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Dietary inflammatory index, cardiometabolic conditions and depression in the Seguimiento Universidad de Navarra cohort study

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Abstract

Only one prospective study has analysed the relationship between the inflammatory properties of diet and risk of depression thus far. The aim of this study was to assess the association between the dietary inflammatory index (DII) and the incidence of depression. In a cohort study of 15 093 university graduates, participants completed a validated FFQ at baseline and after 10 years of follow-up. The DII was calculated based on the FFQ. Each of the twenty-eight nutrients or foods received a score based on findings from the peer-reviewed literature reporting on the relationships between diet and inflammatory biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein). Participants were classified as having depression if they reported a new clinical diagnosis of depression by a physician, antidepressant drugs, or both. Multivariable Cox regression models were used to estimate hazard ratios (HR) of depression according to quintiles of the DII. After a median 8·5 years of follow-up, we observed 1051 incident cases of depression. The HR for participants in the highest quintile of DII (strongly pro-inflammatory) was 1·47 (95 % CI 1·17, 1·85) compared with those in the bottom quintile, with a significant dose–response relationship (P_{trend} = 0·01). In the subgroup analyses, the association between DII and depression was stronger among participants >55 years and among those with cardiometabolic comorbidities (HR 2·70; 95 % CI 1·22, 5·97 and HR 1·80; 95 % CI 1·27, 2·57, respectively). A pro-inflammatory diet was associated with a significantly higher risk of depression in a Mediterranean population. This association was stronger among older subjects and subjects with cardiometabolic diseases.

Key words: Cohort studies: Dietary patterns: Depression: Anti-inflammation: Diabetes

Unipolar depression affects >151 million people worldwide and it is projected to be the leading cause of disability-adjusted life years lost in 2030[1]. Depression shares common mechanisms with obesity, metabolic syndrome (MetS), type 2 diabetes (DM2) and CVD. In fact, the comorbidity of depression with cardiovascular risk factors is frequent[2–4]. Metabolic and inflammatory processes, such as reduced insulin sensitivity, elevations in plasma homocysteine levels and, perhaps more importantly, increased production of pro-inflammatory cytokines and endothelial dysfunction, seem to be the major factors responsible for the link between depression and cardiometabolic disorders[5–7].

In general, prospective cohort studies that have analysed the association between dietary patterns and risk of depression have found an inverse association with depression for diets rich in fruits, vegetables, olive oil, legumes and other food items with an anti-inflammatory effect[8–11]. In contrast, increased risks have been observed for 'pro-inflammatory' dietary patterns[11,12]. However, to our knowledge, only one cohort study, the Nurses' Health Study, has analysed the role of an inflammatory dietary pattern on the risk of depression[13]. Our aim was to assess whether a more pro-inflammatory dietary pattern increased the risk of depression in a population from Southern Europe where dietary patterns are substantially different from those followed in the USA. In addition, we aimed to determine whether the association between the dietary inflammatory index (DII) and depression risk was modulated by the cardiometabolic status of the participants.

Abbreviations: DII, dietary inflammatory index; DM2, type 2 diabetes; HR, hazard ratio; HTA, hypertension; MetS, metabolic syndrome..

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Methods

Study population

The 'Seguimiento Universidad de Navarra' (SUN) Project is a multipurpose Spanish cohort composed of university graduates. Baseline assessment and follow-up information was gathered through postal or web-based questionnaires collected every 2 years. The recruitment of participants started on 21 December 1999. It is a dynamic cohort – that is, recruitment is continuously open. The overall retention in the cohort approaches 90 %. Further details about the methodology and characteristics of the participants can be found in previously published reports[14]. The study was approved by the Institutional Review Board of the University of Navarra. Voluntary completion of the first questionnaire was considered to imply informed consent.

Through June 2014, 22 045 subjects had completed the baseline questionnaire of the SUN project. Subjects who had not completed at least one follow-up questionnaire, who were lost to follow-up, who were outside the pre-defined limits for energy intake (<3347·2 kJ/d (<800 kcal/d) or >16 736 kJ/d (>4000 kcal/d) in men and <2092 kJ (<500 kcal) or 14 644 kJ/d (>3500 kcal/d) in women[15]) and those who used antidepressant medication or had reported a previous clinical diagnosis of depression (lifetime prevalence) at baseline, or without date of diagnosis of incident depression (*n* 60), were excluded from the analyses. After these exclusions, 15 093 participants were finally included in this study (Fig. 1).

Exposure assessment

Dietary intake was assessed at baseline and after 10 years of follow-up with a validated semi-quantitative FFQ[16,17]. Nutrient intakes of 136 food items were calculated as frequency multiplied by the nutrient composition of a specified portion size for each food item, using an *ad hoc* computer programme specifically developed for this aim. A trained dietitian updated the nutrient database using the latest available information included in the food composition tables for Spain.

The dietary inflammatory index. The design and development of the DII has been described elsewhere[18]. In brief, the DII is a scoring algorithm based on an extensive review of the literature published from 1950 to 2010, linking 1943 articles focussing on the effect of diet on six inflammatory biomarkers (IL-1β, IL-4, IL-6, IL-10, TNF-α and C-reactive protein). A total of forty-five food parameters including various macronutrients, micronutrients, flavonoids and individual food items linked to these inflammatory biomarkers were scored according to whether they increased (+1), decreased (−1) or had no effect (0) on inflammation. An overall food parameter-specific inflammatory effect score was calculated for each food item. This percentile was calculated by first linking the dietary data from a study to the regionally representative world database intake, which is 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 then become the multipliers to express an individual's exposure relative to the 'standard global mean' as a *Z*-score. This is 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 is then converted to a centred percentile score. The centred percentile score for each food parameter for each

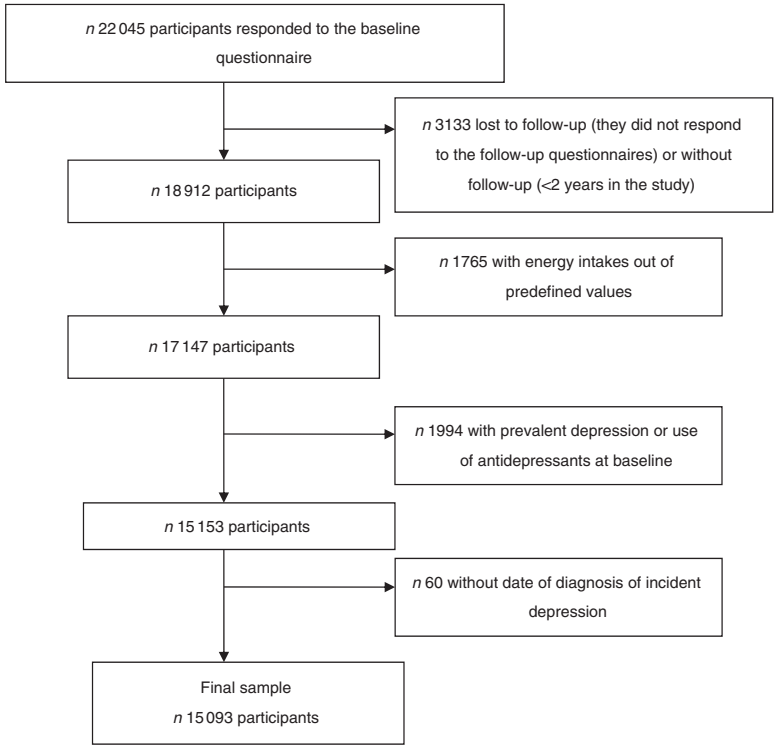

Fig. 1. Flow chart of participants. The Seguimiento Universidad de Navarra Project.

individual was then multiplied by the respective food parameter effect score, which is derived from the literature review, in order to obtain a food parameter-specific DII score for an individual. All 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. More negative values represent more anti-inflammatory diets. The DII score could take on values ranging from about +8 (maximally pro-inflammatory) to −9 (maximally anti-inflammatory).

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[18]. Thus far, the DII has been found to be associated with inflammatory cytokines including C-reactive protein and IL-6[19–21], the glucose intolerance component of MetS[20], increased odds of asthma and reduced forced expiratory volume in 1 s in an Australian population[21], shift work[22], colorectal cancer among women in the Iowa Women's Health Study[23], prostate cancer[24] and pancreatic cancer[25].

In this study, a total of twenty-eight food parameters were available from the FFQ, and therefore could be used to calculate DII (energy, carbohydrate, protein, total fat, alcohol, fibre, cholesterol, SFA, MUFA, PUFA, *n*-3, *n*-6, *trans*-fat, niacin, thiamin, riboflavin, vitamin B_{12}, vitamin B_6, Fe, Mg, Se, Zn, vitamin A, vitamin C, vitamin D, vitamin E, folic acid and caffeine.) The literature-derived inflammatory effect scores assigned to each of the food parameters are shown in Table 1.

Table 1. Scoring for each food parameter used for dietary inflammatory index calculation

Food parameter	Inflammatory effect score*
Energy	0·180
Carbohydrate	0·097
Fat	0·298
Alcohol	−0·278
Fibre	−0·663
Protein	0·021
Vitamin B_{12}	0·106
Vitamin B_6	−0·365
β Carotene	−0·584
n-3	−0·436
n-6	−0·159
MUFA	−0·009
SFA	0·373
Trans-fat	0·229
Fe	0·032
PUFA	−0·337
Riboflavin	−0·068
Thiamin	−0·098
Niacin	−0·246
Vitamin A	−0·401
Mg	−0·484
Zn	−0·313
Se	−0·191
Vitamin C	−0·424
Vitamin D	−0·446
Vitamin E	−0·419
Folate	−0·190
Caffeine	−0·110

* A negative value indicates anti-inflammatory effect and a positive score indicates pro-inflammatory effect.

Outcome assessment

Incident cases of depression were defined as participants who positively responded to the following question 'Have you ever been diagnosed of depression by a medical doctor?' or who reported the habitual use of antidepressant drugs in any of the biennial follow-up questionnaires (Q_2–Q_14). Although antidepressants could have been prescribed for conditions other than depression, this situation is highly unusual in Spain. Therefore, we considered both, the use of antidepressants and/or physician diagnosis as depression criteria.

A self-reported physician-provided diagnosis of depression has demonstrated acceptable validity in a subsample of our cohort using the Structured Clinical Interview for DSM-IV as 'gold standard' applied by experienced psychiatrists blinded to the answers of the questionnaires[26]. The percentage of confirmed depression was 74·2 % (95 % CI 63·3, 85·1). The percentage of confirmed non-depression was 81·1 % (95 % CI 69·1, 92·9).

Other covariate assessment

Information about socio-demographic (e.g. sex, age, marital status and employment status) and lifestyle-related variables (e.g. smoking status, physical activity and use of vitamin supplements) were obtained from the baseline questionnaire (Q_0). Physical activity was assessed using a validated physical activity questionnaire with data about seventeen activities[27]. Leisure-time activities were computed by assigning a metabolic equivalent score to each activity, multiplied by the time spent for each activity and summing up all activities. A participant was considered as a user of vitamin supplements if he/she reported at least the consumption of one of the following vitamin supplements: A, B_1, B_2, B_3, B_6, B_9, B_{12}, C, D or E.

BMI was calculated as weight (kg) divided by the square of height (m^2) using data collected at baseline and after 10 years of follow-up.

The prevalence and history of CVD, cancer obesity, dyslipidaemia, hypertension (HTA) and DM2 was ascertained at baseline and updated until the end of follow-up or until depression diagnosis was reported. CVD included myocardial infarction, stroke, atrial fibrillation, paroxysmal tachycardia, coronary artery bypass grafting or other re-vascularisation procedures, heart failure, aortic aneurism, pulmonary embolism or peripheral venous thrombosis. All the diagnoses were based on participants self-reporting. The validity of self-reported obesity, dyslipidaemia and HTA diagnoses has been assessed in different subsamples of the cohort[28–30]. Self-reported cardiovascular events, cancer and DM2 have been confirmed by medical record review.

Energy and alcohol intake were calculated from the baseline FFQ and after 10 years of follow-up.

Statistical methods

For each participant, we computed person-years of follow-up from the date of returning the baseline questionnaire to the date of depression diagnosis, the date of death or the date of returning the last follow-up questionnaire, whichever came first.

Cox regression models (proportional hazards models) were fitted to assess the relationship between the adherence to the DII and the incidence of depression. Hazard ratios (HR) and their 95 % CI were calculated considering the lowest quintile of DII (more anti-inflammatory) as the reference category. To control for potential confounding factors, successive degrees of adjustment were used: (1) in model 1, we adjusted for sex and age (years, continuous); (2) in model 2, we additionally adjusted for BMI (kg/m^2, continuous), smoking (non-smoker, ex-smoker, current smoker, missing), physical activity during leisure time (quintiles), use of vitamin supplements and total energy intake (kJ/d (kcal/d), continuous); and, finally, (3) in model 3, we additionally adjusted for the presence of several diseases at baseline (CVD, DM2, HTA and dyslipidaemia). An indicator variable for missing responses was created for smoking. Additional adjustments for cancer history, marital status, unemployment, alcohol intake and menopause status within women were also performed.

Tests of linear trend across increasing quintiles of adherence were conducted by assigning the medians to each quintile and treating it as a continuous variable.

To minimise any effect of a variation in diet, we also calculated the average of DII using an updated DII score with dietary data collected after 10 years of follow-up. To increase accuracy, energy intake and BMI also were updated with the information obtained after 10 years of follow-up. The prevalence of diseases was updated using the information containing in any of the follow-up questionnaires.

Sensitivity analyses were performed by changing several parameters: (1) adopting different allowed limits for total energy intake; (2) excluding participants with long follow-up (≥6 years); (3) excluding early cases (diagnosed during the 1st year of follow-up); (4) excluding participants with special diets (i.e. hypoenergetic, hyperproteic and gluten-free); and HRs were estimated comparing quintiles of the DII in the fully adjusted model.

In addition, subgroup analyses were performed by sex, age group and the presence of several diseases as stratification variables. To assess a possible interaction between DII and sex, age group (≤55 *v.* >55 years), obesity, DM2, CVD and a composite of CVD and CVD risk factors (obesity, DM2, HTA or dyslipidaemia) and product terms were introduced in the different multivariable models. *P* values for the interaction were calculated using the log-likelihood ratio test.

Results

We recorded 1051 incident cases of depression during a median follow-up time of 8·5 years. Table 2 shows the distribution of

Table 2. Characteristics of participants according to quintiles of the dietary inflammatory index (Mean values and standard deviations; percentages)

	Quintile 1: most anti-inflammatory (*n* 3019)	Quintile 2 (*n* 3019)	Quintile 3 (*n* 3018)	Quintile 4 (*n* 3019)	Quintile 5: most pro-inflammatory (*n* 3018)	*P*
Age (years)						<0·001
Mean	40·6	38·9	38·0	37·2	36·7	
SD	12·9	12·2	11·8	11·5	11·4	
Male (%)	41·6	36·8	37·0	42·9	48·5	<0·001
Married (%)	53·0	53·0	52·5	52·5	49·3	0·019
Unemployment (%)	3·5	4·2	3·8	4·1	4·1	0·557
Smoking status (%)						<0·001
Ex-smoker	33·0	29·8	30·0	29·5	27·1	
Current smoker	17·8	20·3	20·6	23·3	25·8	
Vitamin supplements' use* (%)	1·9	2·2	2·5	1·9	1·8	0·339
Special diet at baseline (%)	10·3	8·8	7·6	6·8	5·3	<0·001
Post-menopause† (%)	15·3	13·6	11·1	8·8	6·4	<0·001
Prevalence of diseases (%)						
CVD	5·1	4·1	4·6	3·9	3·3	0·004
Cancer	4·4	3·1	3·9	3·2	3·5	0·030
DM2	2·4	2·2	1·4	1·4	1·0	<0·001
HTA	9·0	7·3	6·2	6·0	7·0	<0·001
Dyslipidaemia	21·5	18·2	17·1	17·2	16·8	<0·001
Obesity	4·3	4·8	4·2	4·5	5·1	0·456
BMI (kg/m^2)						0·04
Mean	23·6	23·4	23·4	23·6	23·6	
SD	3·4	3·5	3·4	3·4	3·6	
Total energy intake (kJ/d)						<0·001
Mean	11 497·6	10 669·2	10 024·9	9175·5	7815·7	
SD	2397·4	2355·6	2209·2	2092	2154·8	
Total energy intake (kcal/d)						<0·001
Mean	2748	2550	2396	2193	1868	
SD	573	563	528	500	515	
Physical activity during leisure time (METs-h/week)						<0·001
Mean	26·7	23·2	21·4	20·1	17·7	
SD	27·1	24·2	21·3	20·6	18·9	

DM2, type 2 diabetes; HTA, hypertension; METs, metabolic equivalents.
* Use of at least one of the following vitamin supplements: A, B_1, B_2, B_3, B_6, folic acid, B_{12}, C, D or E.
† A total of 8847 women were included.

the baseline characteristics of the participants according to the baseline DII categorised in quintiles. Participants with the highest DII were more likely to be men, single and younger and showed lower prevalence of CVD, DM2 or dyslipidaemia and lower daily energy intake. Some unhealthy lifestyle characteristics such as smoking behaviour and physical inactivity during leisure time were also more prevalent among participants with a more pro-inflammatory diet.

The association between the DII and the risk of depression is shown in Table 3. A higher risk was found for the highest DII in the three models. In model 3 (adjusted for lifestyle factors and the presence of chronic diseases), a higher DII scores (fourth and fifth quintiles) compared with the lowest quintile of DII was associated with an approximately 25–35 % higher risk of depression (multiple-adjusted HR 1·24; 95 % CI 1·00, 1·53 for the fourth quintile and HR 1·37; 95 % CI 1·09, 1·73 for the fifth quintile). Moreover, a significant dose–response relationship was found ($P_{trend}=0·015$). When DII was updated using the information collected after 10 years of follow-up, the magnitude of the association was even higher. A relative increment in the risk of depression of approximately 50 % for the comparison between extreme quintiles of DII (HR 1·47; 95 % CI 1·17, 1·85; $P_{trend}=0·010$) was found. Additional adjustment for personal cancer history, marital status, alcohol intake and unemployment in the overall sample or for menopause status within women did not change the reported associations (data not shown).

Table 4 shows the adjusted HRs in the sensitivity analyses after modifying some of our assumptions. The reported results did not change when the analyses were restricted to those participants with <6 years of follow-up. Participants in the highest quintile of the DII had a 47 % higher relative risk of developing depression during the first 6 years of follow-up than participants in the lowest quintile. However, when the analyses were restricted to those participants with a depression diagnosis

Table 3. Risk of incident depression according to the adherence to quintiles of the dietary inflammatory index (DII) (Hazard ratios (HR) and 95 % confidence intervals)

	Quintile 1: most anti-inflammatory		Quintile 2		Quintile 3		Quintile 4		Quintile 5: most pro-inflammatory		
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	P_{trend}
Median DII	−3·16		−2·38		−1·75		−0·94		0·66		
Cases	185		227		211		211		217		
Person-years	25 594		26 487		26 143		26 437		26 586		
Crude rates/10^3*	7·2	6·2, 8·3	8·6	7·5, 9·8	8·1	7·0, 9·2	8·0	6·9, 9·1	8·2	7·2, 9·3	
Model 1†											
Baseline DII	1	Ref.	1·19	0·98, 1·44	1·12	0·92, 1·37	1·15	0·94, 1·40	1·22	1·00, 1·48	0·12
Repeated measures	1	Ref.	1·22	1·00, 1·48	1·15	0·94, 1·40	1·27	1·04, 1·55	1·29	1·06, 1·58	0·269
Model 2‡											
Baseline DII	1	Ref.	1·20	0·99, 1·46	1·16	0·95, 1·42	1·22	0·99, 1·51	1·35	1·07, 1·71	0·022
Repeated measures	1	Ref.	1·25	1·03, 1·52	1·21	0·99, 1·48	1·38	1·11, 1·70	1·48	1·18, 1·86	0·008
Model 3§											
Baseline DII	1	Ref.	1·21	0·99, 1·47	1·17	0·95, 1·43	1·24	1·00, 1·53	1·37	1·09, 1·73	0·015
Repeated measures	1	Ref.	1·24	1·02, 1·51	1·21	0·98, 1·48	1·37	1·11, 1·69	1·47	1·17, 1·85	0·010

Ref., referent value.
* Crude rates and 95 % confidence intervals.
† Model 1: adjusted for age and sex. Repeated measures. Cumulative average for DII (at baseline and after 10 years of follow-up). Energy intake, BMI and prevalence of diseases were also updated.
‡ Model 2: this includes all variables from model 1 plus BMI, smoking, physical activity during leisure time, use of vitamin supplements and total energy intake.
§ Model 3: this includes all variables from model 2 with additional adjustment for the presence of CVD, type 2 diabetes, hypertension and dyslipidaemia at baseline.

Table 4. Sensitivity analyses*
(Hazard ratios (HR) and 95 % confidence intervals)

			Quintile 5 *v.* quintile 1 (Ref.)		
	Cases	*n*	HR	95 % CI	P_{trend}†
Energy limits: 5th to 95th percentiles‡	1067	15 043	1·41	1·11, 1·80	0·008
Energy limits: 1st to 99th percentiles§	1159	16 338	1·43	1·13, 1·81	0·005
Excluding participants with ≥6 years of follow-up	685	3156	1·47	1·11, 1·95	0·005
Excluding cases diagnosed during the first 2 years of follow-up	868	14 910	1·27	0·98, 1·64	0·14
Excluding cases diagnosed during the first 3 years of follow-up	777	14 819	1·28	0·97, 1·69	0·16
Excluding subjects with an special diet at baseline or without this information	909	13 587	1·29	1·00, 1·66	0·07

Ref., referent value.
* The association between extreme quintiles of adherence to the dietary inflammatory index and depression. Adjusted for age, sex, BMI, smoking, physical activity during leisure time, use of vitamin supplements, total energy intake and presence of several diseases at baseline (CVD, diabetes mellitus type 2, hypertension and dyslipidaemia).
† For the five quintiles.
‡ >5648·4 kJ/d (>1350 kcal/d) and <17 405·4 kJ/d (<4160 kcal/d) in men and >4020·8 kJ/d (>961 kcal/d) and <16 970·3 kJ/d (<4056 kcal/d) in women.
§ >3711·2 kJ/d (>887 kcal/d) and <22 781·9 kJ/d (<5445 kcal/d) in men and >5744·6 kJ/d (>1373 kcal/d) and <23 735·8 kJ/d (<5673 kcal/d) in women.

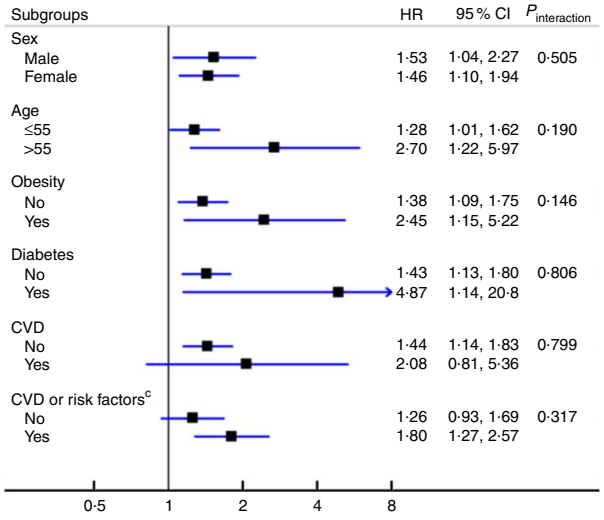

Fig. 2. Subgroups analyses. Hazard ratios (HR) (95 % CI)[a] for the association between extreme quintiles of adherence to the dietary inflammatory index (DII) and depression. [a]Adjusted for age, sex, BMI, smoking, physical activity during leisure time, use of vitamin supplements, total energy intake and prevalence of several diseases (CVD, type 2 diabetes, hypertension and dyslipidaemia). [b]Repeated measures. Cumulative average for DII (at baseline and after 10 years of follow-up). Energy intake, BMI and prevalence of diseases were also updated. [c]Prevalence of obesity, type 2 diabetes, hypertension or dyslipidaemia.

after 2 or 3 years of follow-up, the association was attenuated and it was no longer statistically significant.

The association between the DII score and depression risk according to categories of several baseline characteristics is shown in Fig. 2. Although none of the interaction terms included in the multivariable models were statistically significant, a stronger association with depression was evident when comparing DII quintile 5 to quintile 1 for participants aged ≥55 years (HR 2·70; 95 % CI 1·22, 5·97) and for those with concomitant diseases including obesity (HR 2·45; 95 % CI 1·15, 5·22); DM2 (HR 4·87; 95 % CI 1·14, 20·81); CVD (HR 2·08; 95 % CI 0·81, 5·36); or a composite of cardiometabolic diseases or risks (HR 1·80; 95 % CI 1·27, 2·57).

Discussion

In this analysis from the SUN cohort study, participants with the highest DII score (representing the most pro-inflammatory dietary potential) showed a 47 % higher risk of developing depression compared with participants with the lowest DII (those consuming diets with the greatest anti-inflammatory potential). This result is consistent with that reported in another prospective cohort study, the Nurses' Health Study, which found a 41 % higher risk for the highest v. the lowest quintile of inflammatory properties of the diet[13]. Although it used an identical definition of the outcome, the American cohort used a different approach (reduced rank regression) to classify participants according to the inflammatory potential of their dietary patterns.

The results obtained in our analyses confirm those found in other analyses evaluating the role of diet in depression. Numerous prospective studies have reported inverse associations between diet quality or the adherence to prudent or traditional diets and the risk of depression with consistent results across different countries and cultures[8–11,31]. Similarly, the Mediterranean diet has shown an anti-inflammatory effect[32,33]. In contrast, Western dietary patterns, characterised by the consumption of processed foods, have been directly associated with depressive disorders[11,12] as well as with elevated levels of some pro-inflammatory markers[34,35].

A large number of studies have reported the possible role of inflammation in depression through mechanisms such as activation of the hypothalamic–pituitary–adrenal axis, tryptophan depletion and decrease in brain-derived neurotrophic factor availability[36]. Cross-sectional evidences from epidemiological studies seem to confirm a bidirectional relationship[37]. Although systemic inflammatory markers have been prospectively associated with depression[38,39], not all longitudinal studies have found a significant relationship[40]. Thus, the contribution of a pro-inflammatory dietary pattern to the development of depression has not been easy to understand.

One of the most remarkable results obtained in our analysis suggests that the effect of a pro-inflammatory diet (stressor) on depression could be particularly detrimental among individuals with some cardiometabolic conditions (prevalent chronic conditions such as CVD, DM2 or/and obesity) or among those ≥55 years of age. Although the interaction was not statistically significant, its magnitude could be biologically relevant. These results are in accordance with those recently obtained in the PREDIMED trial. In that trial, the adherence to a Mediterranean dietary pattern supplemented with nuts was particularly important to prevent depression among participants with DM2[41]. Similarly, this hypothesis has been suggested in a cross-sectional study conducted recently in Australia, which found that a healthy dietary pattern was associated with a reduced likelihood of depressive symptoms, especially for those with DM2[42].

One possible explanation for our observed results is that the presence of several chronic conditions might lead to maladaptive stress responses within this group, including heightened low-grade inflammation and HPA axis non-habituation. In fact, cytokine levels are strongly affected by socio-demographic and environmental factors such as age, sex, smoking, exercise, obesity or insulin resistance. The link between CVD, inflammation and depressive disorders has been repeatedly suggested. Over the last few years, several studies have established the possible link between inflammation, depression and not only CVD events but also other related conditions such as DM2, MetS or obesity[5,6,43–45]. In fact, hyperleptinaemia or insulin resistance in obesity, MetS and DM2 have been linked to inflammatory processes[46], which also are common in depressive disorders. Similarly, obesity (a pro-inflammatory condition[47]) has been found to be associated with elevated cortisol secretion and higher HPA axis reactivity to psychological stress as well as physiological and pharmacological stimulation[48]. Moreover, in a recent study, McInnis *et al.*[49] found that individuals with higher measures of adiposity showed less efficient HPA axis habituation as well as sensitisation of IL-6 responses to repeated acute stress, indicating that increased adiposity would be related to altered

endocrine and IL-6 stress responses. Consistent with our findings, Grosse *et al.*[50] reported that monocyte immune activation was not uniformly elevated in all depressive patients, but it was increased only in older subjects. Indeed, the pro-inflammatory effect of the diet could be more relevant among older subjects by inducing sensitisation with increased activation of the inflammatory response system.

Some potential limitations of our study need to be mentioned. Self-reporting of a clinical diagnosis or the use of medication was used as the criteria to establish depression. Our validation study found low sensitivity (0·37) but very high specificity (0·96) for the self-reported diagnosis of depression[26]. Theoretically, with perfect specificity, non-differential sensitivity of disease misclassification will not bias the relative risk estimate[51]. Similarly, although the validity and reliability of the FFQ have been evaluated[16,17], some degree of misclassification may exist in the dietary assessment. However, the use of a cohort design mitigates this to some extent. In this context, misclassification is more likely to be non-differential, and therefore would bias the results towards the null. Another concern is the potential of reverse causation. Participants with subclinical depression at the beginning of our study might have changed their food habits precisely because of their mood disorder. In fact, when the analyses were restricted to those participants who reported a depression diagnosis after 2 or 3 years of follow-up, the association was attenuated. To avoid the possibility that the induction period for the effect of baseline diet might be shorter than the time of follow-up of these 'late' cases (some of them diagnosed after 14 years of follow-up), we excluded participants with >6 years of follow-up from the main analyses, updated nutritional data and used cumulative DII after 10 years of follow-up. Both analyses reported similar results, and with an even higher relative risk for depression associated with high DII scores. Another possible weakness is the inability to control for several potential confounders related to psychological features. Finally, our participants are not representative of the general Spanish population. We restricted our cohort to highly educated participants to obtain a better quality of self-reported information, to improve the retention rate and to minimise confounding by educational level, and therefore by socio-economic status[52].

Several strengths of our study also deserve to be mentioned. They include its large sample size, prospective design, long-term follow-up, the use of updated nutritional data, the ability to control for a variety of major potential confounders, the existence of published validation studies of our assessments and the restriction to highly educated participants who may be able to provide more reliable information.

In conclusion, a higher DII (indicative of a more pro-inflammatory diet) was associated with an increased risk of developing depression among participants from the SUN cohort study. This effect could be even more important among older individuals and those with prevalent comorbidities related to inflammation such as CVD, DM2 or obesity. Further studies analysing the link between inflammation, depression and cardiometabolic conditions are warranted to deepen our understanding about the role of diet in developing depression and other mental disorders.

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