activity (irregular, $<$1 h/d walking equivalent, or $\geq$1 h/d walking equivalent), smoking status (never, former, or current), educational level (primary, secondary, or university), first-degree family history of CVD (yes or no), first-degree family history of cancer (yes or no), daily mean energy intake without alcohol (residual method) (42), and daily mean alcohol intake.

Two-factor interactions were tested between the DII (continuous and sex-specific tertiles) and the antioxidant supplementation group of the initial SU.VI.MAX trial (antioxidant/placebo), alcohol intake (median cutoff), and smoking status

**TABLE 1**
Baseline characteristics of the study population, SU.VI.MAX cohort, France, 1994–2007[1]

| | Noncases ($n$ = 7882) | Overall mortality ($n$ = 207) | Mortality by CVD or cancer ($n$ = 164) | Cancer-specific mortality ($n$ = 123) | $P$ value |
|---|---|---|---|---|---|
| DII | 0.7 ± 1.9[2] | 0.8 ± 1.7 | 0.8 ± 1.7 | 0.8 ± 1.7 | 0.6 |
| Age, y | 48.9 ± 6.3 | 52.5 ± 5.4 | 53 ± 5.4 | 52.9 ± 5.4 | <0.0001 |
| Sex, $n$ (%) | | | | | <0.0001 |
| Male | 3209 (40.7) | 117 (56.5) | 89 (54.3) | 56 (45.5) | |
| Female | 4673 (59.3) | 90 (43.5) | 75 (45.7) | 67 (54.5) | |
| Intervention group, $n$ (%) | | | | | 0.7 |
| Antioxidants | 3951 (50.1) | 101 (58.8) | 79 (48.1) | 57 (46.3) | |
| Placebo | 3931 (49.9) | 106 (51.2) | 85 (51.8) | 66 (53.7) | |
| Educational level, $n$ (%) | | | | | 0.1 |
| Primary | 1575 (20.0) | 54 (26.1) | 42 (25.6) | 26 (21.6) | |
| Secondary | 2982 (37.8) | 73 (35.3) | 60 (36.6) | 48 (39.0) | |
| University | 3325 (42.2) | 80 (38.6) | 62 (37.8) | 49 (39.8) | |
| Smoking status, $n$ (%) | | | | | 0.0003 |
| Never smoker | 3809 (48.3) | 73 (33.2) | 58 (35.4) | 45 (36.6) | |
| Former smoker | 3031 (38.5) | 92 (44.4) | 72 (43.9) | 52 (42.3) | |
| Current smoker | 1042 (13.2) | 42 (20.3) | 34 (20.7) | 26 (21.1) | |
| Physical activity, $n$ (%) | | | | | 0.04 |
| Irregular | 1966 (24.9) | 36 (17.4) | 27 (16.5) | 20 (16.3) | |
| <1 h/d of walking or equivalent | 2374 (30.1) | 71 (34.3) | 58 (35.4) | 47 (38.2) | |
| ≥1 h/d of walking or equivalent | 3542 (44.9) | 100 (48.3) | 79 (48.2) | 56 (45.5) | |
| BMI, $n$ (%) | | | | | 0.05 |
| <25 kg/m$^2$ | 5099 (64.7) | 118 (57.0) | 93 (56.7) | 76 (61.8) | |
| ≥25–30 kg/m$^2$ | 2289 (29.0) | 70 (33.8) | 55 (33.5) | 35 (28.5) | |
| ≥30 kg/m$^2$ | 494 (6.3) | 19 (9.2) | 16 (9.8) | 12 (9.8) | |
| 24-h Dietary records, $n$ | 9.4 ± 3.4 | 9.6 ± 3.1 | 9.5 ± 3.1 | 9.5 ± 3.1 | 0.4 |
| Without alcohol energy intake, kcal/d | 1962 ± 551.3 | 1984.6 ± 563.5 | 1997.6 ± 547.9 | 1989.5 ± 565.8 | 0.6 |
| Alcohol intake, g/d | 18.1 ± 20.7 | 23.2 ± 23.4 | 23.9 ± 23.2 | 22.4 ± 22.0 | 0.002 |
| Family history of cancer[3] | 2728 (34.6) | 69 (33.3) | 53 (32.3) | 38 (30.9) | 0.7 |
| Family history of CVD[3] | 3190 (40.5) | 87 (42.0) | 66 (40.2) | 49 (39.8) | 0.6 |

[1] $P$ value for the comparison between noncases and all death causes, by Student's $t$ test or $\chi^2$ test where appropriate. CVD, cardiovascular disease; DII, Dietary Inflammatory Index; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants.

[2] Mean ± SD (all such values).

[3] In first-degree relatives.

(never/ever smokers) with the introduction of the corresponding product of 2 variables into the model. Each dietary component included in the DII has a unique inflammatory effect score and is derived from literature review of the association between each of these dietary components and inflammation (12). However, because PUFAs and n–3 and n–6 fatty acids are all included as independent components in the original DII, we also performed a sensitivity analysis by using a DII including PUFAs but excluding n–3 and n–6 fatty acids. Moreover, because available data for zinc composition were of poor quality in our data set (either missing or not validated), they were not included in the DII for the main analysis. However, sensitivity analyses were carried out with a modified DII that included zinc information (although limited).

All tests were 2-sided, and $P < 0.05$ was considered statistically significant. The SAS software version 9.3 (SAS Institute) was used for analyses.

## RESULTS

During follow-up, 207 deaths occurred within the population, including 123 caused by cancer and 41 by CVD. Thus, with a type I error probability of 0.05 and a power of 0.8, we were able to detect RRs ≤0.6 or ≥1.5 for the comparison of the incidence of all-cause mortality between tertiles 3 and 1 of the DII. The median follow-up time was 12.4 y. DII scores ranked from −5.4 to 6.0 for women (mean ± SD: 0.6 ± 1.7) and −5.1 to 6.1 for men (mean ± SD: 0.8 ± 1.5). The characteristics of the study population are described in **Table 1**. At baseline, subjects who died during follow-up were older, were more often men, consumed more alcohol, had a higher physical activity, were more frequently former or current smokers, and were more likely to be overweight or obese compared with those who did not die during follow-up. Participants who provided at least three 24-h dietary records ($n$ = 8112) were more likely to be men and to have a higher education level and were less likely to be smokers or obese compared with participants who provided fewer than three 24-h dietary records ($n$ = 4905).

Associations between the DII and mortality are shown in **Table 2**. The DII was positively associated with CVD + cancer mortality (HR per 1-point increment of the DII score = 1.14; 95% CI: 1.02, 1.27; $P$ = 0.02; HR for tertile 3 compared with tertile 1 = 1.53; 95% CI: 1.01, 2.32; $P$ = 0.05) and cancer-specific mortality (HR per 1-point increment of the DII score = 1.18; 95% CI: 1.04, 1.34; $P$ = 0.01; HR for tertile 3 compared with tertile 1 = 1.83; 95% CI: 1.12, 2.99; $P$ = 0.02). For all-cause mortality, the corresponding $P$ values were 0.08 (continuous DII score) and 0.07 (DII score as sex-specific tertiles). The $P$-interaction between sex-specific tertiles of DII and the antioxidant supplementation group of the trial on all-cause mortality was 0.098 (**Table 3**). Mean ± SD DII scores were 0.7 ± 1.9 in the placebo group and 0.7 ± 1.9 in the antioxidant supplementation group ($P$ = 0.4). In stratified analysis, the DII was positively associated with all-cause mortality within the placebo group (HR per 1-point increment of the DII score = 1.17; 95% CI: 1.02, 1.35; $P$ = 0.03; HR for tertile 3 compared with tertile 1 = 2.10; 95% CI: 1.15, 3.84; $P$ = 0.02) but not in the antioxidant supplementation group (both corresponding $P$ values = 0.8). No interaction was detected between the DII and alcohol intake or smoking status (all $P$-interaction ≥ 0.3).

**TABLE 2**
Associations between sex-specific tertiles of DII and mortality from multivariate Cox proportional hazards models, SU.VI.MAX cohort, France, 1994–2007[1]

| | $n$ (cases/ noncases) | HR (95% CI) | $P$-trend |
|---|---|---|---|
| All-cause mortality | | | |
| Continuous DII score | 207/7882 | 1.09 (0.99, 1.20) | 0.08 |
| T1 | 63/2633 | 1.00 (referent) | 0.07 |
| T2 | 69/2628 | 1.21 (0.83, 1.76) | |
| T3 | 75/2621 | 1.41 (0.97, 2.04) | |
| Mortality by CVD or cancer | | | |
| Continuous DII score | 164/7882 | 1.14 (1.02, 1.27) | 0.02 |
| T1 | 49/2633 | 1.00 (referent) | 0.05 |
| T2 | 52/2628 | 1.15 (0.75, 1.77) | |
| T3 | 63/2621 | 1.53 (1.01, 2.32) | |
| Cancer-specific mortality | | | |
| Continuous DII score | 123/7882 | 1.18 (1.04, 1.34) | 0.01 |
| T1 | 35/2633 | 1.00 (referent) | 0.02 |
| T2 | 38/2628 | 1.19 (0.71, 1.99) | |
| T3 | 50/2621 | 1.83 (1.12, 2.99) | |

[1]Sex-specific cutoffs for tertiles of DII adjusted for energy intake by the residual method were used. In men, lower bounds of tertiles 2 and 3 were 0.20 and 1.46. In women, lower bounds of tertiles 2 and 3 were −0.09 and 1.41. Multivariate Cox proportional hazards models were adjusted for age (timescale in the Cox model), sex, intervention group of the initial SU.VI.MAX trial, number of 24-h dietary records, BMI, physical activity, smoking status, educational level, family history of cancer in first-degree relatives, family history of CVD in first-degree relatives, energy intake without alcohol, and alcohol intake. CVD, cardiovascular disease; DII, Dietary Inflammatory Index; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants; T, tertile.

Sensitivity analyses have been carried out with a DII including PUFAs but excluding n–3 and n–6 fatty acids and with a DII including zinc intake. Similar results were observed. Both modified DIIs were positively associated with CVD + cancer mortality [$P$-trend = 0.02 (tertiles) and 0.04 (tertiles), respectively] and with cancer-specific mortality [$P$-trend = 0.01 (tertiles) for both]. The antioxidant supplementation of the SU.VI.MAX trial modified the association between both modified DII and all-cause mortality [$P$-interaction = 0.09 (tertiles) for both]: a positive association was observed in the placebo group [$P$-trend = 0.01 (tertiles) and 0.02 (tertiles), respectively] but not in the antioxidant-supplemented group [$P$-trend = 0.7 (tertiles) and 0.8 (tertiles), respectively] (data not tabulated).

## DISCUSSION

For the first time in a large French cohort, this prospective study showed that a proinflammatory diet reflected by a higher DII score was associated with increased mortality (CVD + cancer and cancer-specific mortality). Because of its double-blind randomized placebo-controlled design, the SU.VI.MAX trial allowed us to investigate how this relation might be modulated by antioxidant supplementation. We found that a proinflammatory diet was positively associated with all-cause mortality in the placebo group of the trial only but not in the antioxidant-supplemented group.

The DII reflects the pro- and anti-inflammatory potential of an individual's usual diet. Prior studies have shown the DII to be significantly and positively associated with several inflammatory

**TABLE 3**
Associations between sex-specific tertiles of DII and mortality from multivariate Cox proportional hazards models stratified by the antioxidant supplementation group, SU.VI.MAX cohort, France, 1994–2007[1]

| | *n* (cases/noncases) | HR (95% CI) | *P*-trend | *P*-interaction |
|---|---|---|---|---|
| All-cause mortality (*n* = 207) | | | | 0.098 |
| Placebo group | | | | |
| Continuous DII score | 106/3931 | 1.17 (1.02, 1.35) | 0.03 | |
| T1 | 25/1323 | 1.00 (referent) | 0.02 | |
| T2 | 41/1315 | 2.17 (1.21, 3.91) | | |
| T3 | 40/1293 | 2.10 (1.15, 3.84) | | |
| Antioxidant supplementation group | | | | |
| Continuous DII score | 101/3951 | 1.02 (0.89, 1.16) | 0.8 | |
| T1 | 38/1310 | 1.00 (referent) | 0.8 | |
| T2 | 28/1313 | 0.76 (0.46, 1.27) | | |
| T3 | 35/1328 | 1.09 (0.67, 1.77) | | |
| Mortality by CVD or cancer (*n* = 164) | | | | 0.4 |
| Placebo group | | | | |
| Continuous DII score | 85/3981 | 1.18 (1.01, 1.39) | 0.04 | |
| T1 | 23/1323 | 1.00 (referent) | 0.06 | |
| T2 | 29/1315 | 1.65 (0.85, 3.21) | | |
| T3 | 33/1293 | 1.92 (0.99, 3.71) | | |
| Antioxidant supplementation group | | | | |
| Continuous DII score | 79/3951 | 1.11 (0.96, 1.28) | 0.2 | |
| T1 | 26/1310 | 1.00 (referent) | 0.3 | |
| T2 | 23/1313 | 0.88 (0.50, 1.56) | | |
| T3 | 30/1328 | 1.32 (0.77, 2.26) | | |
| Cancer-specific mortality (*n* = 123) | | | | 0.3 |
| Placebo group | | | | |
| Continuous DII score | 66/3931 | 1.24 (1.03, 1.50) | 0.03 | |
| T1 | 16/1323 | 1.00 (referent) | 0.02 | |
| T2 | 23/1315 | 2.09 (0.92, 4.78) | | |
| T3 | 27/1293 | 2.65 (1.18, 5.98) | | |
| Antioxidant supplementation group | | | | |
| Continuous DII score | 57/3951 | 1.13 (0.95, 1.34) | 0.2 | |
| T1 | 19/1310 | 1.00 (referent) | 0.3 | |
| T2 | 15/1313 | 0.79 (0.40, 1.59) | | |
| T3 | 23/1328 | 1.43 (0.76, 2.68) | | |

[1]Sex-specific cutoffs for tertiles of DII adjusted for energy intake by the residual method were used. In men, lower bounds of tertiles 2 and 3 were 0.20 and 1.46. In women, lower bounds of tertiles 2 and 3 were −0.09 and 1.41. Multivariate Cox proportional hazards models were adjusted for age (timescale in the Cox model), sex, number of 24-h dietary records, BMI, physical activity, smoking status, educational level, family history of cancer in first-degree relatives, family history of CVD in first-degree relatives, energy intake without alcohol, and alcohol intake. CVD, cardiovascular disease; DII, Dietary Inflammatory Index; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants; T, tertile.

biomarkers such as blood IL-6 (6, 8, 26, 43) and CRP (6, 24, 43) concentrations. In line with our findings, in a cohort of US women, the DII was associated with all-cause, cancer, and CVD mortality (30). In another cohort including Swedish women, the DII was associated with all-cause and digestive tract cancer mortality (31). To our knowledge, no other prospective study has previously tested for the association between the DII and mortality, and none had tested this relation in men. Our results are also consistent with epidemiologic studies that observed a direct relation between inflammatory biomarkers and mortality. The Emerging Risk Factors Collaboration team published a meta-analysis including 1.31 million person-years of observation from 54 long-term prospective studies and concluded that elevated CRP concentrations were positively associated with vascular mortality and mortality due to several cancers (2). After this meta-analysis, other studies also observed prospective associations between biomarkers of inflammation, such as CRP (3), IL-6 (3, 4), TNF-$\alpha$ receptor 1 (4), and chitinase 3–like protein 1 (5), and mortality.

Chronic diseases were responsible of 68% of deaths in the world in 2012 (44). Among them, CVD, cancer, diabetes, and chronic respiratory diseases were the 4 leading causes of death. Thus, our results also are consistent with prospective studies that have investigated the relations between the DII and the incidence of chronic diseases (14, 17, 19, 23, 25). Of these, one showed positive associations with lung cancer risk (17), 3 with colorectal cancer risk (19, 23, 25), and another with CVD risk (14). In addition, nonprospective case-control investigations found positive associations with colorectal (22, 27), prostate (20, 28), esophageal (13, 29), and pancreatic (21) cancers and asthma (26). However, no relation has been observed between the DII and breast cancer (16). In the SU.VI.MAX cohort, the DII was associated with increased risk of CVD (unpublished results, 2015) and some cancers (45).

The results of the present study also are in line with epidemiologic findings on the association between inflammatory biomarkers and chronic disease incidence. In their meta-analysis, Kaptoge et al. (2) showed that CRP concentration was associated with the risk of coronary heart disease, ischemic stroke, and lung disease. Gan et al. (46) found in a meta-analysis that chronic obstructive pulmonary disease risk was positively associated with several systemic inflammatory markers (circulating leukocytes, TNF-$\alpha$, and fibrogen concentrations). As shown in meta-analyses (47, 48), epidemiologic studies reported positive associations between inflammatory biomarkers such as CRP or IL-6 and an increased risk of overall and lung cancer. In a previous prospective case-control study nested in the SU.VI.MAX cohort, we found that baseline plasma concentration of high-sensitivity CRP was associated with an increased risk of overall cancer and prostate cancer (49).

A prominent finding of this study is that a proinflammatory diet was associated with an increase in all-cause mortality in the placebo group of the SU.VI.MAX trial but not in the antioxidant-supplemented group. This result suggests that antioxidants may contribute to counteract some of the potentially deleterious effects of a proinflammatory diet. Mechanistic data from experimental studies support these observations. First, they show that inflammation figures in chronic disease etiology and mortality (1, 50). Second, they demonstrate the interrelation between inflammation and oxidative stress with respect to several chronic diseases (CVD and tumors) and metabolic dysregulation (diabetes and metabolic syndrome) (1, 32). Finally, long-term exposure to oxidative stress damages cellular and organ system structures and functions via pathways involving chronic inflammation (32).

Strengths of our study include its prospective design with long follow-up, the implementation of a literature-derived index to assess the overall inflammatory potential of the diet, and the randomized control trial design to test the potential modulatory effect of antioxidant supplementation at nutritional doses on the studied relation. Also, dietary intake was assessed by repeated 24-h dietary records (mean of 9.5 records per subject) accounting for intraindividual variability, including day-to-day and seasonal variations. Finally, a large range of confounding factors has been taken into account, thus limiting potential bias. Despite the study's strengths, some limitations should be acknowledged. First, the limited number of deaths may have impaired our ability to detect some of the hypothesized associations. In particular, the limited number of cardiovascular deaths did not allow us to perform the analysis for this cause of death separately. This limited number of deaths is probably due to this study being performed on middle-aged adults (mean $\pm$ SD age at inclusion: 49.0 $\pm$ 6.3 y). Thus, caution is needed when extrapolating these results to an older population. Second, subjects were volunteers involved in a long-term nutrition study and thus were more health conscious than the general French population and, concomitantly, had potentially healthier behaviors. Also, the selection of participants who provided at least three 24-h dietary records increased the quality of dietary data but overrepresented compliant and healthy subjects (less obese, nonsmokers, better educated). In addition, although most of the 45 DII variables were taken into account ($n$ = 36), some items ($n$ = 9) were missing in our database and thus could not be included: caffeine, eugenol, saffron, selenium, turmeric, zinc, thyme/oregano, and rosemary (anti-inflammatory factors) and *trans* fatty acids (proinflammatory factor). However, it is unlikely that these missing variables have drastically influenced the results, because it has been shown that the ability of the DII to predict inflammation remained the same when the number of food variables was decreased from 45 to 28 (6). In addition, sensitivity analyses performed in this study (e.g., including the nonvalidated zinc information or including only PUFAs but not n–3 and n–6 fatty acids) showed very consistent and stable results.

To our knowledge, this study was the first to investigate the prospective association between the DII and mortality in a large population-based French cohort including both men and women. The randomized controlled design of the SU.VI.MAX trial allowed us to test the potential effect modification of the relation between the DII and mortality by antioxidant supplements. The results showed that a proinflammatory diet was associated with increased all-cause mortality in the placebo group but not in the antioxidant-supplemented group. Thus, in line with results from laboratory studies, our findings suggest that antioxidants may contribute to counteract some of the potential deleterious effects of a proinflammatory diet on mortality. These results provide interesting insights into the understanding of the relations between diet-related inflammation and mortality.

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The authors' responsibilities were as follows—LG and MT: designed the research; SH, PG, EK-G, and MT: conducted the research; NS, JRH, and MDW: designed and computed the DII score; LG: performed statistical analysis and wrote the manuscript; MT: supervised the study and had primary responsibility for final manuscript content; MD, FM, LN, NS, JRH, MDW, PL-M, SH, PG, CJ, EK-G, and MT: contributed to the data interpretation and revised each draft for important intellectual content; and all authors: read and approved the final manuscript. JRH owns controlling interest in Connecting Health Innovations LLC, a company planning to license the right to his invention of the DII from the University of South Carolina to develop computer and smartphone applications for patient counseling and dietary intervention in clinical settings. NS and MDW are employees of Connecting Health Innovations LLC. The other authors declared no conflicts of interest.

## REFERENCES

1. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006; 444:860–7.
2. Kaptoge S, Di AE, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375:132–40.
3. Adriaensen W, Mathei C, Vaes B, van Pottelbergh G, Wallemacq P, Degryse JM. Interleukin-6 as a first-rated serum inflammatory marker to predict mortality and hospitalization in the oldest old: a regression and CART approach in the BELFRAIL study. Exp Gerontol 2015;59: 53–61.
4. Varadhan R, Yao W, Matteini A, Beamer BA, Xue QL, Yang H, Manwani B, Reiner A, Jenny N, Parekh N, et al. Simple biologically informed inflammatory index of two serum cytokines predicts 10 year all-cause mortality in older adults. J Gerontol A Biol Sci Med Sci 2014;69:165–73.
5. Mygind ND, Iversen K, Kober L, Goetze JP, Nielsen H, Boesgaard S, Bay M, Johansen JS, Nielsen OW, Kirk V, et al. The inflammatory biomarker YKL-40 at admission is a strong predictor of overall mortality. J Intern Med 2013;273:205–16.
6. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, Tabung F, Hebert JR. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). Public Health Nutr 2014;17: 1825–33.

7. Nanri A, Yoshida D, Yamaji T, Mizoue T, Takayanagi R, Kono S. Dietary patterns and C-reactive protein in Japanese men and women. Am J Clin Nutr 2008;87:1488–96.
8. Shivappa N, Hebert JR, Rietzschel ER, De Buyzere ML, Langlois M, Debruyne E, Marcos A, Huybrechts I. Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study. Br J Nutr 2015;113:665–71.
9. Chakrabarti S, Jahandideh F, Wu J. Food-derived bioactive peptides on inflammation and oxidative stress. Biomed Res Int 2014;2014:608979.
10. Hardman WE. Diet components can suppress inflammation and reduce cancer risk. Nutr Res Pract 2014;8:233–40.
11. Julia C, Meunier N, Touvier M, Ahluwalia N, Sapin V, Papet I, Cano N, Hercberg S, Galan P, Kesse-Guyot E. Dietary patterns and risk of elevated C-reactive protein concentrations 12 years later. Br J Nutr 2013; 110:747–54.
12. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr 2014;17:1689–96.
13. Shivappa N, Zucchetto A, Serraino D, Rossi M, La VC, Hebert JR. Dietary inflammatory index and risk of esophageal squamous cell cancer in a case-control study from Italy. Cancer Causes Control 2015; 26:1439–47.
14. Garcia-Arellano A, Ramallal R, Ruiz-Canela M, Salas-Salvado J, Corella D, Shivappa N, Schroder H, Hebert JR, Ros E, Gomez-Garcia E, et al. Dietary inflammatory index and incidence of cardiovascular disease in the PREDIMED Study. Nutrients 2015;7:4124–38.
15. Alkerwi A, Shivappa N, Crichton G, Hebert JR. No significant independent relationships with cardiometabolic biomarkers were detected in the Observation of Cardiovascular Risk Factors in Luxembourg study population. Nutr Res 2014;34:1058–65.
16. Ge I, Rudolph A, Shivappa N, Flesch-Janys D, Hebert JR, Chang-Claude J. Dietary inflammation potential and postmenopausal breast cancer risk in a German case-control study. Breast 2015;24:491–6.
17. Maisonneuve P, Shivappa N, Hebert JR, Bellomi M, Rampinelli C, Bertolotti R, Spaggiari L, Palli D, Veronesi G, Gnagnarella P. Dietary inflammatory index and risk of lung cancer and other respiratory conditions among heavy smokers in the COSMOS screening study. Eur J Nutr 2015 May 8 (Epub ahead of print; DOI: 10.1007/s00394-015-0920-3).
18. Ruiz-Canela M, Zazpe I, Shivappa N, Hebert JR, Sanchez-Tainta A, Corella D, Salas-Salvado J, Fito M, Lamuela-Raventos RM, Rekondo J, et al. Dietary inflammatory index and anthropometric measures of obesity in a population sample at high cardiovascular risk from the PREDIMED (PREvencion con DIeta MEDiterranea) trial. Br J Nutr 2015;113:984–95.
19. Shivappa N, Prizment AE, Blair CK, Jacobs DR Jr., Steck SE, Hebert JR. Dietary inflammatory index and risk of colorectal cancer in the Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prev 2014;23:2383–92.
20. Shivappa N, Bosetti C, Zucchetto A, Montella M, Serraino D, La VC, Hebert JR. Association between dietary inflammatory index and prostate cancer among Italian men. Br J Nutr 2014 Nov 17 (Epub ahead of print; DOI: 10.1017/S0007114514003572).
21. Shivappa N, Bosetti C, Zucchetto A, Serraino D, La VC, Hebert JR. Dietary inflammatory index and risk of pancreatic cancer in an Italian case-control study. Br J Nutr 2014 Dec 17 (Epub ahead of print; DOI: 10.1017/S0007114514003626).
22. Shivappa N, Zucchetto A, Montella M, Serraino D, Steck SE, La VC, Hebert JR. Inflammatory potential of diet and risk of colorectal cancer: a case-control study from Italy. Br J Nutr 2015;114:152–8.
23. Tabung FK, Steck SE, Ma Y, Liese AD, Zhang J, Caan B, Hou L, Johnson KC, Mossavar-Rahmani Y, Shivappa N, et al. The association between dietary inflammatory index and risk of colorectal cancer among postmenopausal women: results from the Women's Health Initiative. Cancer Causes Control 2015;26:399–408.
24. Wirth MD, Burch J, Shivappa N, Violanti JM, Burchfiel CM, Fekedulegn D, Andrew ME, Hartley TA, Miller DB, Mnatsakanova A, et al. Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers. J Occup Environ Med 2014; 56:986–9.
25. Wirth MD, Shivappa N, Steck SE, Hurley TG, Hebert JR. The dietary inflammatory index is associated with colorectal cancer in the National Institutes of Health-American Association of Retired Persons Diet and Health Study. Br J Nutr 2015;113:1819–27.
26. Wood LG, Shivappa N, Berthon BS, Gibson PG, Hebert JR. Dietary inflammatory index is related to asthma risk, lung function and systemic inflammation in asthma. Clin Exp Allergy 2015;45:177–83.
27. Zamora-Ros R, Shivappa N, Steck SE, Canzian F, Landi S, Alonso MH, Hebert JR, Moreno V. Dietary inflammatory index and inflammatory gene interactions in relation to colorectal cancer risk in the Bellvitge colorectal cancer case-control study. Genes Nutr 2015;10:447.
28. Shivappa N, Jackson MD, Bennett F, Hebert JR. Increased Dietary Inflammatory Index (DII) is associated with increased risk of prostate cancer in Jamaican men. Nutr Cancer 2015;67:941–8.
29. Lu Y, Shivappa N, Lin Y, Lagergren J, Hebert JR. Diet-related inflammation and oesophageal cancer by histological type: a nationwide case-control study in Sweden. Eur J Nutr 2015 Jul 19 (Epub ahead of print; DOI: 10.1007/s00394-015-0987-x).
30. Shivappa N, Blair CK, Prizment AE, Jacobs DR Jr, Steck SE, Hebert JR. Association between inflammatory potential of diet and mortality in the Iowa Women's Health study. Eur J Nutr 2015 Jul 1 (Epub ahead of print; DOI: 10.1007/s00394-015-0967-1).
31. Shivappa N, Harris H, Wolk A, Hebert JR. Association between inflammatory potential of diet and mortality among women in the Swedish Mammography Cohort. Eur J Nutr 2015 Jul 31 (Epub ahead of print; DOI: 10.1007/s00394-015-1005-z).
32. Duracková Z. Some current insights into oxidative stress. Physiol Res 2010;59:459–69.
33. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med 2010;49:1603–16.
34. Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, Roussel AM, Favier A, Briancon S. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. Arch Intern Med 2004;164:2335–42.
35. Hercberg S, Preziosi P, Briancon S, Galan P, Triol I, Malvy D, Roussel AM, Favier A. A primary prevention trial using nutritional doses of antioxidant vitamins and minerals in cardiovascular diseases and cancers in a general population: the SU.VI.MAX study—design, methods, and participant characteristics. SUpplementation en VItamines et Mineraux AntioXydants. Control Clin Trials 1998;19:336–51.
36. Hercberg S, Galan P, Preziosi P, Roussel AM, Arnaud J, Richard MJ, Malvy D, Paul-Dauphin A, Briancon S, Favier A. Background and rationale behind the SU.VI.MAX Study, a prevention trial using nutritional doses of a combination of antioxidant vitamins and minerals to reduce cardiovascular diseases and cancers. SUpplementation en VItamines et Mineraux AntioXydants Study. Int J Vitam Nutr Res 1998;68:3–20.
37. Le Moullec N, Deheeger M, Preziosi P, Montero P, Valeix P, Rolland-Cachera M, Potier de Courcy G, Christides J, Galan P, Hercberg S. Validation du manuel photo utilisé pour l'enquête alimentaire de l'étude SU.VI.MAX [Validation of the food portion size booklet used in the SU.VI.MAX study]. Cah Nutr Diet 1996;31:158–64 (in French).
38. Hercberg S. Table de composition SU.VI.MAX des aliments [SU.VI.MAX food composition table]. Paris: Les éditions INSERM/Economica; 2005 (in French).
39. Neveu V, Perez-Jimenez J, Vos F, Crespy V, du Chaffaut L, Mennen L, Knox C, Eisner R, Cruz J, Wishart D, et al. Phenol-Explorer: an online comprehensive database on polyphenol contents in foods. Database (Oxford) 2010;2010:bap024.
40. Touvier M, Druesne-Pecollo N, Kesse-Guyot E, Andreeva VA, Fezeu L, Galan P, Hercberg S, Latino-Martel P. Dual association between polyphenol intake and breast cancer risk according to alcohol consumption level: a prospective cohort study. Breast Cancer Res Treat 2013;137:225–36.
41. WHO. ICD-10: International classification of diseases and related health problems. 10th revision. Geneva (Switzerland): WHO; 2010.
42. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65:1220S–8S.
43. Cavicchia PP, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, Hebert JR. A new dietary inflammatory index predicts interval changes in serum high-sensitivity C-reactive protein. J Nutr 2009; 139:2365–72.
44. WHO. Global status report on noncommunicable diseases 2014 "Attaining the nine global noncommunicable diseases targets; a shared responsibility." Geneva (Switzerland): World Health Organization; 2014.

45. Graffouillère L, Deschasaux M, Mariotti M, Neufcourt L, Shivappa N, Hébert JR, Wirth MD, Latino-Martel P, Hercberg S, Galan P, et al. The Dietary Inflammatory Index (DII) is associated with prostate cancer risk in French middle-aged adults in a prospective study. J Nutr. In press.
46. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 2004;59:574–80.
47. Heikkilä K, Harris R, Lowe G, Rumley A, Yarnell J, Gallacher J, Ben-Shlomo Y, Ebrahim S, Lawlor DA. Associations of circulating C-reactive protein and interleukin-6 with cancer risk: findings from two prospective cohorts and a meta-analysis. Cancer Causes Control 2009;20:15–26.
48. Guo YZ, Pan L, Du CJ, Ren DQ, Xie XM. Association between C-reactive protein and risk of cancer: a meta-analysis of prospective cohort studies. Asian Pac J Cancer Prev 2013;14:243–8.
49. Touvier M, Fezeu L, Ahluwalia N, Julia C, Charnaux N, Sutton A, Mejean C, Latino-Martel P, Hercberg S, Galan P, et al. Association between prediagnostic biomarkers of inflammation and endothelial function and cancer risk: a nested case-control study. Am J Epidemiol 2013;177:3–13.
50. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860–7.