TITLE PAGE

Dietary inflammatory index and anthropometric measures of obesity in a population sample at high cardiovascular risk from the PREDIMED trial

Running title: Dietary inflammatory index and obesity

Ruiz-Canela M[1,2,*], Zazpe I[2,3], Shivappa N[4,5], Hébert JR[4,5], Sánchez-Tainta A[2], Corella D[2,6], Salas-Salvadó J[2,7], Fitó M[2,8], Lamuela-Raventós RM[2,9], Rekondo J[2,10], Fernández-Crehuet J[2,11], Fiol M[2,12], Santos-Lozano JM[2,13], Serra-Majem L[2,14], Pinto X[2,15], Martínez JA[2,3], Ros E[2,16], Estruch R[2,17], Martínez-González MA[1,2]

[1]Department of Preventive Medicine and Public Health, School of Medicine, University of Navarra, Pamplona, Spain

[2]CIBER Fisiopatología de la Obesidad y Nutrición (CIBER obn), Instituto de Salud Carlos III, Madrid, Spain

[3]Department of Nutrition, Food Science and Physiology, University of Navarra, Pamplona, Spain

[4]Cancer Prevention and Control Program, University of South Carolina, Columbia, USA

[5]Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, USA

[6]Department of Preventive Medicine, University of Valencia, Valencia, Spain

[7]Human Nutrition Unit, Sant Joan University Hospital, IISPV, Universitat Rovira i Virgili, Reus, Spain

[8]Inflammatory and Cardiovascular Disease Programme (RICAD), IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain

[9]Department of Nutrition and Food Science, School of Pharmacy, Instituto de Investigación en Nutrición y Seguridad Alimentaria, University of Barcelona, Barcelona, Spain

[10]Department of Cardiology, University Hospital Txagorritxu-University Hospital of Alava, Vitoria, Spain

[11]Department of Preventive Medicine, University of Malaga, Malaga, Spain

[12]Institute of Health Sciences (IUNICS), University of Balearic Islands, Palma de Mallorca, Spain

[13]Department of Family Medicine, Primary Care Division of Sevilla, Centro de Salud San Pablo, Sevilla, Spain

[14]Department of Clinical Sciences. University of Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain

[15]Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain

[16]Lipid Clinic, Department of Endocrinology and Nutrition, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS), Hospital Clinic, Barcelona, Spain
[17]Department of Internal Medicine, IDIBAPS, Hospital Clinic, University of Barcelona, Barcelona, Spain

*Correspondence and reprints: Miguel Ruiz-Canela, MPH, PhD. Department of Preventive Medicine and Public Health, Facultad de Medicina- Clínica Universidad de Navarra, Universidad de Navarra, Irunlarrea 1, 31080 Pamplona, Navarra, Spain. E-mail: mcanela@unav.es. Tel: +34 948 42 56 00 Ext:806395. Fax: + 34 948 42 56 49.

Key words: Inflammation, diet, obesity, BMI, waist circumference, and waist-to-height ratio

Abstract

The dietary inflammatory index (DII) is a new tool to assess the inflammatory potential of diet. We aimed to determine the association between the DII and body mass index (BMI), waist circumference and waist to height ratio (WHtR). We conducted a cross-sectional study of 7,236 participants recruited into the PREDIMED trial (*PREvención con DIeta MEDiterránea*). Information from a validated 137-item food frequency questionnaire was used to calculate energy, foods and nutrients. A 14-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% confidence intervals) in BMI, waist circumference and WHtR across quintiles of the DII. All nutrient intakes, healthy foods and adherence to the MeDiet were higher in the quintile with lowest DII score (more *anti*-inflammatory values) except for animal protein, saturated and monounsaturated fat. Though an inverse association between 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 WHtR for women and men between the highest and lowest quintile of DII was 1.60% (95% CI 0.87-2.33) and 1.04% (95% CI 0.35-1.74), respectively. Pro-inflammatory scores remained associated with obesity after controlling for the effect that adherence to a MeDiet had on inflammation. In conclusion, this study shows a direct association between the DII and indices of obesity and supports the hypothesis that diet may have a role in the development of obesity through inflammatory modulation mechanisms.

Trial Registration International Standard Randomised Controlled Trial Number Registry ISRCTN35739639

Introduction

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[1]. In 2008 more than 10% of the World's adult population, i.e. around 500 million people, were obese according to the WHO[2]. It is estimated that 3.4 million adult deaths worldwide were in 2010 attributable to obesity or overweight[1]. This is a global crisis since 65% of the world's population live in countries where overweight and obesity kill more people than underweight[2].

Obesity is the result of the accumulation of excess body fat and it is often characterized as a state of low-grade chronic inflammation[3]. This obesity-induced inflammation has multi-organ metabolic effects affecting adipose tissue, liver, muscle, pancreas and brain[4]. Metabolic differences exist according to the location of the 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 to height ratio (WHtR) are used to assess the role of adiposity in cardiovascular disease 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, 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 Mediterranean diet may also attenuate inflammation in the absence of weight loss[22]. A recent hypothesis is that obesity could be also partly the consequence of a previous chronic low grade inflammation and, therefore, a bidirectional association between inflammation and obesity may exist[23].

Consequently, it can be useful to characterize 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 this article 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 PREDIMED trial.

Methods

Ethics statement

The protocol was approved by the Research Ethics Committees at all recruiting centers: 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 Balearic Islands, University of Las Palmas de Gran Canaria, University Hospital of Bellvitge, Hospital Clinic.
Participants signed a written informed consent.

Study design and participants

The "PREvención con DIeta MEDiterránea" (PREDIMED) study was a parallel group, multicenter, clinical trial that aimed to assess the effects of the traditional MedDiet on the primary prevention of cardiovascular disease (protocol available at 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 11 recruiting centers in Spain.

Eligible participants were men 55 to 80 years of age and women 60 to 80 years of age with no previous cardiovascular disease. 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 1 cig/day during the last month), hypertension (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or antihypertensive medication), elevated low-density lipoprotein cholesterol levels (≥ 160 mg/dl), low high-density lipoprotein cholesterol levels (≤ 40 mg/dl in men or ≤ 50 mg/dl in women, independently of lipid-lowering therapy), BMI ≥ 25 kg/m^2, or a family history of premature coronary heart disease.

A total of 7447 participants were randomized in a 1:1:1 ratio to a parallel-design intervention trial of dietary advice: a) a MedDiet supplemented with extra-virgin olive oil, b) a MedDiet supplemented with nuts, or c) advice to follow a low-fat diet (control group). Medical conditions and risks factors related to eligibility were collected with a questionnaire during the first screening visit. Participants, with the assistance of trained dietitians, completed a food frequency questionnaire (FFQ). This FFQ was adapted from the Willett questionnaire and validated in Spain[28]. It includes 137 items plus

vitamin/minerals supplements and with 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[30], and a 14-item dietary screener to assess adherence to the MedDiet[31]. 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 (<800 or >4200 kcal/d for men and <600 or >3500 kcal/d for women). These limits were set in accordance with those recommended by Willett in Nutritional Epidemiology[32]. Another 78 participants were excluded because of lack of information on the FFQ needed to calculate the DII.

The Dietary Inflammatory Index (DII)

The design and development of the DII has been described elsewhere[25]. 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 including various macronutrients, micronutrients, flavonoids and food items (figure 1). These dietary parameters were scored according to whether they increased (+1), decreased (-1) or had no effect (0) on six inflammatory biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein). An overall food parameter-specific inflammatory effect score was calculated and multiplied by a centered 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 11 populations from different parts of the world that provided a robust estimate of a mean and standard deviation for each parameter. These 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 minimize the effect of "right skewing", this value was then converted to a centered percentile score. The centered percentile score for each food parameter for each individual was multiplied by the respective food parameter effect score, which 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)[25].

Construct validation of the DII was performed using data derived from two different sources of dietary intake information and serum high-sensitivity C-reactive protein as the construct validator[33].

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-to-height ratio equal to 1 was taken as 100%. Baseline weight was measured using a calibrated balance beam scale with the subject 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 analysis

Statistical analyses were stratified by sex. Comparisons of quantitative variables across quintiles of the DII were done using 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) were expressed as percentages of total energy intake (Table 1). Categorical variables were compared using the Pearson Chi-squared test.

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

Sex-specific multiple linear regression models were used to estimate the differences (95% confidence intervals) in the indices of general obesity and abdominal obesity according to 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 (MET-min/d), educational level (illiterate/elementary education, secondary education or university), marital status (married, widowed, single or other), total energy intake (kcal/d), and research center. In addition, tests of linear trend across successive quintiles of DII index were conducted using the median value for each quintile category as a continuous variable and after adjusting for the confounding variables mentioned above.

Residuals of the DII were obtained in a linear regression analysis of the association between the DII and a previously validated 14-item PREDIMED screener of adherence to the MeDiet.[31] These residuals represent the information provided by the DII that 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 previously listed (residual model).

All P values presented are 2-tailed and differences were considered statistically significant at $p \leq 0.05$. All statistical analyses were carried using the STATA® software for Windows version 12.0.

Results

A total number of 7236 participants out of the 7447 initially randomized subjects in the PREDIMED trial were included in this study. The 211 (2.8%) remaining participants were excluded because of incomplete data on their FFQs (n=78) or baseline energy intake out of predefined values (n=133). Among the 7236 participants, 57% were women. The mean age of participants was 68 (±5.8) years for women and 66 (±6.6) years for men. The median DII score for women was -0.78 (from -4.90 to 3.68) and -0.91 (from -5.23 to 3.69) for men.

Table 1 shows the main characteristics of participants according to categories of the DII score by sex. All differences between quintiles of this index were statistically significant among women except for the percentage of subjects with a family history of early CHD, the presence of hypertension and the smoking status. Among men, differences between quintiles of DII according to age, hypertension, diabetes and smoking 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 *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 successive quintiles of DII scores (from anti-inflammatory to pro-inflammatory levels). A significant positive correlation was observed between these obesity indexes 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 of 0.79 kg/m^2 in the BMI (95%CI, 0.35-1.23) compared with the lowest quintile (p for trend = 0.001). This association was not statistically significant for men.

Waist circumference and WHtR increased progressively across quintiles 2 to 4 and 5 compared with the lowest quintile of DII, both in women and men (p for trend statistically significant in all comparisons).

Table 5 shows the association of the DII with the anthropometric indices after considering the possible contribution of the Mediterranean diet elements to the *anti*- or *pro*-inflammatory capacity of the diet. A higher pro-inflammatory level of diet (beyond the effect of lower adherence to the MeDiet) was associated with higher adjusted means of BMI, waist circumference and WHtR (p for trend < 0.05 in all comparisons except for BMI among men). The predicted increase in anthropometric measures was statistically significant in women except for the increase in BMI and in WHtR when the intermediate DII quintiles (2 to 4) were compared with the lowest category. On the contrary, results were not statistically significant among men except for the waist circumference and the WHtR when comparing the highest *versus* the lowest quintile of the residuals of DII.

Discussion

In our study, we used a score (DII) to appraise the capacity of the overall dietary pattern to promote inflammation. Higher values of DII represent a higher inflammatory potential. As expected, we observed that DII was inversely associated with the intake of healthy foods, nutrients and adherence to MeDiet. A *pro*-inflammatory DII was directly associated with indices of general and abdominal obesity, independent of established risk factors for obesity including total energy intake, age, smoking, diabetes,

hypertension, physical activity, educational level and marital status. These results were consistent for both sexes except for the BMI in men. In the residual model (after removing the variability explained by MeDiet), the association between the inflammatory potential of the diet and higher adiposity indices remained apparent, but there was a clearer association between the DII and the abdominal indices of obesity for women than for men.

The associations observed between nutrient intake or food consumption with the DII are consistent with previous research. Several studies have shown an inverse association between healthy diets and markers of inflammation as well as a direct association with "Western-like" dietary patterns[8-14]. Specifically, a lower C-reactive protein concentration has been associated with higher intake of fruits and vegetables[34-36], legumes[37], nuts[38], and low-fat dairy consumption[39]. Previous studies also have observed associations of specific nutrients such as total dietary fiber intake[40], moderate alcohol consumption[41], vitamin E and vitamin C intake[42] with lower levels of inflammation markers. On the contrary, animal protein seems to increase the inflammatory status of obese individuals[43].

We also found that a higher consumption of dairy products and meat (or meat products) was less frequent in the highest DII quintile. A systematic review has found no impact of dairy products consumption on biomarkers of inflammation on overweight and obese adults[44]. However, only 1 out of 8 trials included in this review defined inflammation as its primary outcome and there were some methodological limitations in them such as insufficient statistical power[44]. Concerning the consumption of meat, a cross-sectional analysis of data from 3690 diabetes-free female participants found that higher intake of meat protein was associated with higher plasma levels of inflammatory markers[45]. However, a cross-sectional study has shown that the association between red meat intake and inflammatory markers was no longer observed after adjustment for BMI[46]. Therefore, it is suggested that the association between red meat intake and inflammation is probably mediated by obesity.

In our study, a higher pro-inflammatory diet was observed in participants with higher BMI, waist circumference and WHtR. This result suggests the hypothesis that a diet-induced inflammation might be contributing to increase or maintain 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[4,5], but this relationship can be bidirectional (i.e., a

pro-inflammatory diet can increase or maintain adiposity), thus creating a vicious circle, 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-fiber or low-fat/high-fiber diet) and single specific nutrients (e.g., dietary fiber) appear to have important consequences in the gut microbiota which is also involved in the low-grade inflammation associated with obesity[49-52].

The residuals of the DII (from a regression model on adherence to the Mediterranean diet) 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 that could not be explained by adherence to the Mediterranean diet. A highest *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 showing that central adiposity-related indices are more strongly correlated with plasma pro-inflammatory markers than indices assessing total adiposity in healthy young adults[5]. Moreover, abdominal adiposity has been associated with elevated CRP levels independent of BMI in older adults[53]. As a consequence, our results are reinforcing the usefulness of the DII to assess the inflammatory properties of a diet and the association between inflammation and central obesity indices.

Our results are also consistent with those of studies reporting a stronger association of CRP and BMI in women than in men[54,55] This between-sexes 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 tissues as well as in the association between leptin and CRP may also explain these differences[56,57].

The strengths of the current study include a large sample size, the use of a validated instrument to measure the inflammatory potential of the diet, the adjustment for a large number of factors associated with obesity, the detailed measures of obesity indexes and the validation of all assessment instruments including the MedDiet screener, the FFQ, and the physical activity questionnaire. This study also has limitations, the main of which is 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 promote or maintain 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(Eroglu, Tagawa & Somlo 2014). Waist circumference and WHtR 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 current knowledge of the inflammatory factors involved in obesity. However, the DII has been found to be associated with inflammatory cytokines including C-reactive protein and interleukin-6[33,59,60], the glucose intolerance component of the metabolic syndrome[59], and the odds of asthma and of reduced FEV_1 in an Australian population[60]. It has been also reportedly associated with a higher risk of colorectal cancer[61], prostate cancer[62] and pancreatic cancer[63].

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

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Conflict of interest

Dr. Estruch reports serving on the board of and receiving lecture fees from the Research Foundation on Wine and Nutrition (FIVIN); serving on the boards of the Beer and Health Foundation and the European Foundation for Alcohol Research (ERAB);

receiving lecture fees from Cerveceros de España and Sanofi-Aventis; and receiving grant support through his institution from Novartis. Dr. Ros reports serving on the board of and receiving travel support, as well as grant support through his institution, from the California Walnut Commission; serving on the board of the Flora Foundation (Unilever); serving on the board of and receiving lecture fees from Roche; serving on the board of and receiving grant support through his institution from Amgen; receiving consulting fees from Damm and Abbott Laboratories; receiving consulting fees and lecture fees, as well as grant support through his institution, from Merck; receiving lecture fees from Aegerion, AstraZeneca, Danone, Pace, and Rottapharm; receiving lecture fees and payment for the development of educational presentations, as well as grant support through his institution, from Ferrer; receiving payment for the development of educational presentations from Recordati; and receiving grant support through his institution from, Daiichi Sankyo, Feiraco, Karo Bio, Nutrexpa, Pfizer, Sanofi-Aventis, Synageva, Takeda, and, Unilever. Dr. Salas-Salvadó reports serving on the board of and receiving grant support through his institution from the International Nut and Dried Fruit Council; receiving consulting fees from Danone; and receiving grant support through his institution from Eroski and Nestlé.

Authorship

Study concept and design: Ruiz-Canela, Martínez-González. Acquisition of data: Shivappa, Hébert, Sánchez-Tainta, Corella, Salas-Salvadó, Fitó, Rekondo, Fernández-Crehuet, Fiol, Santos-Lozano, Serra-Majem, Pinto, Estruch, Martínez-González. Analysis and interpretation of data: Ruiz-Canela, Shivappa, Martínez-González. Drafting of the manuscript: Ruiz-Canela. Critical revision of the manuscript for important intellectual content: all co-authors.

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