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Original article

Associations between dietary inflammatory scores and biomarkers of inflammation in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort

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Abbreviations: A, antagonist; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DII, dietary inflammatory index; E-DII, dietary inflammatory index adjusted for energy intakes using the density method; E-DII$_n$, dietary inflammatory index adjusted for energy intakes using the residual method; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; HMW, High Molecular Weight; hs-CRP, high-sensitivity C-reactive protein; IARC, International Agency for Research on Cancer; IL, interleukin; ISD, Inflammatory Score of the Diet; LOD, Limit of Detection; LLOQ, Lower Limit of Quantification; R, Receptor; s, soluble; SD, standard deviation; TNF, tumor necrosis factor; ULOQ, Upper Limit of Quantification.

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SUMMARY

Background: Since the first version of the dietary inflammatory index (DII®) developed in the past decade, several other versions have been developed. However, to date no study has attempted to compare these versions with respect to their associations with biomarkers of inflammation.
Objective: We aimed to investigate the relationship between four dietary inflammatory scores [DII, two energy-adjusted derivatives (E-DII and E-DII$_r$), and the Inflammatory Score of the Diet (ISD)], and circulating levels of several inflammatory markers and adipokines.
Methods: This study included 17 637 participants from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort with at least one marker of inflammation measured in blood. Associations between the four scores and C-reactive protein (CRP), interleukin (IL)6, IL10, IL1RA, tumor necrosis factor-α (TNFα), soluble tumor necrosis factor receptor-1 (sTNFR1), sTNFR2, leptin, soluble leptin receptor (sLeptin R), adiponectin, and High Molecular Weight (HMW) adiponectin were evaluated using multivariable linear regressions adjusted for potential confounders.
Results: Positive associations were observed between the four dietary inflammatory scores and levels of CRP, IL6, sTNFR1, sTNFR2 and leptin. However, only the DII and the ISD were positively associated with IL1RA levels and only the DII and the E-DII$_r$ were positively associated with TNFα levels. The proportion of variance of each biomarker explained by the scores was lower than 2%, which was equivalent to the variance explained by smoking status but much lower than that explained by body mass index.
Conclusions: Our results suggest that the four dietary inflammatory scores were associated with some biomarkers of inflammation and could be used to assess the inflammatory potential of diet in European adults but are not sufficient to capture the inflammatory status of an individual. These findings can help to better understand the inflammatory potential of diet, but they need to be replicated in studies with repeated dietary measurements.

1. Introduction

Chronic inflammation promotes the development of numerous chronic disorders such as diabetes [1,2], cardiovascular disease [3,4], and cancer [5–7], and is characterized by elevated concentrations of circulating pro-inflammatory markers, including C-Reactive Protein (CRP), Interleukin (IL) 6, and Tumor Necrosis Factor-α (TNFα) [8,9]. Adiponectin and leptin are the most abundant adipokines produced by adipocytes, and are thought to provide an important link between obesity, insulin resistance and related inflammatory disorders [10]. Inflammation is influenced by both non-modifiable (e.g. genetic, sex-related hormonal factors) and modifiable factors (e.g. obesity, smoking, alcohol consumption, physical activity, diet) [11,12].

Nutrition is known as one of the key modifiable factors affecting circulating inflammatory markers [13,14], and several food groups have been previously associated with these markers. For instance, inverse associations were found between consumption of fruits and vegetables and circulating levels of CRP, IL6 and TNFα [15]. Some nutrients have also been associated with lower levels of inflammation (measured by CRP, adiponectin, TNFα, IL6, interleukin 1 receptor antagonist (IL1RA) and IL10 levels), such as carbohydrates [16], n-3 polyunsaturated fatty acids [17,18], or fiber [19]. On the other hand, red and processed meat intake has been reported to be positively associated with higher levels of leptin in men and women, and of CRP in women, and with lower levels of adiponectin in women [20]. A previous study has observed a J-shaped association between alcohol intake and high-sensitivity CRP (hs-CRP) in women but positive and linear-shaped association in men [21]. Nevertheless, as individual nutrients and foods are never consumed alone, and to consider potential synergistic or antagonist effects on biomarkers of inflammation between several dietary factors, tools such as dietary scores or patterns are required. In this context, recently, several dietary inflammatory scores have been developed to assess the quality of diet with regard to its inflammatory potential [8,22–24], where higher scores reflect a more pro-inflammatory diet and lower scores reflect a more anti-inflammatory diet. These scores have been shown to be positively associated with risk of many chronic diseases including cancer [24–28]. Among these scores, the Dietary Inflammatory Index (DII®) [23] has been associated with higher circulating inflammatory markers, mainly CRP and IL6, in numerous studies conducted in USA, Europe or Australia [14,29–31]. More recently, two variants of the DII, corresponding to the DII adjusted for energy intake using the density method (E-DII) [32] or using the residual method (E-DII$_r$) [9], were proposed. The E-DII has been reported to be positively associated with CRP in several studies conducted in North America, Europe and Asia [33–39], as well as to IL6, TNF, adiponectin and leptin in one study conducted in Ireland [36]. Only one study has explored the association between the E-DII$_r$ and inflammation, using hs-CRP levels in Japanese, and found a positive association [9]. In addition, another variant of the DII, namely, the Inflammatory Score of the Diet (ISD) [24] has been developed in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study and has been associated with the risk of developing several cancers [24,40–43]. The ISD differs from the DII by the reference population used for the standardization of dietary index and by the way total fat and ethanol are taken into account.

To our knowledge, no studies have been undertaken on the associations between this latter score and circulating biomarkers of inflammation. There are other dietary scores of different conceptions and designs mostly based on food groups, developed to measure the inflammatory potential of the diet. For this study, we focused on the original DII® proposed by Shivappa et al. [23] and its variants, and the ISD that are nutrients-based, and used interchangeably in the literature. The objective of the present study is therefore to assess and compare the association between four dietary inflammatory scores, the DII, the E-DII, the E-DII$_r$ and the ISD, and levels of several inflammatory markers and adipokines, in a large European cohort, the EPIC study.

2. Methods

2.1. Study population and data collection

The EPIC cohort is a multicenter prospective study including 521 323 men and women, designed to investigate the associations between nutritional, lifestyle, metabolic, and genetic risk factors, and cancer risk. Participants were enrolled between 1992 and 1999, mostly aged 30–70 years, from the general population of 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and United Kingdom). Characteristics of the study population and baseline data collection methods have been described previously [44]. All participants gave written informed consent, and the study was approved by the Ethics Review Committee of the International Agency for Research on Cancer (IARC) and by the local ethical committees of the individual EPIC centers.

Lifestyle questionnaires were used to collect data on sociodemographic characteristics, tobacco smoking, physical activity, education, medical history, and reproductive history [44]. Anthropometric variables were measured according to standardized protocols [44]. The usual diet over the previous year was assessed at recruitment using a validated country/center-specific dietary questionnaire [44,45]. In most countries, extensive quantitative food frequency questionnaires (FFQs) or semi quantitative FFQs were used. The standardized EPIC Nutrient Database was used to estimate total energy and nutrient intakes [46].

About 386 000 participants also provided a blood sample at recruitment, collected according to a standardized protocol in France, Germany, Greece, Italy, the Netherlands, Norway, Spain and the United Kingdom [44]. From each subject, about 30 ml of blood was drawn, and serum, plasma, erythrocytes and buffy coat were aliquoted in plastic straws of 0.5 ml each, which were stored in liquid nitrogen (−196 °C) in a centralized biobank. In Denmark, blood fractions were aliquoted into 1 ml tubes, and stored in the vapor phase of liquid nitrogen containers (−150 °C). In the Swedish center of Umeå, blood samples were divided into 10 aliquots of 1.5 ml each (six plasma, two buffy coat and two erythrocytes), which were rapidly frozen at −80 °C in standard freezers.

2.2. Selection of participants

Prior to statistical analysis, the following exclusions were made: 1) participants with an incident or a prevalent cancer at baseline (n = 25 944), 2) participants with missing follow-up information (n = 4148), 3) subjects from Greece due to data restriction issues (n = 26 916), 4) subjects with missing dietary information (n = 5900), 5) participants in the highest or lowest 1% of the distribution for the ratio of energy intake to estimated energy requirement (n = 9064). From the remaining individuals, we included 17 637 participants from 12 nested case–control or case-cohort studies previously conducted within EPIC on associations between inflammatory biomarkers and cancer or other chronic diseases [47–58] (see Supplementary Table S1) who had at least one measurement of biomarkers of inflammation performed and centralized at IARC, among CRP, adiponectin, High Molecular Weight (HMW) adiponectin, IL1RA, IL6, IL10, leptin, soluble leptin receptor (sLeptin R), TNFα, soluble tumor necrosis factor receptor-1 (sTNFR1) and sTNFR2 (see flowchart in Supplementary Fig. S1). The number of participants included for each biomarker was below 1000 for IL1RA, IL10, sTNFR1, sTNFR2, and sLeptin R, between 1000 and 3500 for IL6, TNFα, leptin, adiponectin, and HWM adiponectin, and >15 000 for CRP only (see Table 1).

2.3. Laboratory measurements

Serum was used for laboratory assays except for samples from Norway (citrated plasma) and Umeå, Sweden (heparin plasma). Biomarker analyses for each study were previously described in detail [47–58] (for references per study see Supplementary Table S1). Mean concentrations by study and analytical method, and number of batches for each biomarker are presented in Supplementary Table S2. The name of the study was added before the batch number, thus study information was included in batch information. For two studies (CLRT_04 and INTE_01) batch numbers were missing for all observations so a single value was imputed with the name of the study, otherwise, observations with missing batch number were excluded (n = 4 in OVAR_05 study for IL6). Values below LOD (Limit of Detection), below LLOQ (Lower Limit of Quantification), or above ULOQ (Upper Limit of Quantification) were set to LOD/2, LLOQ/2 and ULOQ, respectively. When biomarker levels were measured more than once on the same sample in different nested case control or cohort studies in the EPIC cohort, only values from the study with the highest number of quantified values on the biomarker were retained.

2.4. Dietary inflammatory scores computation

Four dietary inflammatory scores reflecting inflammatory potential of the diet were computed: the dietary inflammatory index (DII®) [23], the original dietary inflammatory index adjusted for energy intake using the density method (E-DII), the dietary inflammatory index adjusted for energy intake using the residual method (E-DII$_r$), and the Inflammatory Score of the Diet (ISD) [24]. Computation of the four scores was previously described in a study evaluating the associations of these scores and differentiated thyroid cancer risk in the EPIC cohort [43]. Briefly, to compute these scores, literature-derived coefficients were assigned to every micronutrient, macronutrient, or other food parameter associated with an increase (+1), a decrease (−1), or no effect (0) on the following six inflammatory biomarkers: IL1β, IL4, IL6, IL10, TNFα, and CRP, based on a detailed literature review [23]. These coefficients were weighted based on study design, multiplied by the standardized intakes of the food parameters, then summed across all food parameters to obtain the dietary inflammation scores, with higher scores reflecting a more pro-inflammatory diet. The four scores differed in the manner in which total energy intake was considered, the reference population used to standardize the dietary intakes, and the food parameters included. The list of these parameters and the methods used for calculating the dietary inflammatory scores are summarized in Supplementary Table S3.

2.5. Normalization and statistical analyses

We compared the four dietary inflammatory scores two-by-two by calculating Spearman correlations.

Table 1
Selected characteristics of the study population from the EPIC cohort for each biomarker at blood collection (from 1992 to 1999).

	CRP (N = 17 522)	IL6 (N = 3183)	IL10 (N = 859)	IL1RA (N = 443)	TNFα (N = 1306)	sTNFR1 (N = 742)	sTNFR2 (N = 752)	Leptin (N = 2427)	sLeptin R (N = 988)	Adiponectin (N = 3281)	HMW Adiponectin (N = 1574)
Age (years), Mean ± SD	52.5 ± 9.0	54.5 ± 8.4	49.7 ± 8.4	56.0 ± 7.3	51.9 ± 8.6	56.8 ± 7.5	56.8 ± 7.4	55.1 ± 8.5	58.0 ± 7.1	55.5 ± 8.2	58.2 ± 6.8
Sex, N (%)											
Men	5980 (34.1)	463 (14.6)	183 (21.3)		183 (14.0)	135 (18.2)	143 (19.0)	953 (39.3)	465 (47.1)	1123 (34.2)	777 (49.4)
Women	11 542 (65.9)	2720 (85.5)	676 (78.70)	443 (100)	1123 (86.0)	607 (81.8)	609 (81.0)	1474 (60.7)	523 (53.0)	2158 (65.8)	797 (50.6)
Country, N (%)											
France	773 (4.4)	230 (7.2)	105 (12.2)	25 (5.6)	130 (10.0)	45 (6.1)	46 (6.1)	148 (6.1)	35 (3.5)	202 (6.2)	43 (2.7)
Italy	2460 (14.0)	563 (17.7)	241 (28.1)	94 (21.2)	336 (25.7)	127 (17.1)	130 (17.3)	461 (19.0)	126 (12.8)	599 (18.3)	208 (13.2)
Spain	3720 (21.2)	352 (11.1)	143 (16.7)	71 (16.0)	215 (16.5)	98 (13.2)	101 (13.4)	279 (11.5)	97 (9.8)	389 (11.9)	141 (9.0)
United Kingdom	1540 (8.8)	337 (10.6)	48 (5.6)	51 (11.5)	98 (7.5)	84 (11.3)	85 (11.3)	252 (10.4)	169 (17.1)	341 (10.4)	204 (13.0)
The Netherlands	1625 (9.3)	288 (9.1)	34 (4.0)	56 (12.6)	91 (7.0)	90 (12.1)	92 (12.2)	180 (7.4)	115 (11.6)	278 (8.5)	147 (9.3)
Germany	2313 (13.2)	397 (12.5)	161 (18.7)	28 (6.3)	190 (14.6)	63 (8.5)	68 (9.0)	389 (16.0)	126 (12.8)	475 (14.5)	232 (14.7)
Sweden	2449 (14.0)	385 (12.10)	45 (5.2)	28 (6.3)	73 (5.6)	90 (12.1)	65 (8.6)	213 (8.8)	59 (6.0)	305 (9.3)	170 (10.8)
Denmark	2533 (14.5)	558 (17.5)	66 (7.7)	90 (20.3)	157 (12.0)	145 (19.5)	165 (21.9)	487 (20.1)	261 (26.4)	674 (20.5)	427 (27.1)
Norway	109 (0.6)	73 (2.3)	16 (1.9)		16 (1.2)			18 (0.7)		18 (0.6)	2 (0.1)
BMI (kg/m^2), Mean ± SD	26.0 ± 4.2	25.7 ± 4.3	25.5 ± 4.3	25.9 ± 4.3	25.6 ± 4.3	25.8 ± 4.0	25.9 ± 4.1	26.0 ± 4.0	26.2 ± 3.7	26.0 ± 4.1	26.3 ± 3.8
Fasting status, N (%)											
No	6988 (39.9)	1398 (43.9)	321 (37.4)	188 (42.4)	513 (39.3)	319 (43.0)	339 (45.1)	1057 (43.6)	485 (49.1)	1422 (43.3)	737 (46.8)
In between	2899 (16.5)	521 (16.4)	142 (16.5)	90 (20.3)	231 (17.7)	133 (17.9)	143 (19.0)	453 (18.7)	217 (22.0)	625 (19.1)	322 (20.5)
Yes	6037 (34.4)	1005 (31.6)	393 (45.8)	165 (37.3)	559 (42.8)	225 (30.3)	230 (30.6)	817 (33.7)	274 (27.7)	1066 (32.5)	416 (26.4)
Not specified	1598 (9.1)	259 (8.1)	3 (0.4)		3 (0.2)	65 (8.8)	40 (5.3)	100 (4.1)	12 (1.2)	168 (5.1)	99 (6.3)
Hour of blood collection, N (%)											
≤ 8h	2231 (12.7)	399 (12.5)	156 (18.2)	50 (11.3)	206 (15.8)	83 (11.2)	92 (12.2)	367 (15.1)	125 (12.7)	466 (14.2)	201 (12.8)
[8 h; 12 h]	7732 (44.1)	1449 (45.5)	432 (50.3)	212 (47.9)	651 (49.9)	330 (44.5)	346 (46.0)	1128 (46.5)	466 (47.2)	1521 (46.4)	708 (45.0)
[12 h; 16 h]	3229 (18.4)	697 (21.9)	147 (17.1)	110 (24.8)	255 (19.5)	176 (23.7)	182 (24.2)	503 (20.7)	244 (24.7)	700 (21.3)	359 (22.8)
> 16 h	1625 (9.3)	233 (7.3)	73 (8.5)	43 (9.7)	115 (8.8)	59 (8.0)	62 (8.2)	197 (8.1)	83 (8.4)	264 (8.1)	122 (7.8)
Not specified	2705 (15.4)	405 (12.7)	51 (5.9)	28 (6.3)	79 (6.1)	94 (12.7)	70 (9.3)	232 (9.6)	70 (7.1)	330 (10.1)	184 (11.7)
Smoking status, N (%)											
Never/Unknown	8741 (49.9)	1747 (54.9)	480 (55.9)	271 (61.2)	753 (57.7)	414 (55.8)	416 (55.3)	1173 (48.3)	442 (44.7)	1637 (49.9)	703 (44.7)
Former	4659 (26.6)	811 (25.5)	214 (24.9)	91 (20.5)	309 (23.7)	184 (24.8)	193 (25.7)	747 (30.8)	333 (33.7)	970 (29.6)	531 (33.7)
Current	4122 (23.5)	625 (19.6)	165 (19.2)	81 (18.3)	244 (18.7)	144 (19.4)	143 (19.0)	507 (20.9)	213 (21.6)	674 (20.5)	340 (21.6)
ISD, Mean ± SD	0.64 ± 1.70	0.73 ± 1.70	0.82 ± 1.68	0.73 ± 1.68	0.73 ± 1.68	0.69 ± 1.63	0.68 ± 1.62	0.67 ± 1.69	0.52 ± 1.71	0.68 ± 1.68	0.6 ± 1.70
DII, Mean ± SD	0.87 ± 1.83	0.98 ± 1.87	1.18 ± 1.89	0.98 ± 1.85	0.98 ± 1.85	0.93 ± 1.79	0.93 ± 1.79	0.95 ± 1.9	0.77 ± 1.93	0.94 ± 1.88	0.84 ± 1.90
E-DII$_r$, Mean ± SD	0.24 1.63	0.22 ± 1.69	0.51 ± 1.70	0.13 ± 1.65	0.13 ± 1.65	0.18 ± 1.6	0.18 ± 1.61	0.31 ± 1.69	0.13 ± 1.72	0.28 ± 1.68	0.21 ± 1.68
E-DII, Mean ± SD	1.15 ± 1.64	1.06 ± 1.67	1.39 ± 1.70	0.95 ± 1.6	0.95 ± 1.6	1.08 ± 1.59	1.06 ± 1.6	1.25 ± 1.66	1.09 ± 1.68	1.21 ± 1.65	1.17 ± 1.64

A, Antagonist; CRP, C-reactive protein; EPIC: European Prospective Investigation into Cancer and Nutrition; HMW, High Molecular Weight; IL, interleukin; R, Receptor; TNF, tumor necrosis factor.
All measures of biomarkers were log-transformed.

The characteristics of participants by biomarker (concentration of the biomarker, age, sex, country, BMI, fasting status, hour of blood collection, smoking status, and the four dietary inflammatory scores) were summarized using percentages for categorical variables, and mean and standard deviation (SD) for continuous variables.

Since different assays were used in different studies, we implemented different steps to be able to compare levels of biomarkers between studies. Concentrations of the biomarkers were logarithmically transformed to approximate the normal distribution. Then, we implemented a normalization step for the data from the 12 studies based on a previously published Pipeline developed on metabolomics data from the EPIC cohort [59]. In this normalization step, linear mixed effect models were used for each biomarker to correct for variation due to analytical method and batch (random effects) and to study center, fasting status (no, in between, yes) and hour of blood draw (≤8h, >8h−12h, >12h−16h, >16h) (fixed effects), and to preserve the variation due to the four dietary inflammatory scores (see description below), sex, BMI (kg/m^2; continuous), and age at recruitment (years; continuous) (fixed effects). sLeptin R concentration was not normalized because only one analytical method was used and batch information was missing. Linear regression models were used to confirm that normalization removed the unwanted sources of variation cited above.

Partial Spearman correlation coefficients adjusted for sex and age at recruitment were estimated between biomarker concentrations, as well as with age, BMI and smoking status. Associations between each standardized biomarker concentration as dependent variable and the standardized dietary inflammatory scores as independent variables were evaluated using two linear regression models: 1) crude (i.e., with no adjustment) and 2) multi-adjusted for the following potential confounders selected *a priori*: sex, BMI (kg/m^2; continuous), age at recruitment (years; continuous), and smoking status (never/unspecified, former, current); and for study center, fasting status and hour of blood draw for sLeptin R. Benjamini-Hochberg correction for multiple testing (based on the number of biomarkers tested) were applied for each score. For a given biomarker, the proportion of variance explained by each score, the BMI and the smoking status was calculated for each multi-adjusted model. Stratified analyses were conducted by sex, age (<50 years, ≥50 years), BMI (<25 kg/m^2, ≥25 kg/m^2) and, in women, according to the use of exogenous hormones (non-user, current user of oral contraceptives or hormonal replacement therapy) and menopausal status (premenopause, perimenopause, natural or surgical postmenopause). Potential interactions between the scores and those variables on biomarker concentrations were tested using the likelihood ratio test, comparing models with and without the interaction terms.

Associations between each score as a dependent variable and concentrations of adiponectin, leptin, CRP, IL6 and TNFα as independent variables adjusted for each other were assessed by linear regression models adjusted for sex, BMI, age at recruitment, and smoking status. Selection of covariates for these five biomarkers was also tested for each score based on the stepwise method with the adjustment covariates previously mentioned forced in the model.

Normalization was performed using R software (v3.5.2), and statistical analyses were performed using SAS Enterprise Guide software (v7.1, Cary, NC, USA). All tests were two-sided and P value < 0·05 was considered significant. The Pipeline for normalization is available at: https://code.iarc.fr/viallonv/pipeline_biocrates.

3. Results

Characteristics of the study populations for each biomarker at blood collection are summarized in Table 1 and mean concentrations of each biomarker after normalization are presented in Supplementary Table S2. The mean age of participants ranged from 50 to 58 years-old, and the mean BMI ranged from 25.5 to 26.3 kg/m^2, for subjects who had IL10 and HMW adiponectin measurements, respectively. Participants were mostly women, non-fasting at blood collection and non-smokers. The DII was strongly correlated with the ISD and the E-DII$_r$ (0.89 and 0.90 respectively), and to a lesser extent with the E-DII (0.59). The E-DII$_r$ was also strongly correlated with the ISD (0.73) and with the E-DII (0.82). The lowest correlation coefficient was observed between the ISD and the E-DII (0.46).

Spearman correlation coefficients adjusted for sex and age at recruitment between biomarkers concentration and with age, anthropometric factors, or smoking status at recruitment are presented in Table 2. CRP, IL6, IL10, IL1RA, TNFα, sTNFR1, sTNFR2 and leptin were positively correlated with each other (coefficients ranging from 0.03 between leptin and IL10 to 0.72 between sTNFR1 and sTNFR2) but inversely correlated with adiponectin, HMW adiponectin and sLeptin R (coefficients from −0.01 between adiponectin and IL10 to −0.54 between sLeptin R and leptin). Age was positively correlated with all biomarkers. BMI and waist circumference were positively correlated with CRP, IL6, IL1RA, TNFα, sTNFR1, sTNFR2, and leptin, and negatively with sLeptin R, adiponectin and HMW adiponectin. Correlations with smoking status were low (coefficients from −0.06 for IL10 to 0.07 for IL6).

Associations between the biomarker concentrations and the dietary inflammatory scores are shown in Table 3. In adjusted models, the four scores were positively associated with CRP (β for 1-SD increase: 0.05−0.06, P < 0.0001), IL6 (β for 1-SD increase: 0.04−0.07, P < 0.01), IL1RA (β for 1-SD increase: 0.08−0.11, P from 0.02 for ISD to 0.10 for E-DII), sTNFR1 and sTNFR2 (β for 1-SD increase: 0.10−0.14, P < 0.007), and leptin (β for 1-SD increase: 0.03−0.04, P < 0.03). TNFα was positively associated with the four scores, but statistically significant only for the DII and the E-DII$_r$. After Benjamini-Hochberg correction, only the associations between CRP, IL6, sTNFR1, sTNFR2 and leptin, and the four scores, and between IL1RA and ISD as well as TNFα and DII remained statistically significant. Adiponectin and HMW adiponectin were negatively associated with the two E-DIIs (β for 1-SD increase from −0.06 to −0.15, P < 0.001) only in the unadjusted models.

The proportion of variance explained by each score, BMI and smoking status for each multi-adjusted model is presented in Table 4. The results were similar between the four dietary inflammatory scores. The highest proportion of variance explained by dietary inflammatory scores was observed for sTNFR1 (2.07%) and sTNFR2 (2.05%) for DII. For all biomarkers except IL10, the proportion of variance explained by BMI was higher than the dietary inflammatory scores or smoking status. Indeed, we observed that BMI explained up to 40% of the variance of leptin levels and 14% of the variance of CRP levels.

In stratified analyses, stronger positive associations between the dietary inflammatory scores and CRP were observed in men compared with women and these interactions were significant after Benjamini-Hochberg correction for all the scores except the E-DII (Supplementary Table S4). We also stratified the associations between the scores and biomarkers by age group (Supplementary Table S5), BMI (Supplementary Table S6), the use of exogenous hormones in women (Supplementary Table S7), and menopausal status (Supplementary Table S8) and we did not find significant interactions after Benjamini-Hochberg correction.

Table 2
Spearman correlations between levels of biomarkers and with age, anthropometric factors, or smoking status at recruitment in the EPIC cohort.

	CRP	IL6	IL10	IL1RA	TNFα	sTNFR1	sTNFR2	Leptin	sLeptin R	Adiponectin	HMW Adiponectin
IL6	C: 0.43 P < 0.0001 N: 3113										
IL10	C: 0.15 P < 0.0001 N: 858	C: 0.21 P < 0.0001 N: 858									
IL1RA	C: 0.27 P < 0.0001 N: 442	C: 0.25 P < 0.0001 N: 434									
TNFα	C: 0.14 P < 0.0001 N: 1302	C: 0.26 P < 0.0001 N: 1295	C: 0.32 P < 0.0001 N: 856	C: 0.15 P: 0.002 N: 439							
sTNFR1	C: 0.31 P < 0.0001 N: 739	C: 0.31 P < 0.0001 N: 722	 N: 0	C: 0.26 P < 0.0001 N: 409	C: 0.23 P < 0.0001 N: 413						
sTNFR2	C: 0.26 P < 0.0001 N: 748	C: 0.30 P < 0.0001 N: 731	 N: 0	C: 0.28 P < 0.0001 N: 409	C: 0.30 P < 0.0001 N: 413	C: 0.72 P < 0.0001 N: 716					
Leptin	C: 0.31 P < 0.0001 N: 2416	C: 0.22 P < 0.0001 N: 1079	C: 0.03 P: 0.37 N: 839	 N: 0	C: 0.14 P < 0.0001 N: 839	N: 2	N: 2				
sLeptin R	C: −0.21 P < 0.0001 N: 987	 N: 2	 N: 0	 N: 0	 N: 0	 N: 2	 N: 2	C: −0.54 P < 0.0001 N: 987			
Adiponectin	C: −0.21 P < 0.0001 N: 3233	C: −0.17 P < 0.0001 N: 1856	C: −0.01 P: 0.69 N: 856	C: −0.20 P: 0.0001 N: 412	C: −0.12 P < 0.0001 N: 1272	C: −0.13 P: 0.0005 N: 741	C: −0.1 P: 0.009 N: 751	C: −0.19 P < 0.0001 N: 2424	C: 0.34 P < 0.0001 N: 988		
HMW Adiponectin	C: −0.18 P < 0.0001 N: 1563	C: −0.06 P: 0.32 N: 242	 N: 0	 N: 0	 N: 0	 N: 2	 N: 2	C: −0.19 P < 0.0001 N: 1556	C: 0.31 P < 0.0001 N: 986	C: 0.95 P < 0.0001 N: 1574	
Age[a]	C: 0.15 P < 0.0001 N: 17522	C: 0.25 P < 0.0001 N: 3183	C: 0.09 P: 0.01 N: 859	C: 0.02 P: 0.61 N: 443	C: 0.20 P < 0.0001 N: 1306	C: 0.27 P < 0.0001 N: 742	C: 0.25 P < 0.0001 N: 752	C: 0.07 P: 0.0009 N: 2427	C: 0.07 P: 0.0368 N: 988	C: 0.13 P < 0.0001 N: 3281	C: 0.14 P < 0.0001 N: 1574
BMI	C: 0.38 P < 0.0001 N: 17522	C: 0.28 P < 0.0001 N: 3183	C: 0.03 P: 0.39 N: 859	C: 0.33 P < 0.0001 N: 443	C: 0.15 P < 0.0001 N: 1306	C: 0.25 P < 0.0001 N: 742	C: 0.15 P < 0.0001 N: 752	C: 0.65 P < 0.0001 N: 2427	C: −0.44 P < 0.0001 N: 988	C: −0.25 P < 0.0001 N: 3281	C: −0.24 P < 0.0001 N: 1574
Waist circumference	C: 0.38 P < 0.0001 N: 16 375	C: 0.27 P < 0.0001 N: 2957	C: 0.04 P: 0.2804 N: 798	C: 0.34 P < 0.0001 N: 415	C: 0.16 P < 0.0001 N: 1217	C: 0.24 P < 0.0001 N: 715	C: 0.16 P < 0.0001 N: 725	C: 0.57 P < 0.0001 N: 2280	C: −0.43 P < 0.0001 N: 929	C: −0.30 P < 0.0001 N: 3106	C: −0.26 P < 0.0001 N: 1487
Smoking status	C: 0.06 P < 0.0001 N: 17 522	C: 0.07 P: 0.0001 N: 3183	C: −0.06 P: 0.07 N: 859	C: −0.04 P: 0.37 N: 443	C: −0.04 P: 0.20 N: 1306	C: 0.01 P: 0.87 N: 742	C: 0.01 P: 0.76 N: 752	C: −0.04 P: 0.031 N: 2427	C: −0.04 P: 0.16 N: 988	C: −0.03 P: 0.13 N: 3281	C: −0.04 P: 0.11 N: 1574

A, Antagonist; BMI, Body Mass Index; C, Coefficient; CRP, C-reactive protein; EPIC: European Prospective Investigation into Cancer and Nutrition; HMW, High Molecular Weight; IL, interleukin; N, number of participants; P, P-value; R, Receptor; TNF, tumor necrosis factor.
Spearman correlations were adjusted for sex and age at recruitment.
[a] Not adjusted for age at recruitment.

Associations between each score and concentrations of adiponectin, leptin, CRP, IL6 and TNFα adjusted for each other are presented in Table 5 (N = 833). We found borderline statistically significant positive associations between TNFα and the ISD (β = 0.11, P = 0.07), the DII (β = 0.13, P = 0.03) and the E-DII$_r$ (β = 0.12, P = 0.06), and between IL6 and the E-DII (β = 0.07, P = 0.09) when adjusted for the other biomarkers. In stepwise regressions, only TNFα was selected for the ISD, the DII and the E-DII$_r$ and no biomarker was selected for the E-DII.

4. Discussion

In this large European study, we found positive associations between circulating levels of CRP, IL6, sTNFR1, sTNFR2 and leptin, and four dietary inflammatory scores, i.e. the DII, its two energy-adjusted variants, and the ISD. The associations were stronger in men. Positive associations also were observed between IL1RA and TNFα and the four scores, although not always reaching statistical significance. These results suggest that these four dietary inflammatory scores can be used to assess the inflammatory potential of the diet in European adults. However, the proportion of variance of the biomarker concentrations explained by the scores did not exceed 2.1%, while the variance explained by BMI reached 40% for leptin. When concentrations of adiponectin, leptin, CRP, IL6 and TNFα were adjusted for each other, only the associations between TNFα and, the ISD, the DII or the E-DII$_r$ remained statistically significant.

Our results were consistent with those from previous studies. Some studies found positive associations between CRP and the DII [14,31], the E-DII [33–36,36–39] and the E-DII$_r$ [9], in American, British, Italian, Irish, Korean and Japanese populations. However, in a Belgian population [29] and in post-menopausal American women [30], no association between CRP and the DII was observed. In two recent studies conducted in Japan, positive associations were observed between the E-DII [34] or DII [60] and hs-CRP concentration in men only. It was noted that the mean hs-CRP concentration was higher in men than in women in the Japanese population. In the present study, we found stronger positive associations between the dietary inflammatory scores and CRP concentrations in men than in women while CRP levels were on average slightly higher in women than in men (Supplementary Table S2). Regarding the other biomarkers, positive associations

Table 3
Associations between levels of biomarkers and dietary inflammatory scores in the EPIC cohort.

	Crude model				Adjusted model[a]			
	beta for 1 SD increase	95%CI	P	P-corrected	beta for 1 SD increase	95%CI	P	P-corrected
CRP (N = 17 522)								
ISD	0.06	(0.04,0.07)	<0.0001	<0.0001	0.05	(0.04,0.07)	<0.0001	<0.0001
DII	0.04	(0.03,0.06)	<0.0001	<0.0001	0.05	(0.04,0.07)	<0.0001	<0.0001
E-DII	0.01	(0.00,0.03)	0.18	0.24	0.06	(0.04,0.07)	<0.0001	<0.0001
E-DII$_r$	0.04	(0.02,0.05)	<0.0001	<0.0001	0.06	(0.05,0.07)	<0.0001	<0.0001
IL6 (N = 3183)								
ISD	0.06	(0.02,0.09)	0.001	0.004	0.04	(0.01,0.08)	0.0097	0.02
DII	0.06	(0.02,0.09)	0.002	0.003	0.06	(0.02,0.09)	0.0006	0.001
E-DII	0.05	(0.02,0.09)	0.004	0.01	0.07	(0.04,0.10)	<0.0001	0.0002
E-DII$_r$	0.06	(0.03,0.10)	0.0004	0.002	0.07	(0.04,0.10)	<0.0001	0.0002
IL10 (N = 859)								
ISD	0.03	(-0.04,0.10)	0.41	0.45	0.04	(-0.03,0.11)	0.23	0.28
DII	0.03	(-0.04,0.09)	0.44	0.58	0.04	(-0.03,0.11)	0.24	0.27
E-DII	0.01	(-0.06,0.07)	0.85	0.86	0.01	(-0.06,0.08)	0.82	0.82
E-DII$_r$	0.03	(-0.03,0.10)	0.34	0.41	0.04	(-0.03,0.11)	0.25	0.27
IL1RA[b] (N = 443)								
ISD	0.14	(0.04,0.23)	0.004	0.009	0.11	(0.01,0.20)	0.02	0.04
DII	0.10	(0.01,0.19)	0.03	0.06	0.09	(0.00,0.18)	0.05	0.07
E-DII	0.08	(-0.01,0.18)	0.08	0.12	0.08	(-0.01,0.17)	0.10	0.16
E-DII$_r$	0.10	(0.00,0.19)	0.04	0.06	0.09	(0.00,0.18)	0.06	0.08
TNFα (N = 1306)								
ISD	0.04	(-0.01,0.10)	0.14	0.22	0.05	(-0.01,0.10)	0.08	0.12
DII	0.04	(-0.01,0.10)	0.11	0.17	0.06	(0.01,0.11)	0.03	0.04
E-DII	0.01	(-0.05,0.06)	0.77	0.85	0.03	(-0.02,0.09)	0.28	0.36
E-DII$_r$	0.04	(-0.02,0.09)	0.19	0.26	0.06	(0.00,0.11)	0.04	0.07
sTNFR1 (N = 742)								
ISD	0.10	(0.03,0.17)	0.007	0.03	0.10	(0.03,0.16)	0.005	0.02
DII	0.12	(0.05,0.19)	0.001	0.01	0.13	(0.07,0.20)	0.0001	0.0003
E-DII	0.09	(0.02,0.16)	0.01	0.003	0.10	(0.03,0.17)	0.007	0.018
E-DII$_r$	0.12	(0.05,0.19)	0.001	0.003	0.13	(0.06,0.19)	0.0002	0.0006
sTNFR2 (N = 752)								
ISD	0.11	(0.04,0.18)	0.003	0.007	0.11	(0.04,0.17)	0.003	0.01
DII	0.13	(0.06,0.20)	0.0004	0.001	0.14	(0.07,0.21)	0.0001	0.0003
E-DII	0.08	(0.00,0.15)	0.04	0.07	0.10	(0.03,0.17)	0.007	0.02
E-DII$_r$	0.12	(0.05,0.19)	0.001	0.003	0.14	(0.07,0.20)	0.0001	0.0005
Leptin (N = 2427)								
ISD	0.09	(0.05,0.13)	<0.0001	0.0001	0.03	(0.00,0.06)	0.03	0.04
DII	0.08	(0.04,0.12)	0.0001	0.0005	0.04	(0.01,0.06)	0.007	0.01
E-DII	−0.11	(-0.15,-0.07)	<0.0001	<0.0001	0.03	(0.00,0.06)	0.02	0.04
E-DII$_r$	−0.01	(-0.05,0.03)	0.60	0.66	0.03	(0.01,0.06)	0.01	0.02
sLeptin R[c] (N = 988)								
ISD	−0.03	(-0.09,0.03)	0.39	0.45	−0.01	(-0.08,0.06)	0.76	0.84
DII	−0.02	(-0.08,0.04)	0.532	0.58	−0.01	(-0.08,0.06)	0.84	0.84
E-DII	0.02	(-0.04,0.09)	0.45	0.55	0.03	(-0.04,0.11)	0.37	0.51
E-DII$_r$	0.00	(-0.07,0.06)	0.92	0.9211	0.01	(-0.06,0.08)	0.76	0.76
Adiponectin (N = 3281)								
ISD	0.02	(-0.02,0.05)	0.29	0.40	−0.01	(-0.04,0.03)	0.73	0.73
DII	0.01	(-0.02,0.05)	0.51	0.58	−0.01	(-0.04,0.02)	0.55	0.55
E-DII	−0.11	(-0.14,-0.07)	<0.0001	<0.0001	−0.01	(-0.04,0.02)	0.46	0.52
E-DII$_r$	−0.06	(-0.09,-0.02)	0.0009	0.003	−0.01	(-0.04,0.02)	0.44	0.44
HMW Adiponectin (N = 1574)								
ISD	0.01	(-0.04,0.06)	0.82	0.82	−0.02	(-0.07,0.02)	0.25	0.28
DII	0.00	(-0.05,0.05)	0.93	0.93	−0.03	(-0.07,0.01)	0.19	0.24
E-DII	−0.15	(-0.20,-0.11)	<0.0001	<0.0001	−0.03	(-0.07,0.02)	0.21	0.29
E-DII$_r$	−0.08	(-0.13,-0.03)	0.001	0.003	−0.03	(-0.07,0.02)	0.22	0.27

A, Antagonist; CRP, C-reactive protein; EPIC: European Prospective Investigation into Cancer and Nutrition; HMW, High Molecular Weight; IL, interleukin; P, P-value; R, Receptor; TNF, tumor necrosis factor.
Levels of biomarkers and the dietary inflammatory scores were standardized.
[a] Linear regression adjusted for sex, BMI, age at recruitment, smoking status.
[b] Not adjusted for sex because only women were included.
[c] Further adjusted for center, fasting status, hour of blood draw.

were found between IL6 and the DII in a cross-sectional study of 2524 Belgian adults [29] and in 2567 post-menopausal American women from the Women's Health Initiative Observational Study [30]. In addition, positive associations have been reported between IL6 and the E-DII in a cross-sectional sample of 1992 Irish adults [36], and between TNFR2 and the DII [30], and TNFα and the E-DII [36]. The latter study also observed a negative association between adiponectin and the E-DII, and no association with leptin [36].

The associations of the dietary inflammatory scores with levels of biomarkers were relatively similar between the scores. The only exception was for TNFα, which was positively associated with the DII, the ISD and the E-DII$_r$ but not with the E-DII. Furthermore, in mutually adjusted models, TNFα only remained significantly associated with the ISD, the DII and the E-DII$_r$ but not with E-DII, and was also the only parameter selected in the stepwise regression.

Table 4
Proportion of variance (expressed in %) explained by each score, BMI and smoking status for each multi-adjusted model in the EPIC cohort.

	DII			ISD			E-DII$_r$			E-DII		
	score	BMI	Smoking status	score	BMI	Smoking status	score	BMI	Smoking status	score	BMI	Smoking status
Adiponectin	0.01	5.81	0.63	<0.01	5.80	0.63	0.02	5.82	0.61	0.02	5.83	0.61
CRP	0.34	14.40	1.26	0.31	14.28	1.22	0.43	14.43	1.21	0.34	14.50	1.22
HMW Adiponectin	0.11	5.90	0.27	0.08	5.88	0.26	0.10	5.90	0.26	0.10	5.93	0.26
IL10	0.16	0.30	0.66	0.17	0.29	0.66	0.16	0.31	0.67	0.01	0.32	0.62
IL1RA[a]	0.89	9.56	0.79	1.18	9.11	0.81	0.82	9.53	0.80	0.63	9.55	0.90
IL6	0.37	7.21	1.50	0.21	7.15	1.50	0.53	7.25	1.44	0.53	7.45	1.44
Leptin	0.31	40.09	0.39	0.21	40.01	0.39	0.27	40.09	0.40	0.22	40.13	0.41
sTNFR1	2.07	5.73	0.16	1.07	5.44	0.15	1.84	5.87	0.14	1.00	5.97	0.15
sTNFR2	2.05	2.55	0.21	1.20	2.35	0.21	1.93	2.62	0.19	0.97	2.66	0.20
sLeptin R[b]	<0.01	11.86	0.23	0.01	11.86	0.23	0.01	11.88	0.21	0.08	11.86	0.19
TNFα	0.38	1.40	0.20	0.23	1.35	0.19	0.31	1.42	0.21	0.09	1.45	0.18

A, Antagonist; BMI, Body Mass Index; CRP, C-reactive protein; DII: dietary inflammatory index; E-DII: dietary inflammatory index adjusted for energy intakes using the density method; E-DII$_r$: dietary inflammatory index adjusted for energy intakes using the residual method; EPIC: European Prospective Investigation into Cancer and Nutrition; HMW, High Molecular Weight; IL, interleukin; ISD: Inflammatory Score of the Diet; R, Receptor; TNF, tumor necrosis factor.
All linear regression models were adjusted for sex, BMI, age at recruitment, smoking status.
[a] Not adjusted for sex because only women were included.
[b] Further adjusted for center, fasting status, hour of blood draw.

Table 5
Associations between levels of biomarkers adjusted for each other and dietary inflammatory scores in individuals with all biomarkers of interest measured from the EPIC cohort (N = 833).

		beta	95%CI	P
ISD	Adiponectin	0.06	(-0.01,0.13)	0.11
	Leptin	0.09	(-0.05,0.22)	0.20
	CRP	0.04	(-0.01,0.10)	0.12
	IL6	0.05	(-0.02,0.13)	0.17
	TNFα	0.11	(-0.01,0.22)	0.07
DII	Adiponectin	0.04	(-0.03,0.12)	0.28
	Leptin	0.11	(-0.03,0.25)	0.11
	CRP	0.04	(-0.02,0.09)	0.20
	IL6	0.05	(-0.03,0.12)	0.26
	TNFα	0.13	(0.01,0.25)	0.03
E-DII	Adiponectin	−0.01	(-0.08,0.07)	0.88
	Leptin	0.09	(-0.05,0.23)	0.20
	CRP	0.04	(-0.02,0.09)	0.17
	IL6	0.07	(-0.01,0.15)	0.09
	TNFα	0.03	(-0.09,0.15)	0.63
E-DII$_r$	Adiponectin	0.02	(-0.05,0.10)	0.58
	Leptin	0.09	(-0.05,0.23)	0.22
	CRP	0.04	(-0.01,0.10)	0.13
	IL6	0.04	(-0.04,0.12)	0.27
	TNFα	0.12	(-0.01,0.24)	0.06

CRP, C-reactive protein; DII: dietary inflammatory index; E-DII: dietary inflammatory index adjusted for energy intakes using the density method; E-DIIr: dietary inflammatory index adjusted for energy intakes using the residual method; EPIC: European Prospective Investigation into Cancer and Nutrition; IL, interleukin; ISD: Inflammatory Score of the Diet; P, P-value; TNF, tumor necrosis factor.
Linear regression including Adiponectin, Leptin, CRP, IL6, TNFα, sex, BMI, age at recruitment, smoking status.
Levels of biomarkers and dietary inflammatory scores were standardized.

The differences between the scores computation were previously detailed [43]. The DII and ISD are not adjusted for energy intake and they differ by the reference population used to standardize the dietary intake and for the food parameters included. The E-DIIs are adjusted for energy intake but differ by the way energy was taken into account: for the E-DII$_r$, the intakes were adjusted for energy intake using the residual method [61] while for the E-DII the density method was used, and the intakes were converted to an amount per 1000 kcal of energy intake and used an energy-adjusted global comparative database. This difference in the consideration of energy intake may partly explain the weaker association between the E-DII score and inflammatory biomarkers (especially in unadjusted models), in comparison to the other dietary inflammatory scores. It is well known that the overall dietary energy intake plays a crucial role in determining the overall inflammatory potential of the diet and that the energy intake is strongly correlated with DII scores in certain populations, which had precisely motivated the development of the energy adjusted inflammatory scores [32]. In some studies investigating the effect of nutriment/food intakes on health conditions, the density adjustment have been suggested to conflates the effects of the exposure and total energy which can lead to an inaccurate estimate [62].

It is worth noting that the proportion of variance of the biomarkers explained by the dietary inflammatory scores did not exceed 2.1%, which was about the same magnitude as the variance explained by smoking status, but far smaller than that explained by BMI (which explained up to 40% of the leptin variance), another factor that can influence inflammation. These results suggest that dietary inflammatory scores alone are not sufficient to capture the inflammatory status of an individual. Finally, BMI was positively correlated with levels of CRP, IL6, IL1RA, TNFα, sTNFR1 and leptin, while it was negatively correlated to sLeptin R, adiponectin and HMW adiponectin. The possible mediating role of BMI between the dietary inflammatory scores and the biomarkers would need further investigation, however it should be noted that the DII, the E-DII$_r$ and the E-DII were negatively associated with BMI in our study (results not shown). We recommend that future longitudinal studies with temporal measurement of inflammatory scores, BMI, and biomarkers explore the potential mediating role of BMI.

Major strengths of this study were the large sample size, the use of a comprehensive list of inflammatory biomarkers, which provided a more thorough assessment of low-grade inflammation and the comparison of four dietary inflammatory scores. However, some limitations need to be addressed. First, this work was based on a single blood draw so we could not investigate the stability of biomarker measurements over time in our study. Second, we cannot infer causal associations between the scores and biomarker levels because of the cross-sectional design, which limits our ability to investigate the mediating role of BMI in the associations between dietary inflammatory scores and inflammatory biomarkers.

Indeed, although the recorded usual diet encapsulated the previous year, biomarkers and diet were both assessed at recruitment. Further studies are required to evaluate the prospective associations between the scores and the biomarkers for assessing causality. Third, biomarkers were measured as part of different studies, at different time points and using different methods. However, these variations were taken into account by applying a normalization step. Furthermore, some items were not available for

the dietary inflammatory scores calculation. Depending on the scores, between 28 and 32 food parameters were included for this study. However, a construct validation study using 24-h dietary recalls and 7-day dietary recalls, reported that the reduction of available food parameters would not lead to a large drop-off in the predictive ability of the DII [14]. On another note, as information on the usual diet was self-reported, we cannot rule out cognitive limitations and social desirability bias. However, we used validated assessment tools [63], and participants with extreme energy intakes were excluded to minimize the potential for measurement error in the usual diet. Finally, although we controlled for several confounding factors, we cannot exclude the possibility that residual confounders also may have influenced our observations.

To conclude, our results suggest that the DII, its two energy-adjusted variants, and the ISD were positively associated with levels of CRP, IL6, IL1RA, TNFα, sTNFR1, sTNFR2 and leptin and can be used to assess the inflammatory potential of diet in European adults. However, the proportion of variance of the biomarkers explained by the scores was very low. Further studies are needed to investigate the stability of the biomarker measurements and to assess causality. Investigating the mediating role of the inflammatory biomarkers between diet and chronic diseases will allow to better understand mechanisms involved and to promote the development of more effective dietary interventions to reduce the inflammatory potential of the diet and consequently chronic diseases related to inflammation.

Author contributions

TT, **SR** and **LD** coordinated the project. **LL**, **NL**, **VV**, **LD**, **SR**, **MCBR** and **TT** designed and conducted the research; Subjects' recruitment, data management and biological material collection were organized and carried out by **AA**, **AT**, **LM**, **RK**, **VAK**, **MBS**, **PF**, **FRM**, **MSDM**, **AM**, **GM**, **CA**, **RT**, **JMAB**, **WMMV**, **TEJ**, **KSO**, **GS**, **MDC**, **DP**, **CCE**, **JRQ**, **MG**, **PA**, **YB**, **MS**, **LMN**, **AKH**, **ALM**, **MCBR**; **NS** and **JRH** designed and computed DII and E-DII scores; **AA** designed the ISD; **LL** and **NL** performed the statistical analyses; **VV**, **FA** and **TT** supervised the statistical analyses; **LL**, **NS**, **LD**, **SR**, **VV** and **TT** interpreted the results. **LL**, **NS** and **TT** drafted the manuscript. All authors reviewed the manuscript and approved the final version of the paper.

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Data availability

EPIC data and biospecimens are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC Centers. The primary responsibility for accessing the data obtained in the frame of the present publication belongs to the EPIC centers that provided them. The use of a random sample of anonymized data from the EPIC study can be requested by contacting epic@iarc.fr. The request will then be passed on to members of the EPIC Steering Committee for deliberation.

Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Ethics approval

The study was conducted according to the guidelines of the Declaration of Helsinki. Approval for the EPIC study was obtained from the ethical review boards of the International Agency for Research on Cancer (IARC) and all national recruitment institutions. Informed consent was obtained from all EPIC participants.

Conflicts of Interest

Dr. James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smartphone applications for patient counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI. The subject matter of this paper will not have any direct bearing on that work, nor has CHI-related activity exerted any influence on this project.

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Appendix A. Supplementary data

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