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Original article

# Dietary inflammatory index and all-cause mortality in large cohorts: The SUN and PREDIMED studies

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SUMMARY

*Background:* Inflammation is known to be related to the leading causes of death including cardiovascular disease, several types of cancer, obesity, type 2 diabetes, depression-suicide and other chronic diseases. In the context of whole dietary patterns, the Dietary Inflammatory Index (DII®) was developed to appraise the inflammatory potential of the diet.

*Objective:* We prospectively assessed the association between DII scores and all-cause mortality in two large Spanish cohorts and valuated the consistency of findings across these two cohorts and results published based on other cohorts.

*Design:* We assessed 18,566 participants in the "Seguimiento Universidad de Navarra" (SUN) cohort followed-up during 188,891 person-years and 6790 participants in the "PREvencion con DIeta MEDiterránea" (PREDIMED) randomized trial representing 30,233 person-years of follow-up. DII scores were calculated in both cohorts from validated FFQs. Higher DII scores corresponded to more proinflammatory

*List of abbreviations:* CRP, C-Reactive Protein; DII, Dietary Inflammatory Index; EVOO, Extra virgin olive oil; FFQs, Food frequency questionnaires; HR, Hazard Ratio; Hs-CRP, high sensitivity C-Reactive Protein; PREDIMED, PREvención con Dieta MEDiterránea; SUN, Seguimiento Universidad de Navarra.

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diets. A total of 230 and 302 deaths occurred in SUN and PREDIMED, respectively. In a random-effect meta-analysis we included 12 prospective studies (SUN, PREDIMED and 10 additional studies) that assessed the association between DII scores and all-cause mortality.

*Results:* After adjusting for a wide array of potential confounders, the comparison between extreme quartiles of the DII showed a positive and significant association with all-cause mortality in both the SUN (hazard ratio [HR] = 1.85; 95% CI: 1.15, 2.98; P-trend = 0.004) and the PREDIMED cohort (HR = 1.42; 95% CI: 1.00, 2.02; P-trend = 0.009). In the meta-analysis of 12 cohorts, the DII was significantly associated with an increase of 23% in all-cause mortality (95% CI: 16%–32%, for the highest vs lowest category of DII).

*Conclusion:* Our results provide strong and consistent support for the hypothesis that a pro-inflammatory diet is associated with increased all-cause mortality.

The SUN cohort and PREDIMED trial were registered at clinicaltrials.gov as NCT02669602 and at isrctn.com as ISRCTN35739639, respectively.



## 1. Introduction

Inflammation is believed to be involved in the development of several of the most important causes of death [1,2], including cardiovascular disease (myocardial infarction, sudden cardiac death and stroke), type-2 diabetes, major cancers, and also suicide resulting from depression [3–8], which represents a growing global public health problem.

Many studies have evaluated the relationship between consumption of different food items and inflammatory responses, due to the interest in the anti-inflammatory properties of food patterns for the prevention of cardio-metabolic diseases and other chronic conditions [9].

The current state of the art in nutritional epidemiology is focused on assessing combinations of foods and nutrients that represent an overall dietary patterns. An advantage of this approach is that a variety of foods and nutrients may interact to produce synergistic or antagonistic effects with respect to one another. In addition, the approach based on whole dietary patterns circumvents the problem of confounding by specific aspects of diet, increases the statistical power, because the effect of a single nutrient is likely to be very small, and avoids statistical issues associated with collinearity and multiple testing. Therefore, the use of overall dietary patterns has the potential to lead to a better understanding of the relationship between diet and disease because many aspects of the diet are considered together [10–12]. Dietary patterns are often constructed according to a specifically defined *a priori* hypothesis. In this context, the Dietary Inflammatory Index (DII®) was developed to estimate the inflammatory potential of the overall diet [9,13]. The use of the DII as a relevant exposure in nutritional epidemiology allows an excellent opportunity to test hypotheses that propose diet acts as a determinant of non-communicable disease incidence and premature mortality through inflammation-related pathways.

A meta-analysis based on 4 observational studies has shown a higher risk of all-cause mortality among participants with the highest DII values (most pro-inflammatory diets) [14]. Similar results have been found in a meta-analysis focused on cardiovascular mortality [15]. Up to March 2018, thirteen reports from prospective cohort studies had been published to assess the association between the DII and all-cause mortality [16–28]. Some of these reports examined the same cohort; i.e., three used the National Health and Nutrition Examination Survey (NHANES)-III study [16,17,28] and two used the Women's Health Initiative [25,26]. Therefore, only ten cohorts contributed data to assessing the association between the DII and all-cause mortality.

We analyzed two new Spanish cohorts with sufficient data to enable adequate control for potential confounders. These two new prospective studies, "Seguimiento Universidad de Navarra" (SUN) cohort and the "PREvención con DIeta MEDiterránea" (PREDIMED) trial, were analyzed as an observational cohort. In addition, we quantitatively appraised the consistency of the DII-mortality association combining data across all twelve studies using meta-analytic techniques.

## 2. Methods

The "Seguimiento Universidad de Navarra" (SUN) study is an ongoing, prospective cohort of university graduates conducted in Spain (www.proyectosun.es) with recruitment continually open (i.e., a dynamic design). The methods, objectives and design of the SUN cohort have been published in detail elsewhere [29,30]. In brief, the study began in December 1999, enrolling university graduates. Subsequently, enrolled participants had been contacted biennially through mailed questionnaires to collect a wide array of information about their lifestyles and medical conditions. In the present study, in addition to the comprehensive baseline assessment of all participants, we have used the information collected in eight subsequent assessments; i.e., those conducted after 2, 4, 6, 8, 10, 12, 14 and 16 years of follow-up with a different number of participants in each wave according to their date of recruitment.

Through December 2016, 22,566 participants had been recruited and had completed the baseline assessment of the SUN project. Among them, 20,307 participants remained available for follow-up after excluding those recently recruited (not allowing sufficient time for the first 2-year follow-up), those with previous history of major chronic disease (cancer, cardiovascular disease [CVD] or diabetes) and those who did not meet predefined limits of total energy intake (men:<400 Kcal/day or >6000; women:<400 Kcal/day or >5000) or had no available data to compute DII scores. We obtained follow-up information from 18,566 participants. Thus, the effective sample size was 18,566 participants, achieving a retention rate of 91.1% (Fig. 1a). The Institutional Review Board of the University of Navarra approved the study protocol. To obtain informed consent of potential participants, we duly informed these individuals of their right to refuse to participate in the SUN study or to withdraw their consent to participate at any time without reprisal, according to the principles of the Declaration of Helsinki. Special attention was given to the specific information needs of individual potential candidates as well as to the methods used to deliver their information and the feedback that they may receive from the research team. After ensuring that the candidates had understood the information, we sought their potential voluntary provision of informed consent, and completion of the baseline questionnaire. These methods were

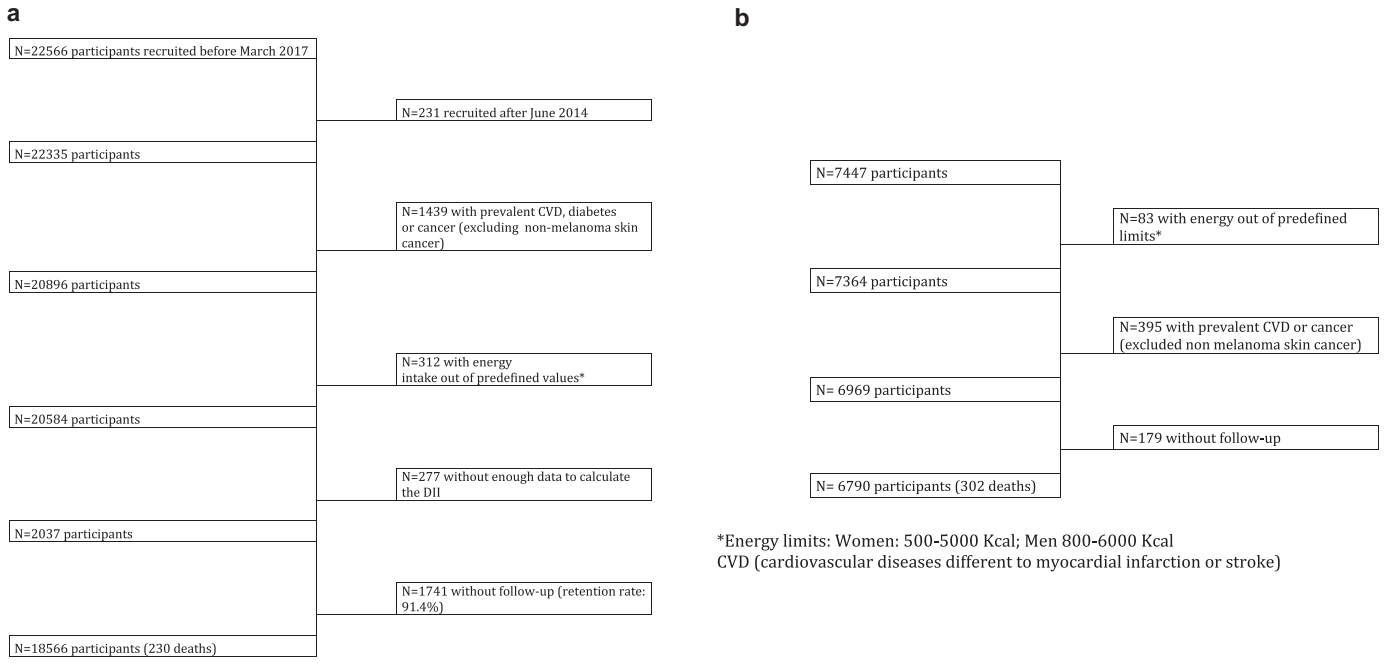



**Fig. 1.** Flow chart of participants. a) The SUN cohort. b) The PREDIMED.

accepted by our Institutional Review Board as to imply an appropriately obtained informed consent.

The PREDIMED study ("PREvención con DIeta MEDiterránea") is a parallel-group, multicenter, randomized trial including 7447 participants followed-up from 2003 to 2012 (http://www.predimed.es). Full details of the methods, design and main results of the PREDIMED trial have been described elsewhere [31,32]. The roster of participants in the PREDIMED trial with expanded follow-up for total mortality has been used as an observational cohort [33,34]. Briefly, participants, who were at high cardiovascular risk, but had no previous history of CVD at enrollment, were randomly assigned to one of three diets: a) a Mediterranean diet (MedDiet) supplemented with extra-virgin olive oil (EVOO), b) a MedDiet supplemented with mixed nuts, or c) a control diet (advice to reduce dietary fat). Participants were men (55–80 years of age) and women (60–80 years of age). Each participant received quarterly individual and group educational sessions and, depending on the group assignment, a free provision of EVOO, mixed nuts, or small nonfood gifts. The protocol of the study was approved by the Institutional Review Boards at all study locations and all participants provided written informed consent. The study began in October 2003. Though the follow-up was planned to last for 6 years, on average, on advice by the Data and Safety Monitoring Board, and based on the results of the fourth interim analysis, which showed early evidence of benefit, the trial was stopped early after a median follow-up of 4.8 years [35]. We excluded from the present analyses participants outside the PREDIMED-specific predefined limits of total daily energy intake (500–5000 kcal in women and 800–6000 kcal in men), participants without any follow-up, and those with a previous history of cancer (Fig. 1b). Data from the remaining participants (n = 6790) were available for the present analyses.

### 2.1. Dietary assessment

The procedure used to calculate the DII scores for all subjects from the FFQs, has been previously described [9,13]. Briefly, the DII was developed after a comprehensive review of peer-reviewed literature published from 1950 to 2010 (Suppl. Fig. 1). A total of 1943 qualifying articles that assessed the role of 45 food macronutrients, micronutrients, flavonoids and individual food items on interleukins (IL-1B, IL-4, IL-6, IL-10), Tumor Necrosis Factor-alpha (TNF-α) and high-sensitivity C-Reactive Protein (CRP). The inflammatory potential for each food parameter was scored according to whether it increased (+1), had no effect (0) or decreased (−1) the above-mentioned inflammatory biomarkers. The DII score for each participant represents the sum of each of the DII components in relation to a comparison global diet database, and characterizes the whole diet of each participant on a continuum from maximally anti-inflammatory (negative values, lower quartiles) to maximally pro-inflammatory (positive values, higher quartiles).

Previously validated semi-quantitative food-frequency questionnaires (FFQs) were used to assess baseline dietary habits in both studies [36–38]. The information derived from the FFQs from both studies was used to calculate the DII scores (137 items in the PREDIMED study and 136 items in the SUN cohort). As previously reported, we used the intake of 32 food/nutrient parameters to compute in the PREDIMED study [40]: alcohol, beta-carotene, caffeine, carbohydrate, cholesterol, energy, iron, fiber, folic acid, garlic, green/black tea, magnesium, monounsaturated fatty acids, *n*-3 fatty acids, *n*-6 fatty acids, niacin, onion, protein, polyunsaturated fatty acids, riboflavin, saturated fat, selenium, thiamin, total fat, trans-fat, vitamin A, vitamin $B_{12}$, vitamin $B_6$, vitamin C, vitamin D, vitamin E and zinc (Suppl. Fig. 2). Of these, beta-carotene, garlic, green/black tea, and onion were not used to calculate the DII score in the SUN cohort because they could not be measured with the FFQ used in this study [39].

### 2.2. Outcome assessment

In the SUN cohort, each new death was identified by means of a continuous and active follow-up of all participants. We contacted every participant on several occasions on a yearly basis, requesting for the completion of follow-up questionnaires, inquiring on eventual changes of postal address, sending Christmas greetings

every December, and frequently sending mailed information on the progress of the study. We kept updated 3 alternative postal addresses of all SUN participants to be able to contact them at any time during the follow-up period. We also frequently used their email addresses and their cellular phones to contact them when postal contact failed. We also had a periodic exchange of information with the alumni associations and other professional associations to inquire about participants who did not answer the follow-up questionnaires. Most of the identified deaths in the SUN cohort (>85%) were reported by next of kin, professional associations, or the postal system. Additionally, we checked the National Death Index every year to confirm the vital status of our participants and to verify and complete the data regarding mortality, including the cause of death. Therefore, we can safely assume 100% coverage of the information on fatalities in the SUN cohort.

In the PREDIMED trial, four different sources of information were used to identify fatalities: 1) continuous contacts with the primary care doctors who were responsible for the routine clinical care of participants; 2) information retrieved from families of participants; 3) very importantly, a comprehensive yearly review of medical records of all participants was done by medical doctors who were blinded with respect to the group allocation and all nutritional information; 4) yearly consultation of the Spanish National Death Index, also was conducted. All medical records related to endpoints were examined by the Event Adjudication Committee, whose members were unaware of the dietary information. Only endpoints that were confirmed by the Event Adjudication Committee and occurred between October 2003 and 30 June 2012 (maximum: 8.7 y; mean: 5.9 y) were included in this analysis.

### 2.3. Statistical analysis

We categorized participants in each cohort into quartiles of DII score. The sample size was estimated by assuming a 2-tailed alpha error = 0.05, RR = 1.50 between extreme quartiles, absolute risk (cumulative incidence) = 2.25% as an average of both cohorts, and statistical power = 0.80. Under these assumptions, the required sample size was 4480 subjects in each extreme quartile, which was achieved with the number of participants only in the SUN cohort. These assumptions need to be viewed as conservative because tests for trend included all data and were associated with higher statistical power. As noted previously, we took into account the large differences in average age and physical activity between both cohorts, which resulted in setting different limits in each cohort for allowable total energy intake.

Baseline characteristics are presented according to quartiles of baseline intake of DII as the mean (SD) for quantitative variables or percentages for categorical variables.

Cox proportional hazards regression models were used to obtain hazard ratios (HR) and their 95% confidence intervals to assess the relationship between categories of baseline DII scores (using the lowest quartile as the reference category) and death during follow-up. The entry time was defined as the date at recruitment. The exit time was defined as the date at death or the date when completing the last interview, questionnaire or visit, whichever came first.

We adjusted the multivariable models for the following potential confounders: sex, age, baseline BMI (adding a quadratic term to account for non-linearity), marital status (single, married, others), educational attainment, family history of premature coronary heart disease (CHD), family history of diabetes, smoking status (current smoker, non-smoker, former smoker), prevalent hypercholesterolemia, prevalent hypertension, physical activity (continuous in the SUN cohort and as quartiles in the PREDIMED to account for a non-linear association), alcohol intake (continuous), and total energy intake (continuous in the SUN cohort, and as quartiles in the PREDIMED to account for a non-linear association). In the SUN cohort, Cox models were stratified by year of recruitment and age was used as the underlying time variable with the model stratified by decades of age. In the PREDIMED cohort, models were stratified by center and intervention arm of the trial and time since randomization was the underlying time variable. We checked the proportional hazards assumption by using Schoenfeld residuals. Tests of linear trend across increasing quartiles of the DII were appraised by assigning the medians to each quartile of the DII and using it as a continuous variable. We conducted stratified analyses and evaluated effect modification (p values for interaction product-term) between adherence to the DII and the following pre-specified variables: sex, age, BMI, smoking and baseline adherence to the MedDiet.

We assessed adherence to the MedDiet with the 0 to 9 score proposed by Trichopoulou [41] in the SUN study and with the study-specific 14-item score in PREDIMED [42]. We dichotomized both scores at their median to run the stratified analyses. We calculated Pearson's correlation coefficients between adherence to MedDiet and the DII score.

In addition, we conducted a stratified analysis in the PREDIMED trial according to the randomized arm of the trial.

To assess the association between DII score and all-cause mortality we ran separated models for each of the cohorts (SUN and PREDIMED) and then we pooled both estimates by using random-effect inverse of variance methods (DerSimonian and Laird method) for meta-analysis. However, the p for trend across successive quartiles for both cohorts combined was calculated by directly pooling the raw data of both cohorts and adjusting for the potential confounders gathered in both cohorts. Non-linear dose–response analysis was modeled using restricted cubic splines with 3 knots.

We combined the estimates of the relative risks of previously existing cohorts with those of the two current cohorts, also by using random-effect meta-analytic methods. We used multivariable-adjusted relative risks comparing the highest vs. the lowest quantiles of DII score and overall mortality.

To compare the consumption of food items between extreme quartiles of the DII we computed z scores of the consumption of each food group and compared the multivariable-adjusted means of these z scores between extreme quartiles after adjusting them for age, sex, BMI and total energy intake using analysis of covariance. Therefore, these means can be interpreted as the number of standard deviations that the respective quartile mean separates from the mean of the overall cohort.

All analyses were run with Stata® 14.0 (Stata Corporation, College Station, TX).

## 3. Results

The mean DII scores (SD) were −1.59 (1.50) and −1.34 (1.81) in the SUN and PREDIMED cohorts, respectively. Their ranges (min; max) were (−5.24; +3.97) and (−5.99; +4.33), respectively.

Table 1 presents the characteristics of subjects in both cohorts according to cohort-specific quartiles of the DII score. Subjects in the fourth DII quartile had higher BMI and lower physical activity than those in the first quartile.

Total energy intake was considerably lower in the most pro-inflammatory quartile (Q4) than in the most anti-inflammatory quartile (Q1). The prevalence of current smokers was higher in the highest quartile of the DII, whereas alcohol intake and adherence to the MedDiet were inversely associated with the DII.

After exclusions, the percentage of participants in PREDIMED allocated to each of the three arms of the trial was not balanced

**Table 1**
Characteristics [mean (SD) or percentage] of participants according to quartiles of the baseline Dietary Inflammatory Index (DII) score.

| | Q1 (n = 4642) | Q2 (n = 4641) | Q3 (n = 4642) | Q4 (n = 4641) | P value |
|---|---|---|---|---|---|
| **The SUN cohort** | | | | | |
| DII score median (min, max) | −3.2 (−5.2, −2.7) | −2.3 (−2.7, −1.9) | −1.4 (−1.9, 0.7) | 0.3 (−0.7, 3.9) | |
| Age (years) | 38.3 (12.2) | 37.6 (12.0) | 36.5 (11.3) | 35.8 (11.1) | <0.001 |
| Sex (%) | | | | | |
| Female | 63.3 | 65.6 | 62.8 | 53.5 | <0.001 |
| Marital status (%) | | | | | |
| Married | 49.2 | 50.9 | 51.2 | 47.9 | |
| Single | 44.8 | 43.6 | 44 | 47.5 | |
| Other | 6.0 | 5.5 | 4.7 | 4.6 | <0.001 |
| BMI (kg/m$^2$) | 23.4 (3.5) | 23.3 (35.5) | 23.4 (3.4) | 23.6 (3.5) | <0.001 |
| Prevalent diseases at baseline (%) | | | | | |
| Hypertension | 7.5 | 6.6 | 5.4 | 5.8 | <0.001 |
| Hyperlipidaemia | 17.9 | 16.3 | 15.3 | 15.5 | 0.002 |
| Physical activity (METs-h/week) | 31.7 (27.7) | 27.5 (23.9) | 25.9 (21.8) | 22.9 (20.7) | <0.001 |
| Smoking status (%) | | | | | |
| Former smoker | 25.9 | 24.4 | 24.2 | 21.5 | |
| Current smoker | 22.9 | 23.9 | 25.5 | 30.5 | |
| Never smoker | 48.6 | 49.2 | 47.5 | 45.6 | |
| Missing | 2.52 | 2.56 | 2.69 | 2.35 | <0.001 |
| Total energy intake (kcal/d) | 3058 (812) | 2614 (670) | 2348 (577) | 1933 (564) | <0.001 |
| Alcohol intake (g) | 8.17 (12.22) | 6.33 (9.74) | 6.12 (8.96) | 6.24 (10.21) | <0.001 |
| Adherence to the Mediterranean diet | 5.55 (1.49) | 4.77 (1.55) | 3.9 (1.45) | 2.79 (1.33) | <0.001 |
| Family history of CVD (%) | 1.21 | 1.62 | 0.95 | 1.14 | 0.028 |
| Family history of diabetes | 16.5 | 15.8 | 14.2 | 14.2 | 0.002 |
| Education level (%) | | | | | |
| Master | 18 | 17.1 | 18.1 | 18.2 | |
| Licentiate degree | 45.2 | 48.5 | 49.4 | 51.7 | |
| Diploma program | 27.1 | 25.4 | 23.5 | 20.5 | |
| Not finished | 9.72 | 8.99 | 8.94 | 9.57 | <0.001 |
| | Q1 (n = 1698) | Q2 (n = 1697) | Q3 (n = 1698) | Q4 (n = 1697) | P value |
| **The PREDIMED trial** | | | | | |
| DII score median (min, max) | −3.4 (−6.0, −2.7) | −2.1 (−2.7, −1.5) | −0.9 (−1.5, −0.1) | 0.9 (−0.1, 4.3) | |
| % Randomly allocated to MedDiet + EVOO | 37.3 | 34.3 | 34.6 | 33.4 | 0.090 |
| % Randomly allocated to MedDiet + Nuts | 36.1 | 34.4 | 30.9 | 30.3 | <0.001 |
| Age (years) | 66.2 (6.1) | 66.7 (6.1) | 67.1 (6.2) | 67.9 (6.2) | <0.001 |
| Female sex (%) | 53.8 | 56.9 | 57.4 | 62.1 | <0.001 |
| Marital status (%) | | | | | |
| Married | 81.2 | 76.7 | 76.7 | 71.1 | |
| Single | 3.47 | 4.01 | 3.65 | 5.01 | |
| Other | 15.3 | 19.3 | 19.6 | 23.9 | |
| BMI (kg/m$^2$) | 29.7 (3.9) | 29.8 (3.8) | 30.1 (3.7) | 30.2 (3.9) | <0.001 |
| Prevalent diseases at baseline (%) | | | | | |
| Diabetes | 50.1 | 46.8 | 47.3 | 51.7 | 0.013 |
| Hypertension | 79.6 | 83 | 84.2 | 83.4 | 0.002 |
| Hyperlipidaemia | 73.6 | 72.9 | 71.5 | 70.2 | 0.128 |
| Physical activity (METs-min/day) | 269 (276) | 239 (251) | 227 (225) | 191 (193) | <0.001 |
| Smoking status (%) | | | | | |
| Former smoker | 26.5 | 26.1 | 24.7 | 21.4 | |
| Current smoker | 13.4 | 14.8 | 14.7 | 14.1 | |
| Never smoker | 60.1 | 59.1 | 60.7 | 64.4 | 0.010 |
| Total energy intake (kcal/d) | 2687 (637) | 2392 (538) | 2153 (450) | 1869 (436) | <0.001 |
| Alcohol intake (g) | 10.53 (15.31) | 8.56 (14.32) | 8.15 (14.42) | 6.8 (12.99) | <0.001 |
| Adherence to the Mediterranean diet (p14) | 9.46 (1.88) | 8.81 (1.88) | 8.49 (1.85) | 7.91 (1.72) | <0.001 |
| Family history of CVD (%) | 23.6 | 23.4 | 21.8 | 20.6 | 0.130 |
| Education level (%) | | | | | |
| Secondary or higher | 26.3 | 22.6 | 20.8 | 19.8 | |

across quartiles of the DII. Therefore, we stratified all PREDIMED models by arm of the trial.

Table 2 shows that the DII was associated with significantly higher mortality in both cohorts, with a highly significant linear trend test and no evidence of heterogeneity between both cohorts. The HR (95% CI) for each additional standard deviation in the DII were 1.31 (1.12–1.54) in the SUN cohort and 1.17 (1.04–1.32) in the PREDIMED cohort.

When we directly pooled the data of both cohorts, the multivariable-adjusted HR (95% CI) for the comparison between extreme quartiles of the DII was 1.56 (1.17–2.07) with a highly significant linear trend ($p = 0.001$). For each additional standard deviation, the multivariable-adjusted HR was 1.18 (1.06–1.32) in the directly pooled analysis of both cohorts (data not shown). This corresponds to an 18% increase for each ≈2-point increase in DII score.

Despite, the highly significant linear trend test across quartiles of the DII, in the spline analyses, the dose–response pattern for both cohorts suggested a non-linear shape with an attenuation of the direct association at higher values of the DII, when the DII became positive (Fig. 2).

In the PREDIMED trial, when we stratified the sample according to the 3 randomized intervention arms of the trial, the

**Table 2**
Hazard ratios (HR) and 95% confidence intervals (95% CI) of all-cause death according to baseline DII score in participants of the SUN Cohort and the PREDIMED trial.

| | Q1 Most anti-inflammatory | Q2 | Q3 | Q4 Most pro-inflammatory | P for trend |
|---|---|---|---|---|---|
| **SUN cohort** | | | | | |
| Cases | 46 | 55 | 64 | 65 | |
| Person-years of follow up | 46,750 | 47,668 | 46,891 | 47,582 | |
| Rate 1000/person years | 0.98 | 1.15 | 1.36 | 1.37 | |
| Crude HR[a] | 1 (ref) | 1.12 (0.75–1.66) | 1.76 (1.20–2.57) | 1.88 (1.29–2.75) | <0.001 |
| HR adjusted for age and sex | 1 (ref) | 1.09 (0.71–1.68) | 1.73 (1.16–2.57) | 1.85 (1.24–2.75) | 0.001 |
| Multivariable adjusted HR[a] | 1 (ref) | 1.02 (0.65–1.71) | 1.79 (1.17–2.73) | 1.85 (1.15–2.98) | 0.004 |
| **PREDIMED trial** | | | | | |
| Cases | 66 | 55 | 94 | 87 | |
| Person-years of follow up | 7468 | 7602 | 7599 | 7565 | |
| Rate 1000/person years | 8.84 | 7.24 | 12.37 | 11.50 | |
| Crude HR[a] | 1 (ref) | 0.81 (0.57–1.16) | 1.40 (1.02–1.92) | 1.31 (1.95–1.80) | 0.013 |
| HR adjusted for age and sex | 1 (ref) | 0.83 (0.58–1.19) | 1.47 (1.07–2.04) | 1.39 (1.00–1.93) | 0.006 |
| Multivariable adjusted HR[b] | 1 (ref) | 0.86 (0.60–1.22) | 1.55 (1.11–2.17) | 1.42 (1.00–2.02) | 0.009 |
| **Pooled cohorts (SUN + PREDIMED)** | | | | | |
| Multivariable adjusted HR[c] | 1 (ref) | 0.91 (0.67–1.22) | 1.64 (1.26–2.13) | 1.56 (1.17–2.07) | 0.001 |
| $\%I^2$ (p for heterogeneity) | | 0% (p = 0.577) | 0% (p = 0.601) | 0% (p = 0.381) | |

[a] Adjusted for sex, age, baseline BMI (adding a quadratic term to account for non-linearity), marital status, educational attainment, family history of premature CHD, family history of diabetes, smoking status (current smoker, never smoker, former smoker), prevalent hypercholesterolemia, prevalent hypertension, physical activity (MET-h/week), alcohol intake, and total energy intake. Stratified by year of recruitment. Age was used as the underlying time variable and the model was stratified by decades of age.
[b] Adjusted for sex, age, baseline BMI (adding a quadratic term to account for non-linearity), marital status, educational attainment, family history of premature CHD, baseline diabetes, smoking status (current smoker, never smoker, former smoker), prevalent hypercholesterolemia, prevalent hypertension, physical activity and total energy intake. Stratified by center and intervention group.
[c] Meta-analysis (weighted by the inverse of variance, random effects model). The p for trend was calculated in a pooled multivariable-adjusted analysis by directly combining both raw data sets.

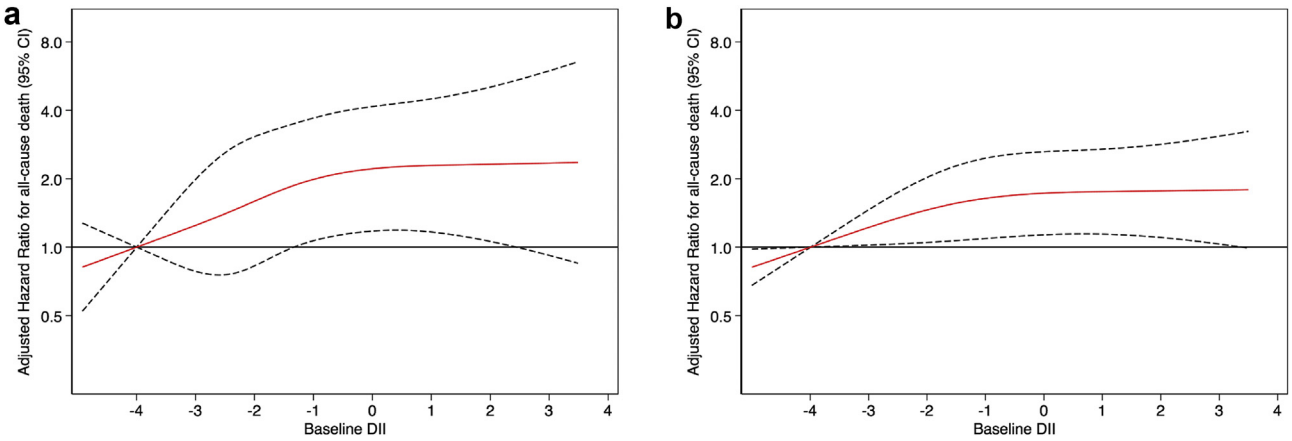


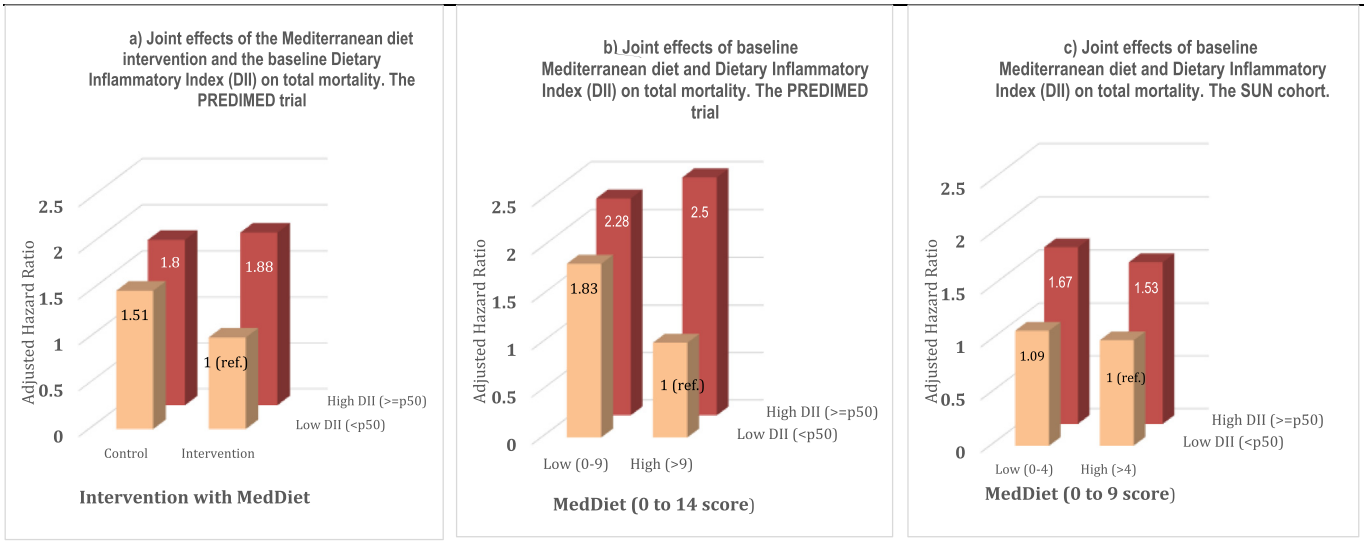

**Fig. 2.** Hazard ratios (continuous lines) and 95% confidence intervals (dotted lines) for all-cause of death along baseline DII levels [Dose–response curve (splines)]. a) The SUN Cohort. b) The PREDIMED trial.

multivariable-adjusted HR for each additional standard deviation in the baseline DII were 1.23 (1.00–1.52), 1.35 (1.05–1.62) and 0.99 (0.80–1.22) in the MedDiet + EVOO, MedDiet + nuts and control group, respectively. We found a statistically significant interaction (p = 0.037, 2 degrees of freedom) between the baseline DII score (continuous) and the intervention effect (3 groups) suggesting that the effectiveness of the PREDIMED intervention was apparently attenuated or even null when the participants presented a higher baseline DII score. Among those with a baseline DII score below the median, the multivariable-adjusted HR for total mortality versus control were 0.64 (0.41–0.99, p = 0.048) and 0.66 (0.42–1.04, p = 0.071) for MedDiet + VOO and MedDiet + nuts, respectively. When both intervention groups were merged together, the adjusted HR versus control was 0.65 (0.44–0.95, p = 0.028). Among those with a baseline DII score above the median, no significant effect of the MedDiet intervention on total mortality was observed (Fig. 3a).

Table 3 shows results of stratified analyses in both cohorts suggesting that the direct association between DII and higher mortality was consistent across the different strata of sex, age, BMI, smoking and baseline adherence to the MedDiet, again with the exception of the significant interaction between MedDiet and DII in the PREDIMED.

We conducted joint analyses (Fig. 3b and c) according to the combined exposure to baseline values of the MedDiet and the DII (both dichotomized at their medians). The correlation coefficients between both dietary scores (MedDiet and DII) were −0.59 in the SUN cohort and −0.31 in PREDIMED.

In Fig. 4 we show in the left panel a meta-analysis of our 2 cohorts and 10 published cohort studies assessing the association between the DII and all-cause death. The pooled relative risk across all cohorts was 1.23 (1.16–1.32) for the highest vs the lowest (reference) category of the DII score. In the right panel we show a cumulative meta-analysis.




MedDiet: Mediterranean diet

**Fig. 3.** (a–c). Joint effects of Mediterranean diet and Dietary Inflammatory Index (DII) on total mortality.

**Table 3**
Hazard ratios (HR) and 95% confidence intervals (95% CI) for the risk of death, according to the dietary inflammatory index score among subgroups.

| | Deaths | HR (Q4 vs. Q1) | 95% CI | p for trend | p for interaction |
|---|---|---|---|---|---|
| **The SUN cohort** | | | | | |
| Male | 170 | 2.01 | 1.17, 3.44 | 0.014 | 0.699 |
| Female | 60 | 1.33 | 0.51, 3.46 | 0.279 | |
| Age < 50 y | 77 | 2.14 | 0.85, 5.41 | 0.257 | 0.738 |
| Age ≥ 50 y | 153 | 1.61 | 0.94, 2.78 | 0.066 | |
| BMI ≤ 25 kg/m$^2$ | 115 | 2.05 | 1.02, 4.15 | 0.042 | 0.408 |
| BMI > 25 kg/m$^2$ | 115 | 1.51 | 0.78, 2.91 | 0.145 | |
| Non-smoker | 152 | 1.75 | 1, 3.08 | 0.043 | 0.903 |
| Current smoker | 78 | 1.76 | 0.72, 4.31 | 0.119 | |
| MedDiet 0–4 (low) | 123 | 2.16 | 0.8, 5.81 | 0.441 | 0.240 |
| MedDiet >4–9 (high) | 107 | 1.97 | 0.87, 4.45 | 0.096 | |
| **The PREDIMED trial** | | | | | |
| Male | 184 | 1.28 | 0.79, 2.06 | 0.122 | 0.399 |
| Female | 118 | 1.31 | 0.76, 2.28 | 0.115 | |
| Age < 70 y | 113 | 1.11 | 0.64, 1.93 | 0.259 | 0.341 |
| Age ≥ 70 y | 189 | 1.62 | 0.99, 2.65 | 0.048 | |
| BMI ≤ 30 kg/m$^2$ | 162 | 1.66 | 1.02, 2.69 | 0.004 | 0.715 |
| BMI > 30 kg/m$^2$ | 140 | 1.14 | 0.68, 1.91 | 0.622 | |
| Non-smoker | 238 | 1.56 | 1.04, 2.35 | 0.008 | 0.983 |
| Current smoker | 64 | 1.19 | 0.57, 2.49 | 0.430 | |
| No Diabetes | 109 | 1.74 | 0.96, 3.15 | 0.034 | 0.503 |
| Diabetes | 193 | 1.27 | 0.82, 1.98 | 0.086 | |
| MedDiet 0–9 (low) | 217 | 1.07 | 0.70, 1.64 | 0.485 | 0.040 |
| MedDiet >9–14 (high) | 85 | 1.41 | 0.68, 2.93 | 0.119 | |

Table 4 presents the differences in the consumption of food groups between extreme quartiles of the DII. These values represent z scores of the consumption of each food group after multivariable-adjustment for age, sex, BMI and total energy intake. These values should be interpreted as the number of standard deviations that the mean of each of the 2 extreme quartiles separates from the mean of the overall cohort. The largest differences were found for the consumption of vegetables, fruit, fish and nuts. In both cohorts there was a considerably higher consumption of these foods in the lowest quartile of the DII compared to the highest quartile. Other foods inversely associated with the DII were legumes in the PREDIMED trial and legumes, olive oil and wine in the SUN cohort. By contrast, consumption of meat, dairy and bakery was positively associated with DII scores in both cohorts.

## 4. Discussion

A consistent association between a higher inflammatory potential of the diet and higher risk of all-cause mortality was found in two Spanish cohorts. We found that a pro-inflammatory diet, as indicated by a higher DII score, was associated with all-cause death. For each additional standard deviation in the DII, the mortality rate showed an 18% relative increase when data from the SUN and PREDIMED cohorts were combined, and this increase was independent of major known risk factors for mortality. This result is consistent with previously reported findings in 10 other longitudinal studies in which DII-mortality relationships have been tested. The pooled relative risk across all available cohorts was 1.23 (1.16–1.32), although the heterogeneity was high ($I^2$ = 71.3%). Consistent with procedure used to develop and validate the DII

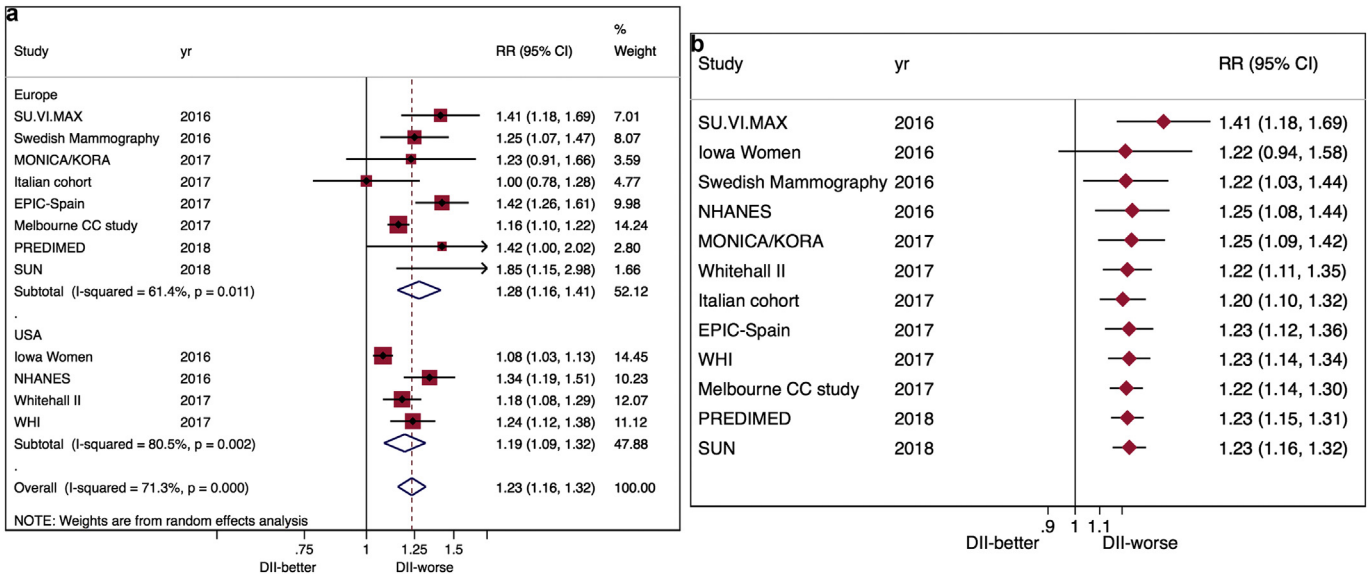



**Fig. 4.** Meta-analysis of prospective cohorts assessing the association between the DII and all-cause mortality (highest vs lowest quantile of DII score). a) Left panel: individual studies meta-analysis. b) Right panel: cumulative meta-analysis.

[13,43–45], the present findings provide strong and direct prospective evidence to support the hypothesis that inflammatory mechanisms may specifically account for the association between unhealthy dietary habits and premature deaths. Our results also support the use of the DII to capture the inflammatory potential of the diet [9,44].

Previous longitudinal studies have found increased risks for major non-communicable diseases [4–6,39,45–50] associated with higher values of the DII score. Mechanistic explanations include associations between higher values of the DII score and increased risks of obesity and metabolic syndrome [40,51,52], disorders of glucose and insulin metabolism [45] and shortening of telomere length [53].

**Table 4**
Z values for food consumption according to quartiles extremes of DII.

| | Q1 Anti-inflam. | Q4 Pro-inflam. | Dif (z) | p value |
|---|---|---|---|---|
| **The SUN cohort** | | | | |
| Vegetables | 0.61 | −0.69 | −1.30 | <0.001 |
| Fish & seafood | 0.62 | −0.46 | −1.08 | <0.001 |
| Fruit | 0.36 | −0.45 | −0.82 | <0.001 |
| Nuts | 0.48 | −0.16 | −0.64 | <0.001 |
| Legumes | 0.20 | −0.23 | −0.43 | <0.001 |
| Olive oil | 0.06 | −0.08 | −0.14 | <0.001 |
| Wine | 0.07 | −0.01 | −0.08 | 0.004 |
| Cereals | −0.06 | 0 | 0.06 | 0.017 |
| Meats | −0.18 | 0.12 | 0.3 | <0.001 |
| Dairy | −0.29 | 0.28 | 0.57 | <0.001 |
| Bakery. biscuits | −0.22 | 0.14 | 0.36 | <0.001 |
| **The PREDIMED trial** | | | | |
| Vegetables | 0.97 | −0.80 | −1.77 | <0.001 |
| Fruit | 0.43 | −0.50 | −0.93 | <0.001 |
| Fish & seafood | 0.46 | −0.37 | −0.83 | <0.001 |
| Nuts | 0.45 | −0.32 | −0.78 | <0.001 |
| Legumes | 0.29 | −0.27 | −0.56 | <0.001 |
| Cereals | −0.05 | −0.03 | 0.02 | 0.521 |
| Meats | −0.04 | 0.01 | 0.05 | 0.195 |
| Wine | −0.03 | 0.04 | 0.07 | 0.060 |
| Dairy | −0.05 | 0.06 | 0.11 | 0.011 |
| Olive oil | −0.18 | 0.18 | 0.35 | <0.001 |
| Bakery & biscuits | −0.24 | 0.22 | 0.45 | <0.001 |

Adjusted for sex, age, BMI and total energy intake.

In order to establish a biological plausibility for the observed associations it is also important to consider that biomarkers of inflammation (high-sensitivity CRP [hs-CRP], IL-1β, IL-6, TNF-α, IL-4 and IL-10) involved in the computation of the DII have been repeatedly associated with obesity, diabetes and CVD. Though hs-CRP should be considered only as a surrogate biomarker of upstream cytokines (IL-6 and IL-1β), hs-CRP is relevant for risk prediction [9]. Regarding obesity, a meta-analysis including 53 studies concluded that hs-CRP was positively associated with BMI and waist circumference [54]. A bidirectional association between inflammation and adiposity is possible and the exposure to a diet with a higher inflammatory potential can be a prospective risk factor for the future development of obesity [9,51,55]. A systematic review of 16 studies reported a positive association between hs-CRP and incident diabetes [56]; however, the association was attenuated after adjusting for central obesity. Additionally, recent studies suggest that this association might be partly explained by differential diagnosis of diabetes among the cases during blood collection [57]. Regarding CVD, a meta-analysis including 54 long-term prospective studies showed a positive continuous association between hs-CRP concentration and the risk of CVD, and death from several cancers and lung disease [58]. In conclusion, all these pathophysiological mechanisms contribute to support the biological plausibility of our findings and strengthen the rationale for drawing a causal inference between a higher pro-inflammatory potential of the diet and shorter survival. The preservation of the temporal sequence by the longitudinal design of our 2 cohort studies, the consistency between our two cohorts and other studies that used the DII (each of them using diverse methods and conducted in many different geographical locations), the strength of the association, and the dose–response trend (biological gradient) also contribute to support causal inference.

The interaction between the intervention with MedDiet in PREDIMED and the baseline DII score was unexpected. It does not have an easy or obvious explanation. The fact that the intervention in the PREDIMED trial was not sufficiently powered to assess total mortality as an outcome should be kept in mind when interpreting this apparent effect modification given that the degree of contrast between intervention and control obtained in the PREDIMED trial was only modest [59]. In any case, we show here that the PREDIMED intervention was able to reduce total mortality among participants

with a lower DII score at baseline. It could be speculated that a stronger contrast between intervention and control would have been needed to bring about this same magnitude of mortality reduction when the baseline DII score was higher. Further exploration of this hypothesis probably deserve additional study.

We observed an inverse correlation between the Mediterranean diet and the DII, both in the SUN cohort (−0.59) and the PREDIMED trial (−0.31). When we combined both dietary patterns, the DII and the Mediterranean diet, we found higher risk of mortality in participants with low adherence to the Mediterranean diet and high DII (most pro-inflammatory) in the SUN cohort (compared with those with high adherence to the Mediterranean diet and low DII) but not in the PREDIMED study. A previous study found a correlation of −0.45 and similar associations between the DII and the Mediterranean diet score with mortality [27]. An anti-inflammatory diet (low DII) was mainly plant-based, rich in vegetables, fruits, fish, nuts and legumes, and low in meats, dairy and bakery. Thus, it is possible that both diets share common mechanisms explaining their association with mortality.

Several limitations of our study deserve consideration. Dietary habits were collected using self-reported information from FFQs. It is likely that the process of collecting dietary information and computing the DII score involved some degree of measurement error and concomitant misclassification. However, this potential measurement error would likely be non-differential because of the prospective design of our studies and, therefore, would probably bias the results towards the null. In addition, it is well known that the most appropriate methodology in large prospective cohorts is the use of validated FFQ, especially in cohorts of highly educated participants [12] as it is the case in the SUN cohort. In addition, a trained dietitian assisted the participants in PREDIMED to adequately complete the FFQs. The use of all-cause mortality as the outcome may seem too non-specific. However, this is a very important outcome for public health and for the general population. Using all deaths as the dependent variable avoids potential criticisms based on choosing specific causes that may have differential effects with respect to dietary inflammation; i.e., it that may reduce one cause of death at the expense of increasing another competitive cause of death.

Strengths of our study include the prospective design of the two cohorts, the materially complete ascertainment of fatal events, and the ability to control for a wider array of potential confounders than previous studies.

In conclusion, a higher inflammatory potential of the diet, as measured by the DII, was associated with higher all-cause mortality in two large prospective Spanish cohorts. The results were basically homogenous in both cohorts and they were consistent with previously published prospective studies. A diet with a higher anti-inflammatory potential (rich in vegetables, fruits, fish, nuts and legumes, and low in meats, dairy and baked goods) is therefore likely to reduce many potential causes of premature death.

## Authors' contribution

AGA, MAM-G and MR-C performed statistical analysis with data from the SUN cohort.

RRM, MAM-G and MR-C performed statistical analysis with data from the PREDIMED study.

MAM-G performed additional statistical analysis, including spline models and meta-analyses.

AGA, RRM and MAM-G drafted the paper and incorporated the suggestions of the rest of authors.

MAM-G, AGA, RR and MR-C designed the research (project conception, development of overall research plan, and study oversight).

MAM-G, AGA, JRH, NS and MR-C conducted research (hands-on conduct of the experiments and data collection).

MAM-G and MR-C had primary responsibility for final content.

All authors provided essential scientific contributions, critically evaluated the content of the manuscript and approved the final version.

## Disclaimers

None.

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## Disclosures

Dr. James R. Hébert owns 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 counseling and dietary intervention in clinical settings. Dr. Nitin Shivappa is an employee of CHI.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.05.003.

## Appendix

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