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Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study

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Abstract

Previous research has shown that nutrients and certain food items influence inflammation. However, little is known about the associations between diet, as a whole, and inflammatory markers. In the present study, we examined the ability of a FFQ-derived dietary inflammatory index (DII) to predict inflammation. Data from a Belgian cross-sectional study of 2524 generally healthy subjects (age 35–55 years) were used. The DII is a population-based, literature-derived dietary index that was developed to predict inflammation and inflammation-related chronic diseases. The DII was calculated from FFQ-derived dietary information and tested against inflammatory markers, namely C-reactive protein (CRP), IL-6, homocysteine and fibrinogen. Analyses were performed using multivariable logistic regression, adjusting for energy, age, sex, BMI, smoking status, education level, use of non-steroidal anti-inflammatory drugs, blood pressure, use of oral contraceptives, anti-hypertensive therapy, lipid-lowering drugs and physical activity. Multivariable analyses showed significant positive associations between the DII and the inflammatory markers IL-6 (>1·6 pg/ml) (OR 1·19, 95 % CI 1·04, 1·36) and homocysteine (>15 μmol/l) (OR 1·56, 95 % CI 1·25, 1·94). No significant associations were observed between the DII and the inflammatory markers CRP and fibrinogen. These results reinforce the fact that diet, as a whole, plays an important role in modifying inflammation.

Key words: **Diet: Inflammation: Inflammatory markers: Cytokines: Chronic disease risk**

Acute inflammation, a necessary process of the body's natural response to tissue injury, helps to heal wounds and promote tissue regeneration[1–4]. A chronic, low-grade inflammatory state results when this process of inflammation is not controlled properly[4]. Chronic inflammation has been shown to be associated with cancer[5,6] and CVD[7–10] such as CHD[11] and myocardial infarction[10]. The major inflammatory markers that are implicated in these chronic diseases are IL-6[10], fibrinogen[11], high-sensitivity C-reactive protein (hs-CRP)[11] and leucocyte count[11].

Dietary factors also have been associated with inflammation. The Western-type diet, which is high in red meat, high-fat dairy products and refined grains, is associated with higher levels of CRP, IL-6 and fibrinogen[12,13]. In contrast, the Mediterranean diet, which is high in whole grains, fruit and green vegetables, and fish and low in red meat and butter, with moderate alcohol consumption and olive oil intake, is associated with lower levels of inflammation[14]. Diets high in fruit and vegetables are associated with lower levels of CRP[15]. Specific nutrients also have been consistently shown to be associated with lower levels of inflammation. These include complex carbohydrates[16], *n*-3 PUFA[17], fibre[18], moderate alcohol intake[19], vitamin E[20], vitamin C[21], β-carotene[22] and Mg[23].

The dietary inflammatory index (DII) was developed to provide a means for estimating the overall inflammatory potential of the diet[24,25]. The DII is based on an extensive literature search incorporating cell culture, animal and

Abbreviations: CRP, C-reactive protein; DII, dietary inflammatory index; hs-CRP, high-sensitivity C-reactive protein.

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epidemiological studies of the effect of diet on inflammation. DII scoring is not dependent on subjective evaluation of the diet or recommendations of intake. Because it is based on the literature that links diet to inflammation, the DII is not limited to micronutrients and macronutrients, but also incorporates commonly consumed components of the diet including flavonoids, spices and tea. Previously, the DII has been shown to predict CRP levels[25,26]. Using the Asklepios Study, we tested the hypothesis that higher DII scores, indicating a more pro-inflammatory diet, are associated with increased systemic inflammation, as shown by increased levels of inflammatory markers.

Methods

Study design

Briefly, the Asklepios Study was a longitudinal population-based study conducted in Belgium, with baseline data collected in October 2002. The primary objective of the study was to explore the interplay between ageing, diet, cardiovascular haemodynamics and inflammation. A total of 2524 healthy volunteers aged between 35 and 55 years were recruited. Subjects were randomly sampled from the twinned communities of Erpe-Mere and Nieuwerkerken in Flanders, Belgium. Inclusion criteria were as follows: male or female volunteers aged 35–55 years at study initiation; living in the communities of Erpe-Mere or Nieuwerkerken. Exclusion criteria were as follows: the presence of clinical atherosclerosis; major comorbidity; diabetes mellitus; pregnancy; atrial fibrillation; irregular heart cycle; inability to give informed consent. More details about the inclusion and exclusion criteria used can be found in the methods and baseline characteristics of the Asklepios Study[27].

For the present study, only baseline data on diet, inflammatory markers and covariates were used to perform a cross-sectional analysis. After excluding thirty-seven participants who did not complete the FFQ, there were 2487 subjects with evaluable data, of whom 1200 were men and 1287 were women. Data on demographic characteristics were obtained using a self-administered questionnaire. Anthropometric measurements and blood samples were collected, and the levels of inflammatory markers were determined[27]. Basic clinical data assessment and routine biochemical assays were performed as described previously[27]. In summary, five markers of inflammation were measured: hs-CRP; leucocyte count; fibrinogen; homocysteine; IL-6.

Dietary intake and dietary inflammatory index

Participants were asked to complete a semi-quantitative FFQ that included questions on their habitual daily consumption of twenty-five food items during the past year[28]. This FFQ was based on an existing FFQ used in this population and on a short FFQ (i.e. sixty items) developed by Willett[29,30]. Participants were asked to indicate how often they consumed each item in a list of frequencies (every day; 5–6 d/week; 2–4 d/week; 1 d/week; 1–3 times/month; never or less than once a month), and to indicate approximate portion size.

FFQ-derived dietary information was used to calculate DII scores for all of the subjects, as described in detail elsewhere[24,25]. Briefly, dietary data for each study participant were first linked to a regionally representative global database that provided a robust estimate of means and standard deviations for each of the food parameters considered (i.e. foods, nutrients and other food components such as flavonoids)[24]. A *z*-score was derived by subtracting the 'standard global mean' from the amount reported, and then this value was divided by the standard deviation. To minimise the effect of 'right skewing' (a common occurrence with dietary data), this value was then converted to a centred percentile score, which was then multiplied by the respective inflammatory effect score of the food parameters (derived from a literature review and scoring of 1943 'qualified' articles) to obtain the subject's food parameter-specific DII score. All of the food parameter-specific DII scores were then summed to create the overall DII score for each subject in the study. For the current FFQ, data were available for a total of seventeen food parameters (carbohydrate, protein, total fat, fibre, cholesterol, saturated fat, monounsaturated fat, polyunsaturated fat, *n*-6 fatty acid, thiamin, riboflavin, vitamin B_{12}, Fe, Mg, Zn, vitamin A and vitamin C). A description of the validation work of the DII score, based on both dietary recalls and a structured questionnaire, the 7 d dietary recall that is similar to an FFQ, is available elsewhere[26]. Thus far, the DII has been found to be associated with inflammatory cytokines, including CRP and IL-6[26,31,32], the glucose intolerance component of the metabolic syndrome, the increased odds of asthma and FEV_1 (reduced forced expiratory volume in 1 min), inflammatory markers in shift workers, and colorectal, prostate and pancreatic cancers[31–38].

Statistical analyses

All markers of inflammation were analysed as categorical variables using conventional cut-off points. As recommended by the Centers for Disease Control and Prevention (CDC) and the American Heart Association, we dichotomised hs-CRP at the level of 3 mg/l[7], categorised homocysteine at the level of 15 μmol/l[39] and fibrinogen at the level of 4·5 g/l, considering measurements greater than this level as indicative of higher CVD risk. IL-6 was categorised at a detection level of 1·6 pg/ml[28]. As there were no clear cut-off values for leucocyte count, it was not analysed.

All statistical analyses were carried out using the SAS® statistical software package (version 9.3; SAS Institute, Inc.). Comparisons of baseline characteristics by sex were made by χ^2 tests for categorical variables and by two-sample *t* tests for continuous variables. BMI was categorised as normal (< 25 kg/m^2), overweight (25–30 kg/m^2) and obese (> 30 kg/m^2). Physical activity is expressed as metabolic equivalents (METS). Analyses were carried out using multivariable logistic regression, adjusting for energy, age, sex, BMI, smoking status, education level, use of non-steroidal anti-inflammatory drugs,

blood pressure, use of oral contraceptives, lipid-lowering drugs, anti-hypertensive therapy and physical activity.

Results

Table 1 shows the baseline characteristics of the study participants and the mean DII scores for both sexes. Women had lower DII scores than did men (−1·01 *v.* 0·90), indicating that women consume a more anti-inflammatory diet than men. Women were more educated, less likely to be obese and more likely to be current smokers compared with men. Women had higher CRP levels; however, other inflammatory markers did not differ by sex. Table 2 presents the distribution of characteristics, various food groups and inflammatory markers across the tertiles of the DII. Tertile 3 had a higher number of current smokers and males than did tertile 1. Participants in tertile 3 had a lower consumption of anti-inflammatory food groups such as vegetables, fish and fruit, and had a higher consumption of pro-inflammatory foods such as sugar-sweetened soft drinks. Participants in tertile 2 had a higher consumption of meat than those in tertile 1; however, participants in tertile 3 had a lower consumption of meat. Participants in tertile 3 had higher levels of IL-6 and homocysteine.

Analysis of inflammatory markers as categorical variables

Multivariable-adjusted analysis showed positive associations between the DII and the inflammatory markers IL-6 (OR 1·19, 95% CI 1·04, 1·36) and homocysteine (OR 1·56, 95% CI 1·25, 1·94). For each unit increase in the DII, the odds of having IL-6 >1·6 pg/ml and homocysteine >15 μmol/l increased by 19 and 56%, respectively. The DII was not found to be associated with hs-CRP (>3 mg/l) and fibrinogen (>4·5 g/l) (Table 3).

Discussion

The results from the present study indicate that a diet with predominantly pro-inflammatory food parameters such as cholesterol and saturated fat, and relatively poor in anti-inflammatory food parameters such as fruit and vegetables, increased inflammation in the study participants as evidenced by the increased levels of IL-6, homocysteine and

Table 1. Characteristics of the Asklepios Study population and mean dietary inflammatory index (DII) scores

(Number of participants and percentages; mean values and standard deviations; medians and interquartile ranges (IQR))

	Women (*n* 1287)		Men (*n* 1200)		
Characteristics	*n*	%	*n*	%	*P**
Age (years)					0·40
Mean	45·9		46·1		
SD	6·0		5·9		
Education (years)†					<0·0001
University	71	5·7	154	13·3	
Beyond secondary	360	28·9	312	26·9	
Secondary and below	813	65·4	693	59·8	
BMI (kg/m^2)†					<0·0001
Normal (<25 kg/m^2)	755	59·2	419	35·0	
Overweight (25–30 kg/m^2)	356	27·9	575	48·0	
Obese (>30 kg/m^2)	165	12·9	204	17·0	
Smoking status†					<0·0001
Non-smoker	770	50·5	282	41·6	
Ex-smoker	279	21·9	418	34·9	
Current smoker	227	17·8	490	23·5	
hs-CRP (mg/l)					<0·0001
Median	1·4		1·0		
IQR	0·6, 3·3		0·5, 1·9		
IL-6 >1·6 pg/ml (yes) (%)	24·5		26·5		0·25
Leucocyte count (×10^3/μl)					0·01
Median	6·6		6·4		
IQR	5·4,7·7		5·2, 7·4		
Homocysteine (μmol/l)					<0·0001
Median	9·4		11·0		
IQR	8·0, 11·1		9·4, 12·8		
Fibrinogen (g/l)					<0·0001
Median	3·27		3·06		
IQR	2·91, 3·70		2·74, 3·38		
DII score	−1·01	0·8	−0·90	0·7	0·003

hs-CRP, high-sensitivity C-reactive protein.
* ANOVA was used for continuous variables and χ^2 test for categorical variables.
† The sum does not add up to the total because of some missing values.

Table 2. Description of population characteristics across the tertiles of the dietary inflammatory index

(Number of participants and percentages*; mean values and standard deviations†)

	Tertile 1 (<−1·38)		Tertile 2 (−1·38 to −0·70)		Tertile 3 (>−0·70)		
Characteristics	*n*	%	*n*	%	*n*	%	*P*‡
Age (years)							0·79
Mean	46·1		45·6		46·2		
SD	6·0		6·0		5·9		
BMI (kg/m^2)							0·83
Mean	25·6		25·9		25·6		
SD	4·1		4·2		4·3		
Smoking status							<0·0001
Non-smoker	441	53·6	421	51·1	406	49·1	
Ex-smoker	256	31·1	243	29·5	198	23·9	
Current smoker	126	15·3	160	19·4	223	27·0	
Sex							0·0004
Females	471	57·2	404	49·0	401	48·5	
Males	352	42·8	420	51·0	426	51·5	
Food group intake							
Vegetables (g/d)							<0·0001
Mean	229·4		183·7		113·2		
SD	65·4		68·4		64·5		
Fish and fish products (g/d)							<0·0001
Mean	24·9		22·3		18·9		
SD	22·2		19·3		17·5		
Fruit (g/d)							<0·0001
Mean	241·2		152·6		86·2		
SD	116·3		110·8		85·5		
Sugared drinks (ml/d)							0·01
Mean	452·9		509·3		504·5		
SD	434·2		418·1		425·6		
Meat (g/d)							<0·0001
Mean	119·0		129·7		107·0		
SD	58·9		62·8		62·6		
Inflammatory markers							
CRP (>3 mg/l)							0·83
High	173	21·0	169	20·5	164	19·8	
Low	650	79·0	655	79·5	663	80·2	
IL-6							0·30
>1·5 pg/ml	194	23·6	221	26·8	214	25·9	
≤1·5 pg/ml	629	76·4	603	73·2	613	74·1	
Homocysteine (>15 μmol/l)							0·002
High	44	5·3	67	8·1	83	10·0	
Low	779	95·7	757	91·9	744	90·0	
Leucocyte count (×10^3/μl)							0·02
Mean	6·4		6·6		6·6		
SD	1·7		1·7		1·7		
Fibrinogen (g/l)							0·57
Mean	3·24		3·23		3·22		
SD	0·58		0·60		0·63		

* Categorical variables.
† Continuous variables.
‡ The *t* test was used for continuous variables and χ^2 test for categorical variables.

leucocyte count. Overall, the results of the present study are consistent with the hypothesis that diet modulates inflammation. The inference is that through this process of modulating inflammation, there is an effect on chronic diseases such as several cancers and CVD.

Previous results from the Asklepios Study have shown that adherence to Flemish food-based dietary guidelines results in lower inflammation[28]. The present results are in accordance with the findings from previous studies that have found a relationship between diet and inflammatory markers[40–44].

We found an independent positive association between adherence to the pro-inflammatory diet (increasing DII score) and the inflammatory markers IL-6, and homocysteine, but not CRP and fibrinogen. This is consistent with the observations from previous studies showing that IL-6 is a more sensitive indicator of CVD such as atherosclerosis and cardiovascular risk than are hs-CRP and fibrinogen[10,45]. IL-6 promotes atherosclerosis, by stimulating the endothelial synthesis of cellular adhesion molecules, procoagulant effects, and stimulation of hepatic hs-CRP synthesis[10,45]. Leucocytosis

Table 3. Associations between the dietary inflammatory index and inflammatory markers as categorical variables

Categorical variables	High/normal	OR*	95 % CI	OR†	95 % CI
hs-CRP (>3 mg/l)	506/1958	0·94	0·82, 1·07	1·03	0·86, 1·17
IL-6 (>1·6 pg/l)	629/1845	1·12	1·00, 1·30	1·19	1·04, 1·36
Homocysteine (>15 μmol/l)	194/2280	1·50	1·25, 1·81	1·56	1·25, 1·94
Fibrinogen (>4·5 g/l)	80/2394	1·15	0·86, 1·54	1·08	0·78, 1·48

hs-CRP, high-sensitivity C-reactive protein.
* Adjusted for age.
† Adjusted for energy, age, sex, BMI, smoking status, education level, use of non-steroidal anti-inflammatory drugs, blood pressure, use of oral contraceptives, anti-hypertensive therapy, lipid-lowering drugs and physical activity.

has consistently been shown to be an independent risk factor and prognostic indicator of future cardiovascular outcomes, regardless of disease status. Mechanisms that link leucocytosis to CHD occur through the mediation of inflammation, resulting in proteolytic and oxidative damage to the endothelial cell that plug the microvasculature, induce hypercoagulability and promote infarct expansion[46]. Hyperhomocysteinaemia is also known to play an important role in the causation of CVD[47]. The results from animal and *in vitro* experimental studies have shown blood homocysteine levels to be positively associated with vascular and platelet damage[47–49]. Homocysteine is not a commonly studied inflammatory marker; however, previous research[50,51] has shown that homocysteine can be considered as an inflammatory marker and higher levels of homocysteine tend to be strongly positively correlated with inflammatory markers related to an increased risk of CVD.

The present study has several limitations. Although the FFQ is typically used to investigate habitual (long-term) dietary intakes in large-scale surveys, its closed structure with limited response options limits its ability to detect between-person variations; this is in contrast to open-ended methods such as food records or 24 h dietary recalls. In addition, the FFQ relies on the respondents' memory and their capabilities to interpret those questions on frequency and quantity of consumption. However, the important strengths of the FFQ are its low respondent burden and cost, and the fact that, at least theoretically, it gives information about the respondents' usual or habitual dietary intakes[30]. Another limitation of this design is that no cause–effect relationships can be inferred from these cross-sectional data, and a single measure of diet notably reduces at least the precision (and, probably, the accuracy) of our estimates. Also, it is possible that multiple testing may have resulted in chance associations being declared significant.

In the DII validation study[26], sensitivity analysis was conducted to compare DII scores calculated from multiple (up to 15/person) 24 h dietary recalls with those calculated from 7 d dietary recalls (providing data on twenty-eight food parameters). We found that the ability to predict CRP was not attenuated when using the more limited list available with the 7 d dietary recalls[26]. In the present study, the DII was calculated using the data on just seventeen food parameters derived from the FFQ, the shortest list on which we have published thus far. This could explain the absence of an association between the DII and CRP in the present study. However, despite the large reduction in the number of food parameters, we still were able to predict various inflammatory markers successfully.

Conclusion

Chronic inflammation appears to play a key role in the development of CVD and certain cancers. The results from the present study suggest that eating a diet high in sugar, saturated fat and other pro-inflammatory foods promote inflammation, which may increase the risk of a variety of chronic diseases. The next logical step would be to use the DII to predict CVD outcomes, such as atherosclerosis, and indicators of CVD including intimal thickening, plaque formation and cardiac output in the Asklepios Study.

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The authors' contributions are as follows: N. S. was involved in the calculation of the DII in the dataset, performed all the analyses and drafted the first version of the manuscript; I. H. helped with the analyses, data acquisition, interpretation of the data, and critical revision of the manuscript; E. R. R., M. L. D. B., M. L., E. D. and A. M. contributed to the data interpretation and drafting of the manuscript; J. R. H. provided expertise and oversight throughout the process. All the authors approved the final version.

All authors declare that there is no conflict of interest.

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