Long-term associations between inflammatory dietary scores in relation to long-term C-reactive protein status measured 12 years later: findings from the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) cohort

Chantal Julia[1,2]*, Karen E. Assmann[1], Nitin Shivappa[3,4,5], James R. Hebert[3,4,5], Michael D. Wirth[3,4,5], Serge Hercberg[1,2], Mathilde Touvier[1] and Emmanuelle Kesse-Guyot[1]

[1]*Equipe de Recherche en Epidémiologie Nutritionnelle (EREN), Centre d'Epidémiologie et Statistiques Sorbonne Paris Cité, Inserm (U1153), Inra (U1125), Cnam, COMUE Sorbonne Paris Cité, Université Paris 13, F-93017 Bobigny, France*
[2]*Département de Santé Publique, Hôpital Avicenne (AP-HP), Bobigny, F-93000, France*
[3]*Cancer Prevention and Control Program, University of South Carolina, 915 Greene Street, Suite 241, Columbia, SC 29208, USA*
[4]*Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC 29208, USA*
[5]*Connecting Health Innovations, LLC, Columbia, SC 29201, USA*

Abstract

Chronic low-grade inflammation has been recognised as a key underlying mechanism for several chronic diseases, including cancer and CVD. Nutrition represents a host of key modifiable factors that influence chronic inflammation. Dietary inflammatory scores were developed to assess the inflammatory potential of the diet and have been associated with inflammatory biomarkers in cross-sectional and short-term longitudinal studies. The objective of this study was to investigate the relationship between the dietary inflammatory index (DII), the alternate dietary inflammatory index (ADII) and long-term C-reactive protein (CRP). We also tested age as an effect modifier of this relationship. Participants were selected in the Supplémentation en Vitamines et Minéraux Antioxydants study, which included subjects aged 45–60 years old for men and 35–60 years old for women in 1994. Participants with ≥3 24-h dietary records at baseline and a CRP measurement at the 12-year follow-up evaluation were included in the present study (*n* 1980). The relationships between the DII and ADII and elevated CRP (>3 mg/l) were investigated using logistic multivariable regression. All analyses were stratified by age (cut-off at median age = 50 years old). The overall associations between DII and ADII and long-term CRP were not statistically significant (P_{trend} across tertiles = 0·16 for DII and 0·10 for ADII). A quantitative interaction was found between ADII score and age (*P* = 0·16 for ADII, 0·36 for DII). In stratified analyses the ADII was significantly prospectively associated with CRP only in younger participants: OR tertile 3 *v.* tertile 1: 1·79 (95 % CI 1·04, 3·07). Pro-inflammatory diets may have long-term effect on CRP only in younger subjects.

Key words: Dietary scores: Inflammation: C-reactive protein

Inflammatory processes are adaptive physiological mechanisms of organism defense against tissue injury or infection[1]. The first description of inflammatory processes in tissue date back to the 19th century by Virchow[2], who had already linked inflammation to chronic conditions[3]. Over the following centuries, the description of cellular and molecular mechanisms involved in the acute inflammatory response has led to the unraveling of some of the most important characteristics of these adaptive processes[1]. Inflammatory response to injury now appears as a highly controlled succession of key stages, the dysregulation of which has been recognised as leading to tissue damage in the long term[1]. In particular, chronic low-grade inflammation has been recognised as a key underlying mechanism for several chronic diseases, including obesity, type 2 diabetes, cancer and CVD[4–9].

Chronic low-grade systemic inflammation appears to be influenced by both non-modifiable and modifiable factors[1,10,11]. Among the former are genetic and hormonal factors, which appear to be affected, in part, by ageing[12,13]. In particular, genetically driven modifications appear to be

involved in the immune system senescence leading to a higher inflammatory status with ageing[12,13]. In contrast, nutrition is now recognised as one of the key modifiable factors in regulating chronic low-grade systemic inflammation[14]. Multiple components of the diet have been identified as having the capacity to intervene in the production or regulation of inflammatory mediators[15,16]. Among the nutritional factors most studied, long-chain fatty acids have been identified as key precursors for pro- or anti-inflammatory mediators[16]. However, investigating the contribution of the whole diet to inflammatory processes requires specific methods such as assigning dietary scores based on culinary practices or dietary recommendations (*a priori* scores), or by conducting analyses of dietary intakes reported in research studies or surveys (*a posteriori* scores) (e.g. principal components analysis)[17]. Investigating dietary patterns is important since nutrients may have synergistic or antagonistic effects in interaction with the food matrix depending on the combination of foods within meals that compose the diet[18]. In a previous paper, we showed that diet characterised by high intakes of antioxidant micronutrients and essential fatty acids were significantly associated with a reduced risk of elevated C-reactive protein (CRP)[19].

To better characterise the inflammatory properties of the diet, *a priori* dietary indices, specifically aiming at measuring the dietary inflammatory load have been developed based on the existing literature examining associations between diet and systemic chronic inflammation[20,21]. The dietary inflammatory index (DII) score has been associated to inflammatory biomarkers in cross-sectional studies and repeated measures short-term studies[20,22–25], as well as with mortality and several chronic diseases: CVD, cancer and the metabolic syndrome[24–46]. Second, an alternative dietary inflammatory index (ADII) has recently been developed based on the DII by Cavicchia *et al.*[20] and validated against biomarkers of inflammation[47]. This ADII differs from the DII by the type and number of items included in the score, and the way energy is taken into account. However, the contribution of the diet to low-grade chronic inflammation in the long term has not been evaluated.

Our objective was to investigate the association between the DII and the ADII scores and levels of CRP in the long term, in a middle-aged French cohort study. Moreover, as the various non-modifiable factors involved in inflammatory processed are reported to be modified with ageing, age was tested as a potential effect modifier of the relationship.

Methods

Study population

The study population was selected from participants of the SUpplémentation en VItamines et Minéraux AntioXydants (SU.VI.MAX) 2 study. The initial SU.VI.MAX study was designed in 1994–1996 as a randomised, double-blind, placebo-controlled, primary prevention trial designed to evaluate the effect of an 8-year supplementation with antioxidant vitamins and minerals at nutritional doses on the incidence of CVD and cancer[48]. In 2007–2009, participants were offered the opportunity to enroll in

an additional observational follow-up study, the SU.VI.MAX2 study – on which our study sample was based[49]. Subjects who agreed to enroll underwent a clinical examination and had blood drawn for biological tests. In the SU.VI.MAX2 study, a subsample selected on geographical criteria for operative and logistical aspects (including availability to travel to the evaluation centres of the SU.VI.MAX2 study) was included in the 'CRP study'.

Both the SU.VI.MAX and the SU.VI.MAX2 studies were approved by the Ethics Committee for Studies with Human Subjects of Paris-Cochin Hospital (no. 706 and no. 2364, respectively) and the Comité National Informatique et Liberté (no. 334641 and no. 907094, respectively). All subjects gave written informed consent to participate in the study. The initial SU.VI.MAX trial was registered at clinicaltrial.gov (no. NCT00272428).

All subjects included in the CRP study were eligible for the present study, whether they were members of the placebo or supplementation group of the initial SU.VI.MAX trial phase. Subjects having less than three dietary records in the first 2 years of the SU.VI.MAX study (1994–1996) and subjects having missing data on covariates were excluded from the analyses.

Data collection

Dietary data assessment. Dietary information was collected every 2 months using 24-h dietary record via computerised questionnaires. A total of six randomly distributed records could be completed per year, covering each day of the week and all seasons. Participants were assisted by an instruction manual, which included validated photographs of >250 generic foods shown in three main portion sizes[50]. A French food composition table was used to estimate the daily nutrient intake[51]. Dietary records were considered as invalid if energy intake was or <418 or >25 104 kJ/d (<100 or >6000 kcal/d). In addition, men reporting <3347 kJ/d (<800 kcal/d) and women reporting <2092 kJ/d (<500 kcal/d) across at least one-third of their dietary records were excluded to account for energy under-reporting. Mean daily nutritional intakes were calculated as the mean of all available 24-h dietary records during the first 2 years of follow-up (mean number of 24 h records/subject = 10·1 (SD 3·07)).

Dietary inflammatory indices. Two DII scores were computed in the present analysis, the DII and ADII. The DII is a score initially designed with forty-five dietary parameters determined from a literature review. A first version of the DII was published in 2009[20], and the score was updated with the inclusion of more than 1943 articles in 2014[21]. The computation of the updated DII has been described in detail previously[21]. A literature-derived inflammatory effect score is assigned to every micronutrient, macronutrient or food parameter associated with an increase (+1), a decrease (−1) or no effect (0) on six of the following inflammatory biomarkers: IL-1β, IL-4, IL-6, IL-10, TNF-α and CRP, based on a detailed literature review. An overall inflammatory weight is attributed to each of the dietary components, based on the number and design of each study investigating that component. The weights of the various components therefore range between −0·908 and 0·429[21].

The mean individual intake of every food parameter in the sample is converted to a z-score using standardised values from a world database, then converted to a percentile and centred, in order to correct for the skewness of the initial variables distribution. Finally, the centred percentile score for each parameter is multiplied with its associated inflammatory weight; then these are summed across the parameters, thus providing an individual DII score. In the present study, the DII was based on thirty-six dietary parameters available in the database: total energy intake, protein, carbohydrate, total fat, SFA, cholesterol, vitamin B_{12}, Fe, MUFA, PUFA, n-3 fatty acids, n-6 fatty acids, alcohol, fibre, Mg, niacin, thiamine, riboflavin, vitamin B_6, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, β-carotene, anthocyanidins, flavan-3-ol, flavonols, flavanones, flavones, isoflavones, garlic, ginger, pepper (seasoning), onion and tea. Lower (i.e. more negative) DII scores represent more anti-inflammatory diets, whereas higher (i.e. more positive) DII scores represented more pro-inflammatory diets.

An alternative score (ADII), based on the DII by Cavicchia *et al.* and following the methodology laid down by van Woudenbergh *et al.*[47] was also computed. In brief, the ADII differs from the original DII, as it does not include those variables for which all subparts are already included in the score (e.g. energy intake, as all macronutrients are already included in the score, total fat, as all fatty acids are included), and it does not take into account polyphenol components (anthocyanidins, flavan-3-ol, flavonols, flavanones, flavones, isoflavones). Moreover, it uses energy-adjusted standardised intakes in the computation of the final score[47]. Energy-adjusted residuals are used in order to reduce the variation in dietary intake resulting from differences in physical activity, body size and metabolic efficiency[52].

Inflammation measurement. Blood samples were drawn from participants in the SU.VI.MAX2 study (2007–2009), immediately centrifuged and stored frozen at −80°C. CRP concentrations were measured using an immunoturbidimetric assay (reagent: Tina quant C-reactive protein (latex) assay; Roche), with a detection limit of 1 mg/l for CRP. Intra-assay and inter-assay CV were 0·61 and 2·87 %, respectively.

Covariate assessment. Baseline self-administered questionnaires were used to collect data regarding socio-demographic factors (marital status (single/cohabiting), educational level (primary, secondary, superior)), physical activity (subjects were asked to report if they regularly practiced physical activity (yes or no) and if yes, if they practiced the equivalent of >1 h walking/d (yes or no), herein coded as: irregular, <1 h equivalent walking/d, ≥1 h equivalent walking/d) and smoking status (never smoked, former smoker, current smoker)). Data were obtained through self-administered questionnaire at baseline (1994–1996).

Anthropometric measurements were taken at a clinical examination 1 year after inclusion in the SU.VI.MAX study (1995–1997) and considered as baseline data. Weight was measured to the nearest 0·1 kg with subjects wearing only light clothing and without shoes. Height was measured to the nearest cm using a wall-mounted stadiometer in the same conditions.

BMI was calculated as the weight (kg) divided by the square of height (m), and obesity was defined as BMI ≥ 30 kg/m^2.

Data from a total of 3476 subjects were included in the CRP study. Of these, 861 were excluded for insufficient number of dietary records, 502 for missing data on anthropometric measurements, forty-three for missing data on socio-demographic variables and thirty-nine for missing data on tobacco use or physical activity. Finally, fifty-one subjects were further excluded for CRP values >10 mg/l, leaving a final sample of 1980 subjects for analyses. Compared with the 8112 subjects having three available dietary records in the SU.VI.MAX study, subjects included in the study were more likely to be male, older, non-smokers and with higher physical activity.

Statistics

For descriptive purposes, nutrient intakes across DII and ADII scores were computed using the residual approach. CRP was categorised as ≤3 and >3 mg/l (considered as 'elevated CRP') and values >10 mg/l were excluded[53]. Logistic regression models were applied to estimate OR (95 % CI) of CRP > 3 mg/l across tertiles of DII scores. P_{trend} across tertiles of DII scores were computed using DII tertiles as continuous variables. Crude associations were investigated, as well as several covariate adjustments: (1) sex and initial allocation in the supplementation/placebo group of the SU.VI.MAX trial (although initial supplementation allocation group had no effect on probability of CRP > 3 mg/l, for consistency the variable was included in the adjustment procedure); (2) model 1 + baseline age, educational level (primary/secondary/university), baseline smoking status (never smoker/former smoker/current smoker), baseline physical activity (irregular/ < 1 h equivalent walking/d/ ≥1 h equivalent walking/d), energy intake and number of available dietary records; (3) model 2 + BMI at baseline. Number of available dietary records was included in the adjustment procedure in order to take into account the accuracy of the collected data. Interactions were tested between DII scores and sex, age (cut-off points at the median age, 50 years old), initial allocation to the supplementation or placebo group in the SU.VI.MAX trial period, overweight status at baseline, energy and alcohol intakes (cut-off points at the median intake). Stratified analyses were conducted in case of significant interactions ($P < 0.20$). Type I error was increased in interaction tests in order to improve power[54]. In sensitivity analyses, we excluded subjects who had provided less than six dietary records (thus augmenting the precision of the dietary data). Additional sensitivity analyses excluded obese subjects at baseline and subjects with a cancer or CVD diagnosis during the first 2 years of follow-up.

All analyses were carried using SAS software (version 9.3; SAS Institute Inc.). All tests were two-sided and a P value < 0·05 was considered significant.

Results

In the included population, DII and ADII were strongly correlated, as the Spearman's correlation between DII and ADII was 0·72 (κ coefficient between tertiles 0·44).

Table 1. Characteristics of the Supplémentation en Vitamines et Minéraux Antioxydants population included in the study (n 1980) according to tertiles of dietary inflammatory index (DII) score
(Numbers and percentages; mean values and standard deviations)

	Tertile 1 (n 660)		Tertile 2 (n 660)		Tertile 3 (n 660)		
	n	%	n	%	n	%	P^*
DII score	−4·96, −0·39		−0·40, 1·24		1·25, 5·67		
Sex							
Men	371	56·2	315	47·7	231	35·0	<0·001
Women	289	43·8	345	52·3	429	65·0	
Age (years)	50·7	5·6	49·5	5·9	49·0	5·8	<0·001
Marital status							
Single/divorced/widowed	88	13·3	80	12·1	102	15·5	0·20
In couple	572	86·7	580	87·9	558	84·5	
Educational level							
Primary	111	16·8	131	19·8	137	20·8	0·006
Secondary	235	35·6	248	37·6	276	41·8	
University	314	47·6	281	42·6	247	37·4	
Smoking status							
Never smoker	322	48·8	334	50·6	353	53·5	0·02
Former smoker	279	42·3	261	39·5	225	34·1	
Current smoker	59	8·9	65	9·8	82	12·4	
Physical activity							
Irregular	116	17·6	159	24·1	172	26·1	0·004
<1 h/d	213	32·3	206	31·2	200	30·3	
≥1 h/d	331	50·2	295	44·7	288	43·6	
Baseline BMI (kg/m^2)							0·30
Mean	24·05		24·13		23·86		
SD	3·2		3·4		3·7		
Number of dietary records							0·30
Mean	10·1		10·3		10·0		
SD	3·1		3·0		3·1		
CRP status							
≤3 mg/l	592	89·7	587	88·9	575	87·1	
>3 mg/l	68	10·3	73	11·1	85	12·9	0·32

CRP, C-reactive protein.
* P values obtained using χ^2 tests or ANOVA tests, as required.

Overall, subjects in the highest tertile of DII scores (i.e. with a pro-inflammatory diet) were more likely to be women, younger, less educated, current smokers and to practice physical activity irregularly (Table 1). Similar results were observed for ADII scores (see online Supplementary Table S1), except for sex, as subjects in the highest tertile of ADII were more likely men. They also were more likely to have lower total energy intakes, lower energy intakes from carbohydrates, lower intakes of PUFA (both n-3 and n-6 fatty acids) and lower intakes of vitamin and fibre. Conversely, they were more likely to have higher energy intakes from lipids and proteins, higher intakes of alcohol and SFA (Table 2). Again, similar results were found with ADII scores (see online Supplementary Table S2), except for energy intakes and macronutrient intakes. For ADII, as expected, energy intakes across tertiles were similar. Carbohydrates and lipid intakes were similar across tertiles, and protein intakes increased with increasing scores, whereas they decreased with increasing scores for DII. Finally, overall, the differences in nutrient intakes between tertile 1 and tertile 3 were higher for ADII compared with DII.

At the 12-year follow-up examination, a total of 266 subjects had elevated CRP measurements. Long-term associations between DII and ADII and low-grade inflammation are tabulated in Table 3. Overall associations between DII, ADII and long-term inflammation were not statistically significant. No interaction was detected between the DII and age ($P = 0.36$) or between DII or ADII and sex, group allocation in the SU.VI. MAX trial period, overweight status at baseline, energy or alcohol intakes. In contrast, a qualitative interaction was found between ADII and age ($P = 0.16$), and stratified analyses according to age showed that the ADII was prospectively associated with CRP only among younger participants of the SU. VI.MAX study (age at inclusion <50 years: tertile 3 v. tertile 1: OR 1·79 (95 % CI 1·04, 3·07)) SU.VI.MAX study participants (Table 4). The restriction to subjects with at least six dietary records led to similar results (n 1748), though the relationships were no longer significant. The exclusion of obese subjects at baseline or subjects diagnosed with CVD or cancer during the first 2 years of follow-up did not modify results.

Discussion

In this study on adults issued from the French general population, the inflammatory potential of the diet, measured through the *a priori* score ADII, which uses energy-adjusted intakes, was prospectively associated with long-term inflammation measured using CRP only in the younger subjects at inclusion (35–50 years old). To the best of our knowledge, this is the first study to investigate the relationship between dietary

Table 2. Dietary intakes of the Supplémentation en Vitamines et Minéraux Antioxydants population included in the study according to tertiles of dietary inflammatory index (DII) scores (*n* 1980)†
(Mean values and standard deviations)

	Tertiles of DII score						
	Tertile 1 (*n* 660)		Tertile 2 (*n* 660)		Tertile 3 (*n* 660)		
	Mean	SD	Mean	SD	Mean	SD	*P**
DII scores	− 4·96, −0·39		− 0·40, 1·24		1·25, 5·67		
Energy (kJ/d)	10 334	2689	9121	2096	7573	1941	<0·001
Energy (kcal/d)	2470	641	2180	501	1810	464	<0·001
Carbohydrates (% energy)	42·3	6·18	41·5	6·16	41·3	5·85	0·004
Lipids (% energy)	40·1	5·34	41	5·1	40·7	4·8	0·03
Proteins (% energy)	17·6	2·64	17·5	2·67	18	2·88	0·01
Alcohol (g/d)	16·5	17·3	19·2	18·1	20·6	16·6	<0·001
SFA (g/d)	35·7	7·38	37·9	5·79	38·7	5·22	<0·001
MUFA (g/d)	34·7	6·27	34·8	5·3	34·1	4·35	0·04
PUFA (g/d)	14·7	3·76	13·5	3·32	12·5	2·76	<0·001
n-3 Fatty acids (g/d)	1·39	0·48	1·25	0·35	1·16	0·29	<0·001
n-6 Fatty acids (g/d)	12·6	3·59	11·6	3·15	10·8	2·61	<0·001
β-Carotene	5260	3020	3910	2080	2960	1460	<0·001
Vitamin C	122	50·3	97·1	38·3	77·2	29·6	<0·001
Vitamin E	14·8	4·3	12·9	3·44	11·5	2·98	<0·001
Na (mg/d)	3550	899	3440	785	3400	621	<0·001
Fibres (g/d)	23	6·24	19	4·17	17·2	3·28	<0·001

* *P* values obtained using ANOVA tests.
† Nutrient intakes expressed as energy-adjusted residuals.

Table 3. Logistic associations between tertiles and continuous dietary inflammatory index (DII) scores with long-term elevated C-reactive protein in the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study (*n* 1980)
(Odds ratios and 95 % confidence intervals)

	Tertiles of DII scores						Continuous DII scores		
	Tertile 1	Tertile 2		Tertile 3					
	OR	OR	95 % CI	OR	95 % CI	P_{trend}	OR	95 % CI	*P*
DII									
Cases (*n*)	68	73		85			226		
Crude	1	1·08	0·76, 1·54	1·29	0·92, 1·81	0·14	1·06	0·98, 1·14	0·16
Model 1*	1	1·08	0·76, 1·53	1·27	0·90, 1·79	0·17	1·05	0·97, 1·14	0·20
Model 2†	1	1·12	0·78, 1·61	1·34	0·91, 1·98	0·13	1·07	0·98, 1·17	0·13
Model 3‡	1	1·09	0·76, 1·58	1·32	0·89, 1·95	0·16	1·07	0·97, 1·17	0·16
ADII									
Cases (*n*)	71	67		88			226		
Crude	1	0·94	0·66, 1·33	1·28	0·91, 1·78	0·14	1·01	0·98, 1·05	0·55
Model 1*	1	0·94	0·66, 1·33	1·29	0·92, 1·80	0·13	1·01	0·98, 1·05	0·52
Model 2†	1	0·95	0·67, 1·36	1·33	0·94, 1·87	0·097	1·01	0·98, 1·05	0·45
Model 3‡	1	0·94	0·66, 1·35	1·33	0·94, 1·88	0·10	1·01	0·98, 1·05	0·45

ADII, alternate dietary inflammatory index.
* Model 1 adjusted on sex and initial allocation in the supplementation/placebo group of the SU.VI.MAX trial.
† Model 2: model 1+baseline age, educational level (primary/secondary/university), baseline smoking status (never smoker/former smoker/current smoker), baseline physical activity (irregular/ <1 h equivalent walking/d/ ≥1 h equivalent walking/d), energy intake and number of dietary records available.
‡ Model 3: model 2 + BMI at inclusion.

inflammatory scores (DIS) with different computational methods and low-grade inflammation with a long-term longitudinal follow-up.

Short-term longitudinal studies and cross-sectional studies investigating the association between DIS and low-grade biological inflammation have shown somewhat mixed results. In a sample of 600 subjects from the Seasonal Variation of Blood Cholesterol (SEASONS) study (mean age =48 years old), an anti-inflammatory diet estimated by the DII was associated with a lower risk of having elevated CRP (high-sensitivity CRP (hs-CRP) > 3 mg/l)[20]; similar results were found in the same population when updating the original DII score, with pro-inflammatory diets being associated with higher odds of having elevated CRP (OR of 3rd tertile *v.* 1st tertile of DII score = 1·47 (95 % CI 1·03, 2·12)[22]. In the Buffalo Cardio-Metabolic Occupational Police Stress study, a similar association between DII score and elevated hs-CRP was found[24]. In other studies, the association between DII scores and hs-CRP were not statistically

Table 4. Multivariate stratified logistic associations between dietary inflammatory index (DII) scores and long-term elevated C-reactive protein in the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study (n 1980)*
(Odds ratios and 95 % confidence intervals)

	Tertile 1	Tertile 2		Tertile 3			
	OR	OR	95 % CI	OR	95 % CI	P_{trend}	n
Age <50 years old							
DII	1	1·47	0·83, 2·60	1·56	0·85, 2·87	0·17	1028
ADII	1	1·30	0·74, 2·27	1·79	1·04, 3·07	0·03	1028
Age ≥50 years old							
DII	1	0·86	0·52, 1·43	1·20	0·70, 2·06	0·53	952
ADII	1	0·76	0·47, 1·24	1·08	0·68, 1·74	0·78	952

ADII, alternate dietary inflammatory index.
* Model adjusted on sex and initial allocation in the supplementation/placebo group of the SU.VI.MAX trial, baseline age, educational level (primary/secondary/university), baseline smoking status (never smoker/former smoker/current smoker), baseline physical activity (irregular/<1 h equivalent walking/d/≥1 h equivalent walking/d), energy intake and number of dietary records available, BMI at inclusion.

significant[23,25,46,55], although the DII was found to be associated with other biological markers of inflammation (namely, IL-6 and IL-4)[23,25]. Overall, these results suggest cross-sectional to short-term associations between DII scores and biological inflammatory biomarkers. However, further studies are needed to better characterise relationships with different types of biomarkers involved.

DII and ADII take into account a wide range of nutrients, some of which also have been identified as being associated with overall quality of the diet. As such, DII and ADII share some components with existing a priori diet quality indices. For instance, the Mediterranean diet score, which shares with DII and ADII some components both directly (ethanol intake or MUFA intakes) or indirectly (through the use of fruit and vegetables or fish and seafood consumption components) has repeatedly been associated with biological inflammatory components in cross-sectional studies[56,57]. In the Multi-Ethnic Study of Atherosclerosis, an a priori defined comprehensive healthy dietary pattern including forty-seven food groups (positive foods groups including fruit, vegetables and whole grains, negative food groups including meat, fats and snacking products) was found to be associated with various biomarkers of inflammation, including CRP[58].

With more relevance for the present results, the investigation of dietary patterns specifically related to intakes in pro- and anti-inflammatory dietary components (with the use of reduced rank regression methods) in the SU.VI.MAX study showed that a diet with high intakes of linoleic acid and antioxidant vitamins (energy-adjusted residuals of β-carotene, vitamins C and E) was negatively associated with long-term elevated CRP[19]. These results underline the difficulty of identifying and quantifying the specific contribution of dietary components to low-grade inflammation and to disentangle their effect from those of the overall nutritional quality of the diet.

The findings of our study also imply that the association between DIS and long-term inflammation depends on the computation algorithm. Indeed, the ADII was only associated with long-term chronic inflammation. Noteworthy, the original ADII developed by van Woudenbergh et al.[47] was associated with a summary score for low-grade inflammation including CRP, IL-6, IL-8, TNF-α, serum amyloid A and soluble intercellular adhesion molecule-1. Differences between the DII and

the ADII reside in: (1) the use of energy-adjusted components using the residual method, (2) the exclusion of certain items of the score, which are already comprised in other components of the score (i.e. total fat and types of fatty acids, and energy and macronutrients) and (3) the exclusion of polyphenol components[47]. Control for energy intake in the development of dietary indices – whether focusing on specific components of the diet or overall diet quality indices – is of major importance, as energy intake is a confounder in the relationship between diet and health outcomes[59]. Energy intakes act as confounders in multiple ways: first, subjects with higher overall food consumption tend to have higher intakes in all micronutrients – therefore higher dietary scores – but also energy intakes; second, energy can act in itself as a pro-inflammatory factor, through the increase in adipose tissue. This second confounding is somewhat taken into account in the DII computation, as energy appears as a parameter of the score. Moreover, the balance between the various types of fatty acids (long-chain n-6 and n-3 fatty acids in particular) rather than their total amount is thought to have a major impact on inflammatory processes[60]. Therefore, the use of both total fat and the various fatty acids in the DII might add a confounding factor to the relationship between diet and long-term inflammation. These computational differences led to a higher discrimination of subjects according to nutrient intakes for ADII compared with DII.

Our results suggest that the inflammatory potential of the diet is associated with long-term CRP only in subjects under 50 years old at baseline. Several hypothesises may be proposed to explain these findings. Ageing is associated with a wide range of modifications in the immune system, both in the adaptive and the innate immunity. These changes include the decline in T-cell functions linked to thymic atrophy, modifications in the cellularity of bone marrow associated with systemic growth hormone decrease or decline in capacity to produce inflammatory cytokines by ageing macrophages[12]. Hormonal replacement therapy in menopausal women has also been shown to increase CRP[61]. Low-grade systemic inflammation has been reported to be a characteristic of ageing processes, so-called 'inflammaging'[62,63]. Inflammaging has been hypothesised to be related to increased production and/or inadequate elimination of damaged cells and molecules with ageing[63], or to

alterations in the balance between pro- and anti-inflammatory mediators and cytokines[13]. Though nutrition may mediate the regulation of inflammatory cytokines, many of the mechanisms involved in the immune system senescence and inflammaging are non-modifiable and genetically driven[13]. In this context, it may be inferred that the inflammatory potential of the diet could be of particular importance during life periods in which non-modifiable ageing processes have not yet become the main determinant of the inflammatory state of an individual. As hormone replacement therapy may be considered as a confounder for the relationship, we ran a sensitivity analysis adjusting for this confounder, and results were not modified.

Strengths of our study include its long-term design with over 12 years of follow-up, the collection of extensively accurate data from repeated dietary records and the investigation of multiple inflammatory dietary scores. Moreover, we were able to investigate DIS, taking in to account multiple confounders, with the use of several sensitivity analyses.

Some limitations need to be addressed. First, we did not have access to hs-CRP. This limited our capacity to investigate low-grade inflammation, as 61% of our sample was under the detection limit for CRP, impeding us to use linear regression methods. However, the lower limit of our CRP measurements (i.e. 1 mg/l) still allowed us to investigate low-grade inflammation using an internationally validated cut-off point[53]. Second, we had only one measurement of CRP at the end of the follow-up and no baseline measurement. Therefore, we were not able to exclude subjects with elevated CRP at baseline or conduct repeated measures analysis. However, the results from our sensitivity analyses, excluding subjects susceptible of having elevated CRP (obese subjects at baseline or subjects diagnosed with cancer or CVD during the first 2 years of follow-up) showed consistent results, therefore suggesting that this bias may be of limited importance. Third, we did not have access to other inflammatory biomarkers or to repeated measurements of CRP. Though the inclusion of multiple biomarkers appears preferable to evaluate inflammatory status, CRP has been shown to be a good marker of low-grade inflammation, acting as an independent inflammatory predictor for multiple chronic diseases[4,6,7,64]. However, generalisation of our results to all inflammatory biomarkers or inflammatory status should be taken with caution. Other studies are needed to confirm the results of our study, and expand to other inflammatory biomarkers. Studies with repeated measurements are also needed to better understand the concurrent modifications of diet and inflammation. Finally, subjects in our study were volunteers recruited for a long-term cohort study (initially a randomised trial followed by an additional observational phase) on nutrition. Compared with subjects with at least three dietary records at baseline, subjects included in our study were more likely older, non-smokers and with higher physical activity levels, which could have strengthened this selection bias. The risk profile of our population is therefore very likely different and non-representative from the general population, with lower risks, which could have led to an underestimation of the associations.

Overall, our results suggest a differential effect of the inflammatory potential of the diet on inflammation according to age. Such results should be taken into account when analysing the prospective association between diet and inflammatory-related diseases.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114517000034

References

1. Medzhitov R (2008) Origin and physiological roles of inflammation. *Nature* **454**, 428–435.
2. Virchow R (1859) De l'inflammation (On inflammation). In *Irritation et Irritabilité*, translated from German by M Philippe Petard. Paris: Germer-Baillière – Libraire Editeur.
3. Heidland A, Klassen A, Rutkowski P, *et al.* (2006) The contribution of Rudolf Virchow to the concept of inflammation: what is still of importance? *J Nephrol* **19**, S102–S109.
4. Coussens LM & Werb Z (2002) Inflammation and cancer. *Nature* **420**, 860–867.

5. Hotamisligil GS (2006) Inflammation and metabolic disorders. *Nature* **444**, 860–867.

6. Libby P (2002) Inflammation in atherosclerosis. *Nature* **420**, 868–874.

7. Mantovani A, Allavena P, Sica A, et al. (2008) Cancer-related inflammation. *Nature* **454**, 436–444.

8. Donath MY & Shoelson SE (2011) Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol* **11**, 98–107.

9. Gregor MF & Hotamisligil GS (2011) *Inflammatory Mechanisms in Obesity*, vol. 29. Palo Alto, CA: Annual Reviews.

10. Delves PJ & Roitt IM (2000) The immune system. *N Engl J Med* **343**, 37–49.

11. Gabay C & Kushner I (1999) Mechanisms of disease: acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* **340**, 448–454.

12. Gruver AL, Hudson LL & Sennpowski GD (2007) Immuno-senescence of ageing. *J Pathol* **211**, 144–156.

13. Maijo M, Clements SJ, Ivory K, et al. (2014) Nutrition, diet and immunosenescence. *Mech Ageing Dev* **136**, 116–128.

14. Calder PC, Albers R, Antoine JM, et al. (2009) Inflammatory disease processes and interactions with nutrition. *Br J Nutr* **101**, Suppl. 1, S1–S45.

15. Hansson GK (2005) Mechanisms of disease – inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* **352**, 1685–1695.

16. Serhan CN, Chiang N & Van Dyke TE (2008) Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat Rev Immunol* **8**, 349–361.

17. Hu FB (2002) Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol* **13**, 3–9.

18. Jacobs DR, Gross MD & Tapsell LC (2009) Food synergy: an operational concept for understanding nutrition. *Am J Clin Nutr* **89**, S1543–S1548.

19. Julia C, Meunier N, Touvier M, et al. (2013) Dietary patterns and risk of elevated C-reactive protein concentrations 12 years later. *Br J Nutr* **110**, 747–754.

20. Cavicchia PP, Steck SE, Hurley TG, et al. (2009) A new dietary inflammatory index predicts interval changes in serum high-sensitivity C-reactive protein. *J Nutr* **139**, 2365–2372.

21. Shivappa N, Steck SE, Hurley TG, et al. (2014) Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr* **17**, 1689–1696.

22. Shivappa N, Steck SE, Hurley TG, et al. (2014) A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Public Health Nutr* **17**, 1825–1833.

23. Shivappa N, Hebert JR, Rietzschel ER, et al. (2015) Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study. *Br J Nutr* **113**, 665–671.

24. Wirth MD, Burch J, Shivappa N, et al. (2014) Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers. *J Occup Environ Med* **56**, 986–989.

25. Wood LG, Shivappa N, Berthon BS, et al. (2015) Dietary inflammatory index is related to asthma risk, lung function and systemic inflammation in asthma. *Clin Exp Allergy* **45**, 177–183.

26. Garcia-Arellano A, Ramallal R, Ruiz-Canela M, et al. (2015) Dietary inflammatory index and incidence of cardiovascular disease in the PREDIMED Study. *Nutrients* **7**, 4124–4138.

27. Ge I, Rudolph A, Shivappa N, et al. (2015) Dietary inflammation potential and postmenopausal breast cancer risk in a German case-control study. *Breast* **24**, 491–496.

28. Grafouillère L, Deschasaux M, Mariotti F, et al. (2016) Prospective association between the Dietary Inflammatory Index and mortality – modulation by antioxidant supplementation in the SU.VI.MAX randomized control trial. *Am J Clin Nutr* **103**, 878–885.

29. Grafouillère L, Deschasaux M, Mariotti F, et al. (2016) The Dietary Inflammatory Index (DII) is associated with prostate cancer risk in French middle-aged adults in a prospective study. *J Nutr* (epublication ahead of print version 9 March 2016).

30. Maisonneuve P, Shivappa N, Hébert JR, et al. (2015) Dietary inflammatory index and risk of lung cancer and other respiratory conditions among heavy smokers in the COSMOS screening study. *Eur J Nutr* **55**, 1069–1079.

31. Neufcourt L, Assmann K, Fezeu L, et al. (2016) Prospective association between dietary inflammatory index and cardiovascular diseases in the SU.VI.MAX cohort. *J Am Heart Assoc* **5**, e002735.

32. Neufcourt L, Assmann K, Fezeu L, et al. (2016) Prospective association between the dietary inflammatory index and metabolic syndrome: findings from the SU.VI.MAX study. *NMCD* **25**, 988–996.

33. O'Neil A, Shivappa N, Jacka FN, et al. (2015) Pro-inflammatory dietary intake as a risk factor for CVD in men: a 5-year longitudinal study. *Br J Nutr* **114**, 2074–2082.

34. Ruiz-Canela M, Zazpe I, Shivappa N, et al. (2015) 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* **113**, 984–995.

35. Sanchez-Villegas A, Ruiz-Canela M, de la Fuente-Arrillaga C, et al. (2015) Dietary inflammatory index, cardiometabolic conditions and depression in the Seguimiento Universidad de Navarra cohort study. *Br J Nutr* **114**, 1471–1479.

36. Shivappa N, Prizment AE, Blair CK, et al. (2014) Dietary inflammatory index and risk of colorectal cancer in the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev* **23**, 2383–2392.

37. Shivappa N, Bosetti C, Zucchetto A, et al. (2014) Association between dietary inflammatory index and prostate cancer among Italian men. *Br J Nutr* **113**, 278–283.

38. Shivappa N, Bosetti C, Zucchetto A, et al. (2014) Dietary inflammatory index and risk of pancreatic cancer in an Italian case-control study. *Br J Nutr* 113(2):292–8.

39. Shivappa N, Zucchetto A, Montella M, et al. (2015) Inflammatory potential of diet and risk of colorectal cancer: a case-control study from Italy. *Br J Nutr* **114**, 152–158.

40. Shivappa N, Jackson MD, Bennett F, et al. (2015) Increased dietary inflammatory index is associated with increased risk of prostate cancer in Jamaican men. *Nutr Cancer* **67**, 941–948.

41. Shivappa N, Hebert JR & Rashidkhani B (2015) Dietary inflammatory index and risk of esophageal squamous cell cancer in a case-control study from Iran. *Nutr Cancer* **67**, 1253–1259.

42. Shivappa N, Hebert JR, Polesel J, et al. (2016) Inflammatory potential of diet and risk for hepatocellular cancer in a case-control study from Italy. *Br J Nutr* **115**, 324–331.

43. Shivappa N, Hebert JR, Zucchetto A, et al. (2016) Dietary inflammatory index and endometrial cancer risk in an Italian case-control study. *Br J Nutr* **115**, 138–146.

44. Tabung FK, Steck SE, Ma Y, et al. (2015) The association between dietary inflammatory index and risk of colorectal cancer among postmenopausal women: results from the Women's Health Initiative. *Cancer Causes Control* **26**, 399–408.

45. Wirth MD, Shivappa N, Steck SE, et al. (2015) 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* **113**, 1819–1827.

46. Zamora-Ros R, Shivappa N, Steck SE, et al. (2015) Dietary inflammatory index and inflammatory gene interactions in relation to colorectal cancer risk in the Bellvitge colorectal cancer case-control study. *Genes Nutr* **10**, 447.

47. van Woudenbergh GJ, Theofylaktopoulou D, Kuijsten A, *et al*. (2013) Adapted dietary inflammatory index and its association with a summary score for low-grade inflammation and markers of glucose metabolism: the Cohort study on Diabetes and Atherosclerosis Maastricht (CODAM) and the Hoorn study. *Am J Clin Nutr* **98**, 1533–1542.

48. Hercberg S, Galan P, Preziosi P, *et al*. (2004) The SU.VI.MAX study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med* **164**, 2335–2342.

49. Kesse-Guyot E, Fezeu L, Jeandel C, *et al*. (2011) French adults' cognitive performance after daily supplementation with antioxidant vitamins and minerals at nutritional doses: a post hoc analysis of the Supplementation in Vitamins and Mineral Antioxidants (SU.VI.MAX) trial. *Am J Clin Nutr* **94**, 892–899.

50. Le Moullec N, Deheeger M, Preziosi P, *et al*. (1996) Validation du manuel photos utilisé pour l'enquête alimentaire de l'étude SU.VI.MAX (Validation of photographic document used to estimate the amounts of foods eaten by subjects in the SU.VI. MAX study). *Cahiers de Nutrition et de Diététique* **31**, 158–164.

51. Hercberg S (2005) *Table de composition SU.VI.MAX des aliments (SU.VI.MAX Food Composition Table)*. Paris: Les éditions INSERM/Economica.

52. Willett WC, Howe GR & Kushi LH (1997) Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* **65**, 1220S–1228S.

53. Pearson TA, Mensah GA, Alexander RW, *et al*. (2003) Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* **107**, 499–511.

54. Marshall SW (2007) Power for tests of interaction: effect of raising the type I error rate. *Epidemiol Perspect Innov* **4**, 4.

55. Alkerwi A, Shivappa N, Crichton G, *et al*. (2014) No significant independent relationships with cardiometabolic biomarkers were detected in the Observation of Cardiovascular Risk Factors in Luxembourg study population. *Nutr Res* **34**, 1058–1065.

56. Carter SJ, Roberts MB, Salter J, *et al*. (2010) Relationship between Mediterranean Diet Score and atherothrombotic risk: findings from the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994. *Atherosclerosis* **210**, 630–636.

57. Chrysohoou C, Panagiotakos DB, Pitsavos C, *et al*. (2004) Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: the ATTICA Study. *J Am Coll Cardiol* **44**, 152–158.

58. Nettleton JA, Schulze MB, Jiang R, *et al*. (2008) *A priori*-defined dietary patterns and markers of cardiovascular disease risk in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr* **88**, 185–194.

59. Waijers PM, Feskens EJ & Ocke MC (2007) A critical review of predefined diet quality scores. *Br J Nutr* **97**, 219–231.

60. Simopoulos AP (2008) The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. *Exp Biol Med (Maywood)* **233**, 674–688.

61. Vitale C, Gebara O, Mercuro G, *et al*. (2005) Value of C-reactive protein levels and IL-6 in predicting events levels in women at increased cardiovascular risk. *Maturitas* **50**, 239–246.

62. Chung HY, Cesari M, Anton S, *et al*. (2009) Molecular inflammation: underpinnings of aging and age-related diseases. *Ageing Res Rev* **8**, 18–30.

63. Franceschi C & Campisi J (2014) Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A* **69**, S4–S9.

64. Pradhan AD, Manson JE, Rifai N, *et al*. (2001) C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* **286**, 327–334.