Dietary inflammatory index and anthropometric measures of obesity in a population sample at high cardiovascular risk from the PREDIMED (PREvención con Dieta MEDITerránea) trial


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Abstract
The dietary inflammatory index (DII) is a new tool to assess the inflammatory potential of the diet. In the present study, we aimed to determine the association between the DII and BMI, waist circumference and waist:height ratio (WHtR). We conducted a cross-sectional study of 7236 participants recruited into the PREvención con Dieta MEDITerránea trial. Information from a validated 137-item FFQ was used to calculate energy, food and nutrient intakes. A fourteen-item dietary screener was used to assess adherence to the Mediterranean diet (MeDiet). Sex-specific multivariable linear regression models were fitted to estimate differences (and 95% CI) in BMI, waist circumference and WHtR across the quintiles of the DII. All nutrient intakes, healthy foods and adherence to the MeDiet were higher in the quintile with the lowest DII score (more anti-inflammatory values) except for intakes of animal protein, saturated fat and monounsaturated fat. Although an inverse association between the DII and total energy was apparent, the DII was associated with higher average BMI, waist circumference and WHtR after adjusting for known risk factors. The adjusted difference in the WHtR for women and men between the highest and lowest quintile of the DII was 0.03 and 0.08, respectively.

Abbreviations: CRP, C-reactive protein; DII, dietary inflammatory index; MeDiet, Mediterranean diet; PREDIMED, PREvención con Dieta MEDITerránea; WHtR, waist:height ratio.

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The obesity pandemic constitutes a major public health problem in most high-income countries, and it is emerging as a threat in more affluent sectors of developing countries[15–19]. In 2008, more than 10% of the World’s adult population, i.e. about 500 million people, were obese according to the WHO[2]. It was estimated that 3-4 million adult deaths worldwide were, in 2010, attributable to obesity or overweight[1]. This is a global crisis because 65% of the world’s population live in countries where overweight and obesity kill more people than being underweight[2].

Obesity usually is the result of the accumulation of excess body fat, and it is often characterised as a state of low-grade chronic inflammation[25]. This obesity-induced inflammation has multi-organ metabolic effects affecting the adipose tissue, liver, muscle, pancreas and brain[19]. Metabolic differences exist according to the location of fat cells. For example, excessive deposition of fat in visceral adipose tissue (i.e. intra-abdominal fat) is associated with higher health risks than subcutaneous fat accumulation in the extremities[5]. In fact, different anthropometric adiposity measures including waist circumference or waist:height ratio (WHtR) are used to assess the role of adiposity in CVD risk[6,7].

A number of studies have shown an association between diet and inflammatory biomarkers, and how this translates into increased or decreased risk of chronic metabolic diseases[8–15]. Part of the preventive role of healthy dietary patterns, such as the Mediterranean diet (MeDiet), could be attributed to the anti-inflammatory properties of some of their main components[15–19]. This anti-inflammatory effect may decrease the low-grade inflammation usually found in obese patients[20,21]. However, a MeDiet may also attenuate inflammation in the absence of weight loss[22]. A recent hypothesis is that obesity could also be partly the consequence of a previous chronic low-grade inflammation; therefore, a bidirectional association between inflammation and obesity may exist[23]. Consequently, it can be useful to characterise an individual’s diet according to its inflammatory properties in order to investigate the inflammatory links between obesity and diet[24]. The dietary inflammatory index (DII) is a new tool to assess this inflammatory potential of the diet[25]. In the present study, we examine the relationships between nutrient intake or food group consumption and the DII, as well as the association between the DII and indices of both general and abdominal obesity in the PREvencio´n con DIeta MEDiterranea (PREDIMED) trial.

Methods

Ethics statement

The protocol was approved by the Research Ethics Committees at all recruiting centres: University of Navarra; University of Valencia; University Rovira i Virgili; IMIM-Hospital del Mar Medical Research Institute; University of Barcelona; University Hospital of Alava; University of Malaga; University of the Balearic Islands; University of Las Palmas de Gran Canaria; University Hospital of Bellvitge; Hospital Clinic. Participants signed a written informed consent form.

Study design and participants

The ‘PREDIMED’ study was a parallel-group, multi-centre, clinical trial that aimed to assess the effects of the traditional MeDiet on the primary prevention of CVD (protocol available at http://www.predimed.es). A detailed description of methods and patients has been published elsewhere[26,27]. The study was conducted between October 2003 and December 2010 by eleven recruiting centres in Spain.

Eligible participants were men aged 55–80 years and women aged 60–80 years with no previous CVD. At baseline, participants should have a diagnosis of type 2 diabetes mellitus or at least three of the following major cardiovascular risk factors: smoking (more than one cigarette per d during the last month); hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or antihypertensive medication); elevated LDL-cholesterol levels (≥1600 mg/l); low HDL-cholesterol levels (≤400 mg/l in men or ≤500 mg/l in women, independently of lipid-lowering therapy); BMI ≥25 kg/m²; family history of premature CHD.

A total of 7447 participants were randomised in a 1:1:1 ratio to a parallel-design intervention trial of dietary advice: (1) a MeDiet supplemented with extra-virgin olive oil; (2) a MeDiet supplemented with nuts; (3) a low-fat diet (control group). Medical conditions and risk factors related to eligibility were collected using a questionnaire during the first screening visit. Participants, with the assistance of trained dietitians, completed an FFQ. This FFQ was adapted from the Willett questionnaire and validated in Spain[26]. It includes 137 items plus vitamin/mineral supplements, and specific questions for patterns of alcohol consumption. Energy and nutrient intakes were calculated from Spanish food composition tables[29]. Participants also completed the Spanish validated version of the Minnesota physical activity questionnaire[50], and a fourteen-item dietary screener to assess the adherence to the MeDiet[51]. PREDIMED dietitians were responsible for the accurate completion of the questionnaires.

For the present study, 133 participants were excluded from the analyses because they reported values for total energy intake outside of the predefined limits (<3347 kJ (<800 kcal)/d or >17 573 kJ (>4200 kcal)/d for men; <2510 kJ (<600 kcal)/d or >14 644 kJ (>3500 kcal)/d for women). These limits were set in accordance with those recommended by Willett in Nutritional Epidemiology[52]. Another seventy-eight participants were excluded.

Key words: Inflammation; Diet; Obesity; BMI; Waist circumference; Waist:height ratio
Dietary inflammatory index

The design and development of the DII has been described elsewhere\(^2\). Briefly, the DII is a scoring algorithm based on an extensive review of the literature published from 1950 to 2010, linking 1943 articles to a total of forty-five food parameters and including various macronutrients, micronutrients, flavonoids and food items (Fig. 1). These dietary parameters were scored according to whether they increased (+1), decreased (−1) or had no effect (0) on six inflammatory biomarkers (IL-1\( \beta \), IL-4, IL-6, IL-10, TNF-\( \alpha \) and C-reactive protein (CRP)). An overall food parameter-specific inflammatory effect score was calculated and multiplied by a centred percentile value for each food. This percentile was calculated by first linking the dietary data from a study to the regionally representative world database intake, which was based on actual human consumption in eleven populations from different parts of the world that provided a robust estimate of a mean and standard deviation for each parameter. These values then become the multipliers to express an individual’s exposure, relative to the ‘standard global mean’ as a z-score. This was achieved by subtracting the ‘standard global mean’ from the amount reported, and dividing this value by the standard deviation. To minimise the effect of ‘right skewing’, this value was then converted to a centred percentile score. The centred percentile score for each food parameter for each individual was multiplied by the respective food parameter effect score that was derived from the literature review in order to obtain a food parameter-specific DII score for an individual. All of the food parameter-specific DII scores were then summed to create the overall DII score for every participant in the study. The greater the DII score, the more pro-inflammatory the diet, and more negative values represent more anti-inflammatory diets. The DII score could take on values ranging from 7·98 (maximally pro-inflammatory) to −8·87 (maximally anti-inflammatory)\(^2\).

Construct validation of the DII was performed using data derived from two different sources of dietary intake information, and serum high-sensitivity CRP as the construct validator\(^3\).

Outcome

Trained and certified PREDIMED nurses performed all baseline anthropometric adiposity measures including weight and height (from which BMI (kg/m\(^2\)) was computed), waist circumference (cm) and WHtR (%) following validated procedures. A waist-height ratio equal to 1 was taken as 100 %. Baseline weight was measured using a calibrated balance beam scale with the subjects barefoot and wearing light clothes. The nurse measured height using a wall-mounted calibrated stadiometer. Waist circumference was measured using an anthropometric measuring tape, at a horizontal plane midway between the lowest rib and the iliac crest.

Statistical analyses

Statistical analyses were stratified by sex. Comparisons of quantitative variables across the quintiles of the DII were made using a one-way ANOVA. The compared variables included total energy intake, physical activity and nutrient and food consumption. Intakes of carbohydrate, protein and fat (and fat subtypes) are expressed as a percentage of total energy intake (Table 1). Categorical variables were compared using the Pearson \( \chi^2 \) test.

Sex-specific least-squared means of BMI, waist circumference and WHtR were estimated across the quintiles of the DII. Pearson’s correlation coefficients (95 % CI) between these anthropometric adipose measures and the DII were also calculated.

Sex-specific multiple linear regression models were used to estimate the differences (and 95 % CI) in the indices of general obesity and abdominal obesity according to the quintiles of the DII. Covariates included in these models were age (years), smoking status (never, current or former smoker), diabetes (yes or no), hypertension (yes or no), leisure-time physical activity (metabolic equivalents-min/d), educational level (illiterate/elementary education, secondary education or university), marital status (married, widowed, single or other), total energy intake (kJ/d) and study centre. In addition, tests of linear trend across the successive quintiles of the DII were conducted using the median value for each quintile category as a continuous variable, and after adjusting for the aforementioned confounding variables.

Residuals of the DII were obtained in a linear regression analysis of the association between the DII and a previously validated fourteen-item PREDIMED screener of adherence to the MeDiet\(^3\). These residuals represent the information provided by the DII, which is not explained at all by adherence to the MeDiet (i.e. they exhibit zero correlation with the MeDiet score). They were included as an independent variable after transformation into quintiles in a multivariable regression model with the same covariates listed previously (residual model).

All \( P \) values presented are two-tailed, and differences were considered statistically significant at \( P \leq 0.05 \). All statistical analyses were performed using STATA\textsuperscript{\textregistered} version 12.0 (Stata Corp).

Results

Of the 7447 initially randomised subjects in the PREDIMED trial, 7236 were included in the present study. The remaining participants (\( n = 211, 2·8\% \)) were excluded because of incomplete data on their FFQ (\( n = 78 \)) or baseline energy intake outside of the predefined values (\( n = 133 \)). Among the 7236 participants, 57 % were women. The mean age of the participants was 68 (sd 5·8) years for women and 66 (sd 6·6) years for men. The median DII score for women was −0·78 (−4·90 to 3·68) and −0·91 (−5·23 to 3·69) for men.

Table 1 shows the main characteristics of the participants according to the categories of the DII score by sex. All differences between the quintiles of this index were statistically
Review of articles published from 1950 to 2010, resulting in 1943 studies linking a total of forty-five food parameters with inflammatory biomarkers.

A score for each food parameter was calculated giving:
+1 to each article if the effects were pro-inflammatory (significantly increased IL-1β, IL-6, TNF-α or CRP, or decreased IL-4 or IL-10),
–1 if the effects were anti-inflammatory (significantly decreased IL-1β, IL-6, TNF-α or CRP, or increased IL-4 or IL-10),
0 if the food parameter did not produce any significant change in the inflammatory marker.

The score for each food parameter was weighted according to the study design. The weights were 10 (experimental design), 8 (observational), 7 (case–control), 6 (cross-sectional), 5 (experimental with animals), 3 (cell culture).

A food parameter-specific overall inflammatory effect score was calculated by subtracting the anti-inflammatory fraction from the pro-inflammatory fraction. This score was corrected if the total weighted number of articles was <236. In these cases the raw overall inflammatory score is multiplied by the total weighted number of articles divided by 236.

Twelve food parameters were excluded because they could not be measured with the FFQ used in the PREDIMED trial.

z-Score and centred percentiles for each of the thirty-three food parameters* for each participant of the PREDIMED trial were calculated based on the average and standard deviation for each food parameter obtained from the global database that was created from the consumption of the original forty-five food parameters from eleven countries from around the world.

The centred percentile for each food parameter is multiplied by the respective ‘overall food parameter-specific inflammatory effect score’ to obtain the ‘food parameter-specific DII score’.

All of the ‘food parameter-specific DII scores’ are summed to create the ‘overall DII score’ for each individual.

Fig. 1. Sequence of steps in creating the dietary inflammatory index in the PREvención con Dieta MEDiterránea (PREDIMED) trial. *Alcohol, β-carotene, caffeine, carbohydrate, cholesterol, energy, iron, fibre, folic acid, garlic, green/black tea, magnesium, MUFA, n-3 fatty acids, n-6 fatty acids, niacin, onion, pepper, protein, PUFA, riboflavin, saturated fat, Se, thiamin, total fat, trans-fat, vitamin A, vitamin B12, vitamin B6, vitamin C, vitamin D, vitamin E and Zn. CRP, C-reactive protein; DII, dietary inflammatory index. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).
### Table 1. Description of the main characteristics of the participants according to quintiles (Q) of the dietary inflammatory index (DII) score in the PREvención con Dieta MEDiterránea (PREDIMED) Trial, 2003–9

(Mean values and standard deviations; median values, minimum and maximum values, and percentages)

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MET, metabolic equivalents.
* Highest anti-inflammatory values of the DII.
† Highest pro-inflammatory values of the DII.
<table>
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<tr>
<th>Quintiles of the DII</th>
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<td>Q5†</td>
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<td>Q1*</td>
<td>Q2–Q4</td>
<td>Q5†</td>
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<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate intake (%E)</td>
<td>43·4</td>
<td>7·0</td>
<td>42·6</td>
<td>6·7</td>
<td>40·8</td>
<td>6·8</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17·2</td>
<td>2·6</td>
<td>17·1</td>
<td>2·7</td>
<td>17·2</td>
<td>3·1</td>
<td>0·452</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetable protein intake (%E)</td>
<td>6·1</td>
<td>1·1</td>
<td>5·4</td>
<td>1·0</td>
<td>4·9</td>
<td>1·0</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11·1</td>
<td>2·7</td>
<td>11·6</td>
<td>2·8</td>
<td>12·3</td>
<td>3·2</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total fat intake (%E)</td>
<td>38·4</td>
<td>6·8</td>
<td>39·4</td>
<td>6·6</td>
<td>40·9</td>
<td>6·9</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9·2</td>
<td>2·6</td>
<td>10·0</td>
<td>2·1</td>
<td>10·8</td>
<td>2·4</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monounsaturated fat (%E)</td>
<td>18·2</td>
<td>4·5</td>
<td>19·7</td>
<td>4·5</td>
<td>21·0</td>
<td>4·8</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyunsaturated fat (%E)</td>
<td>7·2</td>
<td>2·2</td>
<td>6·2</td>
<td>2·1</td>
<td>5·6</td>
<td>1·7</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption (g/d)</td>
<td>3·8</td>
<td>7·4</td>
<td>3·0</td>
<td>5·8</td>
<td>2·8</td>
<td>5·8</td>
<td>0·002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>34·6</td>
<td>9·3</td>
<td>24·7</td>
<td>6·1</td>
<td>16·1</td>
<td>3·6</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits (g/d)</td>
<td>12·5</td>
<td>3·7</td>
<td>9·7</td>
<td>3·7</td>
<td>7·0</td>
<td>2·6</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C (mg/d)</td>
<td>289</td>
<td>99</td>
<td>201</td>
<td>70</td>
<td>123</td>
<td>42</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1757</td>
<td>784</td>
<td>1235</td>
<td>640</td>
<td>847</td>
<td>485</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetables (g/d)</td>
<td>483</td>
<td>168</td>
<td>327</td>
<td>107</td>
<td>213</td>
<td>78</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>487</td>
<td>214</td>
<td>379</td>
<td>186</td>
<td>231</td>
<td>118</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cereals (g/d)</td>
<td>143</td>
<td>78</td>
<td>132</td>
<td>76</td>
<td>111</td>
<td>63</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>58</td>
<td>80</td>
<td>48</td>
<td>62</td>
<td>39</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legumes (g/d)</td>
<td>25·6</td>
<td>18·6</td>
<td>19·7</td>
<td>12·9</td>
<td>14·8</td>
<td>7·8</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>18·6</td>
<td>18·4</td>
<td>8·2</td>
<td>10·8</td>
<td>3·3</td>
<td>5·6</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish and seafoods (g/d)</td>
<td>123·9</td>
<td>60·6</td>
<td>95·2</td>
<td>41·7</td>
<td>74·8</td>
<td>36·5</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meat and meat products (g/d)</td>
<td>125·0</td>
<td>57·3</td>
<td>127·2</td>
<td>50·9</td>
<td>114·5</td>
<td>49·1</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dairy products (g/d)</td>
<td>435·5</td>
<td>238·4</td>
<td>408·1</td>
<td>221·0</td>
<td>381·4</td>
<td>218·9</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediterranean diet score (0–14)</td>
<td>9·5</td>
<td>1·9</td>
<td>8·6</td>
<td>1·8</td>
<td>7·7</td>
<td>1·7</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9·8</td>
<td>1·9</td>
<td>8·7</td>
<td>1·9</td>
<td>8·0</td>
<td>1·7</td>
<td>&lt;0·001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

%E, percentage of energy.
* Highest anti-inflammatory values of the DII.
† Highest pro-inflammatory values of the DII.
significant among women, except for the percentage of subjects with a family history of early CHD, the presence of hypertension and smoking status. Among men, differences between the quintiles of the DII according to age, hypertension, diabetes and smoking status were not statistically significant. In both sexes, the level of physical activity was inversely associated with the DII, as was total energy intake and alcohol intake.

All macro- and micronutrient intakes were higher in the quintile with the lowest DII score (anti-inflammatory dietary pattern), except for intakes of animal protein, saturated fat and monounsaturated fat, both among women and men (Table 2). Better adherence to a MeDiet also was associated with lower DII scores.

Table 3 shows the adjusted indices of obesity based on BMI, waist circumference and WHtR, according to the DII score stratified by sex. The lower and upper limits of this score are shown for each quintile. Mean values of all three adiposity indices increased linearly across the successive quintiles of DII scores (from anti-inflammatory to pro-inflammatory levels). A significant positive correlation was observed between these obesity indices and the DII score.

Among women, the DII was directly associated with BMI, after adjusting for multiple factors related to obesity (Table 4). Being in the highest quintile of the DII was associated with an increase in BMI of 0.79 kg/m² (95% CI 0.35, 1.23) compared with the lowest quintile (P for trend=0.001). This association was not statistically significant for men.

Table 4 further shows that waist circumference and WHtR increased progressively across quintiles 2–4 and 5 compared with the lowest quintile of the DII, both in women and men (P for trend being statistically significant in all comparisons).

Table 5 shows the association of the DII with the anthropometric indices, after considering the possible contribution of the MeDiet elements to the anti- or pro-inflammatory capacity of the diet. A higher pro-inflammatory level of the MeDiet was directly associated with a higher inflammatory potential of the diet. As expected, we observed that the DII was inversely associated with the intake of healthy foods, nutrients and adherence to the MeDiet. A pro-inflammatory DII was directly associated with the indices of general and abdominal obesity, independent of the residuals of the DII.

**Discussion**

In the present study, we used the dietary inflammatory index (DII) score to assess the capacity of the overall dietary pattern to promote inflammation. Higher values of the DII represent a higher inflammatory potential of the diet. As expected, we observed that the DII was inversely associated with the intake of healthy foods, nutrients and adherence to the MeDiet. A pro-inflammatory DII was directly associated with the indices of general and abdominal obesity, independent of multiple factors related to obesity (Table 4). Being in the highest quintile of the DII was associated with an increase in BMI of 0.79 kg/m² (95% CI 0.35, 1.23) compared with the lowest quintile (P for trend=0.001). This association was not statistically significant for men.

**Table 3.** General obesity and abdominal obesity according to quintiles (Q) of the dietary inflammatory index (DII) score in the PREvención con Dieta MEDITerránea (PREDIMED) trial, 2003–9

<table>
<thead>
<tr>
<th>Quintiles of the dietary inflammatory index</th>
<th>Q1 (highest anti-inflammatory)</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5 (highest pro-inflammatory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted average indices and 95% confidence intervals</td>
<td>Adjusted average indices and 95% confidence intervals</td>
<td>Adjusted average indices and 95% confidence intervals</td>
<td>Adjusted average indices and 95% confidence intervals</td>
<td>Adjusted average indices and 95% confidence intervals</td>
<td></td>
</tr>
<tr>
<td><strong>Women (n)</strong></td>
<td>829</td>
<td>829</td>
<td>829</td>
<td>829</td>
<td>829</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>29.9, 30.2, 30.5</td>
<td>29.6, 29.9, 30.2</td>
<td>29.3, 29.6, 30.0</td>
<td>29.1, 29.4, 29.7</td>
<td>29.0, 29.3, 29.6</td>
</tr>
<tr>
<td>Waist circumference (cm)*</td>
<td>96.5, 97.2, 97.9</td>
<td>96.2, 96.9, 97.6</td>
<td>95.9, 96.6, 97.3</td>
<td>95.6, 96.3, 97.0</td>
<td>95.4, 96.1, 96.8</td>
</tr>
<tr>
<td>Waist:height ratio (%)*</td>
<td>62.7, 63.4, 64.1</td>
<td>62.4, 63.1, 63.8</td>
<td>62.1, 62.8, 63.5</td>
<td>61.8, 62.5, 63.2</td>
<td>61.6, 62.3, 63.0</td>
</tr>
<tr>
<td><strong>Men (n)</strong></td>
<td>619</td>
<td>618</td>
<td>618</td>
<td>618</td>
<td>618</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>29.2, 29.5, 29.8</td>
<td>28.9, 29.2, 29.5</td>
<td>28.6, 29.0, 29.3</td>
<td>28.3, 28.7, 29.0</td>
<td>28.0, 28.4, 28.7</td>
</tr>
<tr>
<td>Waist circumference (cm)*</td>
<td>102.2, 102.9, 103.6</td>
<td>101.9, 102.6, 103.3</td>
<td>101.6, 102.3, 103.0</td>
<td>101.3, 102.0, 102.7</td>
<td>101.0, 101.7, 102.4</td>
</tr>
<tr>
<td>Waist:height ratio (%)*</td>
<td>61.2, 61.9, 62.6</td>
<td>60.9, 61.6, 62.3</td>
<td>60.6, 61.3, 62.0</td>
<td>60.3, 61.0, 61.7</td>
<td>60.0, 60.7, 61.4</td>
</tr>
</tbody>
</table>

* Adjusted for age, smoking status, diabetes, hypertension, marital status, educational level, physical activity, total energy intake and study centre.

A waist:height ratio equal to 1 was taken as 100%.
Previous studies have also observed associations of specific legumes (37), nuts (38), and low-fat dairy consumption (39). Women with higher adherence index in the PREvención con DIeta MEDiterránea (PREDIMED) trial, 2003–9

* Adjusted for age, smoking status, diabetes status, hypertensive status, physical activity, energy intake, educational level, marital status and study centre.

Table 4. Multivariable-adjusted* differences in the indices of general obesity and abdominal obesity according to quintiles (Q) of the dietary inflammatory index in the PREvención con DIeta MEDiterránea (PREDIMED) trial, 2003–9

(Adjusted differences and 95 % confidence intervals)

<table>
<thead>
<tr>
<th>Quintiles of the dietary inflammatory index</th>
<th>Q1 (highest anti-inflammatory)</th>
<th>Q2–Q4</th>
<th>Q5 (highest pro-inflammatory)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted difference</td>
<td>95 % CI</td>
<td>Adjusted difference</td>
</tr>
<tr>
<td>Women</td>
<td>0 Reference</td>
<td>0.56</td>
<td>0.23, 0.89</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>0 Reference</td>
<td>2.03</td>
<td>1.17, 2.90</td>
</tr>
<tr>
<td>Waist circumference (cm)*</td>
<td>0 Reference</td>
<td>1.19</td>
<td>0.64, 1.74</td>
</tr>
<tr>
<td>Waist:height ratio (%)†</td>
<td>0 Reference</td>
<td>0.05</td>
<td>0.26, 0.37</td>
</tr>
<tr>
<td>Men</td>
<td>0 Reference</td>
<td>0.98</td>
<td>0.07, 1.89</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>0 Reference</td>
<td>0.44</td>
<td>0.09, 0.97</td>
</tr>
<tr>
<td>Waist circumference (cm)*</td>
<td>0 Reference</td>
<td>0.56</td>
<td>0.23, 0.89</td>
</tr>
<tr>
<td>Waist:height ratio (%)†</td>
<td>0 Reference</td>
<td>2.03</td>
<td>1.17, 2.90</td>
</tr>
<tr>
<td>Men</td>
<td>0 Reference</td>
<td>1.19</td>
<td>0.64, 1.74</td>
</tr>
</tbody>
</table>

Table 5. Multivariable-adjusted* differences in the indices of general obesity and abdominal obesity according to adherence to the residuals of the dietary inflammatory index on the fourteen-item PREvención con DIeta MEDiterránea (PREDIMED) score of adherence to the Mediterranean diet in the PREDIMED trial 2003–9

(Adjusted differences and 95 % confidence intervals)

<table>
<thead>
<tr>
<th>Quintiles of the dietary inflammatory index (adjusted for adherence to the Mediterranean diet)</th>
<th>Q1 (highest anti-inflammatory)</th>
<th>Q2–Q4</th>
<th>Q5 (highest pro-inflammatory)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted difference</td>
<td>95 % CI</td>
<td>Adjusted difference</td>
</tr>
<tr>
<td>Women</td>
<td>0 Reference</td>
<td>0.14</td>
<td>0.19, 0.48</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>0 Reference</td>
<td>1.01</td>
<td>0.14, 2.81</td>
</tr>
<tr>
<td>Waist circumference (cm)*</td>
<td>0 Reference</td>
<td>0.34</td>
<td>0.20, 0.91</td>
</tr>
<tr>
<td>Waist:height ratio (%)†</td>
<td>0 Reference</td>
<td>0.06</td>
<td>0.26, 0.36</td>
</tr>
<tr>
<td>Men</td>
<td>0 Reference</td>
<td>0.77</td>
<td>0.14, 1.69</td>
</tr>
<tr>
<td>BMI (kg/m²)*</td>
<td>0 Reference</td>
<td>0.44</td>
<td>0.09, 0.96</td>
</tr>
<tr>
<td>Waist circumference (cm)*</td>
<td>0 Reference</td>
<td>0.56</td>
<td>0.23, 0.89</td>
</tr>
<tr>
<td>Waist:height ratio (%)†</td>
<td>0 Reference</td>
<td>2.03</td>
<td>1.17, 2.90</td>
</tr>
<tr>
<td>Men</td>
<td>0 Reference</td>
<td>1.19</td>
<td>0.64, 1.74</td>
</tr>
</tbody>
</table>

* Adjusted for age, smoking status, diabetes status, hypertensive status, physical activity, energy intake, educational level, marital status and study centre.

† A waist:height ratio equal to 1 was taken as 100 %.
longer observed after adjustment for BMI(60). Therefore, it is suggested that the association between red meat intake and inflammation is probably mediated by obesity.

In the present study, a higher pro-inflammatory diet was observed in participants with higher BMI, waist circumference and WHR. This result suggests the hypothesis that a diet-induced inflammation might contribute to increasing or maintaining obesity, especially abdominal obesity, in a population that is mostly overweight or obese. The origin of inflammation during obesity is not yet fully understood. It is acknowledged that inflammation is induced by adiposity(43,55), but this relationship can be bidirectional (i.e. a pro-inflammatory diet can increase or maintain adiposity), thus creating a vicious cycle, because nutrient excess and some specific foods or nutrients also have been associated with inflammation(47).

The potential mechanisms underlying this association is the activation of pathogen-associated molecular patterns, such as Toll-like receptors and Nod-like receptors, which induce the activation of inflammatory markers in several tissues including the adipose tissue(48). Moreover, dietary patterns (e.g. high-fat/low-fibre or low-fat/high-fibre diet) and single specific nutrients (e.g. dietary fibre) appear to have important consequences in the gut microbiota, which is also involved in low-grade inflammation associated with obesity(49–52).

The residuals of the DII (from a regression model on adherence to the MeDiet) were also associated with obesity indices. These residuals represent the information provided by the DII about the anti- or pro-inflammatory capacity of a diet, which could not be explained by adherence to the MeDiet. The most pro-inflammatory diet showed a stronger association with waist circumference than with other anthropometric indices, both among women and men. These results are in close agreement with previous findings, which showed that central adiposity-related indices are more strongly correlated with plasma pro-inflammatory markers than indices assessing total adiposity in healthy young adults(53). Moreover, abdominal adiposity has been associated with elevated CRP levels, independent of BMI in older adults(53). As a consequence, the present results reinforce the usefulness of the DII to assess the inflammatory properties of a diet, and the association between inflammation and central obesity indices.

The present results are also consistent with those of studies reporting a stronger association between CRP and BMI in women than in men(54,55). This between-sex difference could be partially explained by a greater accumulation of subcutaneous fat in women than in men, and higher lean mass in men(55). Sex differences in the metabolic activity of adipose tissue, as well as in the association between leptin and CRP, may also explain these differences(56,57).

The strengths of the present study include the following: large sample size; use of a validated instrument to measure the inflammatory potential of the diet; adjustment for a large number of factors associated with obesity; detailed measures of obesity indices; validation of all assessment instruments including the MedDiet screener, the FFQ and the physical activity questionnaire. The present study also has its limitations, the main one being the cross-sectional nature of our analyses. It is, therefore, unclear whether obese individuals are more likely to choose pro-inflammatory diets, or if pro-inflammatory diets contribute to promoting or maintaining obesity. Both weight reduction and an overall healthy dietary pattern have the capacity to reduce inflammatory markers. Thus, the association between the DII and obesity indices remains to be confirmed in prospective analyses. Another limitation is that anthropometric measures are surrogate markers of abdominal obesity. Waist circumference and WHR do not differentiate between visceral adipose tissue and subcutaneous abdominal adipose tissue(58). Therefore, we cannot determine whether the DII is more strongly associated with visceral, subcutaneous or both types of abdominal fat mass. Finally, the DII is limited by the existing knowledge of the inflammatory factors involved in obesity. However, the DII has been found to be associated with the following factors: inflammatory cytokines including CRP and IL-6(53,59,60), glucose intolerance component of the metabolic syndrome(59), odds of asthma and of reduced FEV1 (forced expiratory volume in 1 s) in an Australian population(60). It has also been reportedly associated with a higher risk of colorectal cancer(61), prostate cancer(62) and pancreatic cancer(63).

In conclusion, the present findings indicate an association between anti-inflammatory values of the DII and intake of healthy foods and nutrients and higher adherence to the MeDiet. A pro-inflammatory diet is associated with elevated indices of central and abdominal obesity. This association suggests that the DII may have the capacity to help elucidate the role that diet plays in the development of obesity through inflammatory processes.

**Supplementary material**

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S0007114514004401

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from Reus, Spain. CIBERObn and RTIC RD 06/0045 are initiat-
ives of ISCIII, Spain. However, the sponsors played no role in
the design, collection, analysis or interpretation of the data or
in the decision to submit the manuscript for publication.

The authors’ contributions are as follows: M. R.-C. and M. A.
M.-G. contributed to the study concept and design; N. S.,
J. M. S.-L., L. S.-M., X. P., R. E. and M. A. M.-G. contributed to
the acquisition of the data; M. R.-C., N. S. and M. A. M.-G.
analysed and interpreted the data; M. R.-C. drafted the
manuscript. All authors critically revised the manuscript for
important intellectual content.

R. E. served on the board of and received lecture fees from
the Research Foundation on Wine and Nutrition (FIVIN);
serve[d] on the boards of the Beer and Health Foundation
and the European Foundation for Alcohol Research (ERAB);
received lecture fees from Cerveceros de España and Sanofi-
Aventis; and received grant support through his institution
from Novartis. E. R. served on the board of and received
travel support, as well as grant support through his institution
from the California Walnut Commission; served on the board of
the Flora Foundation (Unilever); served on the board of
and received lecture fees from Roche; served on the board of
and received grant support through his institution from
Amen; received consulting fees from Damm and Abbott
Laboratories; received consulting fees and lecture fees, as
well as grant support through his institution from Merck;
received lecture fees from Aegerion, AstraZeneca, Danone,
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J. R. H. owns a controlling interest in Connecting Health
Innovations LLC (CHI), a company planning to license the
right to his invention of the dietary inflammatory index (DII)
from the University of South Carolina in order to develop
computer and smart phone applications for patient counsel-
ing and dietary intervention in clinical settings. N. S. is an
employee of CHI. The subject matter of this paper will not
have any direct bearing on that work, nor has that activity
exerted any influence on this project.

The authors declare that there are no conflicts of interest
despite the various aforementioned activities, payments and
grants received.

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