Clinical Nutrition 41 (2022) 2614–2620

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Proinflammatory dietary pattern and depression risk in older adults: Prospective analyses from the Seniors-ENRICA studies

Bruno Bizzozero-Peroni [a, b], Rosario Ortolá [c, d], Vicente Martínez-Vizcaíno [a, e], Fernando Rodríguez-Artalejo [c, d, f], Rubén Fernández-Rodríguez [a], José R. Banegas [c, d], Esther Lopez-Garcia [c, d, f], Arthur Eumann Mesas [a, g, *]

[a] Health and Social Research Center, Universidad de Castilla-La Mancha, Cuenca, 16071, Spain
[b] Instituto Superior de Educación Física, Universidad de La República, Rivera, 40000, Uruguay
[c] Department of Preventive Medicine and Public Health, Universidad Autónoma de Madrid, Calle Del Arzobispo Morcillo 4, 28029 Madrid, Spain
[d] CIBER of Epidemiology and Public Health (CIBERESP), Avenida de Monforte de Lemos 3-5, Madrid, 28029, Spain
[e] Facultad de Ciencias de La Salud, Universidad Autónoma de Chile, Talca, 1101, Chile
[f] IMDEA Food Institute, CEI UAM+CSIC, Carretera de Canto Blanco 8, Madrid, 28049, Spain
[g] Postgraduate Program in Public Health, Universidade Estadual de Londrina, Londrina, Paraná, 86057-970, Brazil

ARTICLE INFO

Article history:
Received 12 May 2022
Accepted 12 October 2022

Keywords:
Dietary inflammatory index
Health behaviour
Mental health
Older age

SUMMARY

Background & aims: Only a few studies have assessed the association between a proinflammatory diet and the risk of depression in older adults, and they have rendered weak results. The present study analysed the association between the Dietary Inflammatory Index (DII) and incident self-reported diagnosis or symptoms of depression in two cohorts of community-dwelling older adults in Spain.
Methods: We used data from the Seniors-ENRICA-I (SE-I) and Seniors-ENRICA-II (SE-II) cohorts. In both cohorts, the baseline DII was calculated from habitual food consumption estimated with a validated computer-based diet history. The incidence of both physician self-reported diagnosis of depression and mild-to-major depressive symptoms (≥3 on the 10-item Geriatric Depression Scale) was analysed. Logistic regression models were adjusted for the main potential confounders, such as sociodemographics, lifestyles, and comorbidities. The results of both cohorts were pooled using a random effects model.
Results: Among the 1627 participants in SE-I (mean age 71.5 ± 5.5 y, 53.1% women) and the 1579 in SE-II (mean age 71.4 ± 4.2, 46.7% women), 86 (5.3%) and 140 (8.9%) incident cases of depression were identified after a mean 3.2-y and 2.3-y follow-up, respectively. The fully adjusted odds ratio (95% confidence interval) of incident depression for the highest (the highest proinflammatory diet) *versus* the lowest quartile of DII was 2.76 (1.25–6.08, *p-for-trend* = 0.005) in the SE-I, 1.90 (1.04–3.40, *p-for-trend* = 0.005) in the SE-II and 2.07 (1.01–3.13) in the pooled cohorts. The results were consistent across strata defined by sex, age, physical activity, loneliness/poor social network, and morbidity.
Conclusions: A proinflammatory dietary pattern is associated with depression risk in older adults. Future research should evaluate whether reducing the inflammatory component of diet leads to reduced depression symptoms in this population.

1. Introduction

Mental disorders were the seventh leading cause of burden of disease worldwide in 2019 [1]. Among them, depression is the most common [1], with approximately 280 million people suffering from depression every year [2]. Projections support a continuous increase in the prevalence of depression in the coming years, mainly because some determinants of poor mental health, such as lack of social support, have intensified due to the COVID-19 pandemic [3]. Older age is also one of the main risk factors for depression [2]. Therefore, there is an urgent need for public health strategies to prevent depression or reduce the severity of symptoms as well as its health-related consequences in older adults [4].

Although the causes of depression remain unclear, a complex interaction of genetic, social, psychological, behavioural, environmental, and biological factors has been proposed [5–8]. Evidence suggests that inflammatory processes contribute to depression

* Corresponding author. Health and Social Research Center, Universidad de Castilla-La Mancha, C/ Santa Teresa Jornet, s/n, Cuenca, 16071, Spain. Fax: +34 969179100.
E-mail address: Arthur.EMesas@uclm.es (A.E. Mesas).

https://doi.org/10.1016/j.clnu.2022.10.007

through different pathways, such as exposure to psychosocial stress or a processed-food diet, increasing the activation of proinflammatory cytokines or inflammasomes that drive inflammatory responses relevant to depression [9]. Accordingly, nutrition has received more attention in the last decade as a modifiable lifestyle risk factor for depression [10], with a particular focus on the consumption of specific foods that might modulate inflammatory factors [11,12].

Several prospective cohort studies have investigated the associations between the potential inflammatory effects of diet and the incidence of self-reported diagnosis of depression [13,14] or depressive symptoms [15–19] throughout adulthood. However, only a few of these studies have examined this association specifically in older people [19] or stratified by older adult age subgroup [16,17]. Their findings showed a weak nonsignificant [16,17] or null [19] association between the highest versus the lowest inflammatory diet scores and the risk of depression in older adults from Australia, France and Italy [16,17,19]. However, in these studies, the analyses did not account for relevant confounders in the diet-depression relationship, such as loneliness [16,17,19], functional disability [16,17], or a wide range of chronic diseases [16,17,19]. To address these limitations, the present study assessed the association between the inflammatory potential of diet and the risk of depression, defined as a self-reported physician diagnosis of depression or mild-to-major depressive symptoms, adjusting for many risk factors for depression in older adults from Spain.

2. Materials & methods

2.1. Study design and participants

We used data from two cohorts of older adults with very similar designs and the same methods of data collection and variable measurement that have been published in detail elsewhere [20,21]. The first cohort was the Seniors-ENRICA-I (SE-I), established in 2008–2010 with 3289 individuals selected through stratified random sampling of the noninstitutionalized Spanish population aged ≥60 years [20,22]. Of these, 1627 individuals free of self-reported physician diagnosis of depression were followed-up during a mean time of 3.2 years. The second cohort was the Seniors-ENRICA-II (SE-II), established in 2015–2017 through stratified random sampling of all community-dwelling individuals aged ≥65 years holding a national healthcare card and living in Madrid (Spain) [21,23]. Of the 3273 individuals who completed the baseline interviews, we excluded 583 individuals who suffered from a self-reported physician diagnosis of depression or mild-to-major depressive symptoms. After a mean of 2.3 years, 1579 of these participants provided answers in the follow-up.

Both Seniors-ENRICA cohorts were registered on ClinicalTrials.gov (SE-I identifier: NCT02804672; SE-II identifier: NCT03541135) and approved by the Clinical Research Ethics Committee of the La Paz University Hospital in Madrid. Participants provided informed written consent.

2.2. Study variables

2.2.1. Exposure variable: dietary inflammatory index (DII)

The participant's regular diet in daily grams of food was assessed and estimated with a validated computer-based diet history, representing the average intake during a typical week of the previous year [24]. The questionnaire was administered by a trained interviewer and includes 880 foods that can be cooked in 29 different ways and 184 recipes for dishes commonly eaten in Spain or typical of each region. More details about the dietary information collection can be found elsewhere [24]. No missing values were observed because all data were checked for completeness during data collection, and if any data was lacking, a new visit was performed to the house of the participants to obtain the required information [20,21].

The inflammatory potential of the diet was estimated with the Dietary Inflammatory Index (DII) according to Shivappa's procedure [25]. The DII is a scoring algorithm based on a robust review of the literature published up to 2010, involving 1943 articles that analysed the effect of dietary components on inflammation [25]. A total of forty-five food parameters, including whole foods, nutrients and other bioactive compound components, were scored based on their effects on six inflammatory biomarkers (interleukin-1β, interleukin-4, interleukin-6, interleukin-10, tumour necrosis factor-α, and C-reactive protein) [25].

For the present analyses, 32 of the 45 original DII components (daily amounts of food or nutrients) were available in both Seniors-ENRICA cohorts and were used to calculate the DII by multiplying the overall inflammatory effect score for each component by its normalized intake using the global daily mean intakes and standard deviations provided by Shivappa et al. [25] and summing them (Table S1). A higher DII score (positive) indicates a proinflammatory diet, whereas a lower DII score (negative) indicates an anti-inflammatory diet. Participants in both cohorts were classified into quartiles of the DII scores.

2.2.2. Outcome variable: depression

For the SE-I, baseline depression was defined with a positive answer to the question 'Did a physician tell you if you currently have, or have had in the past year, depression (in need of treatment)?' For the SE-II, baseline depression was defined as in the SE-I, or additionally if the participant reported ≥3 depressive symptoms (which indicate mild-to-major depressive symptoms) [26] in the 10-item version of the Geriatric Depression Scale (GDS-10). All participants with depression at baseline according to these cohort-specific criteria were excluded from the analytical sample. In the follow-up, in both cohorts, data were collected on both self-reported physician diagnosis of depression and on depressive symptoms with the GDS-10. Therefore, incident cases of "self-reported physician diagnosis or mild-to-major depressive symptoms" were identified when at least one of the two criteria (i.e., self-reported physician diagnosis of depression and GDS-10 score ≥3) was met in the follow-up among individuals free of depression at baseline.

2.2.3. Covariates

Covariates were selected based on recent research on the potential determinants of depression and their associations with diet [27–32].

At baseline, for both SE-I and SE-II cohorts, self-reported information was obtained on sex (female *vs.* male), age (continuous, years), household economy (difficult *vs.* easy to make ends meet), education (no studies or primary studies *vs.* secondary or university studies), marital status (married *vs.* single, widowed or separated), smoking (never or former *vs.* current smoker), time watching TV (continuous, hours per week), night-time sleep duration (continuous, hours per night), and the number of physician-based diagnoses of the following chronic conditions: diabetes mellitus, cardiovascular disease (ischemic heart disease, stroke, or heart failure), hypertension, chronic respiratory disease (asthma or chronic bronchitis), cancer at any site, musculoskeletal disorder (osteoarthritis, rheumatoid arthritis, or hip fracture) and neurodegenerative disease (Parkinson's disease or dementia).

Physical activity in occupational, leisure and household domains was assessed with the validated EPIC-cohort questionnaire [33] and categorized into two groups: less active (inactive or moderately

inactive) and more active (moderately active or active) [34]. Additionally, we assessed disability in activities of daily living with the Katz scale [35] and loneliness with a short 3-item scale [36] in the SE-II cohort. Moreover, body mass index (BMI) was calculated as weight divided by the square of the height (kg/m^2), both objectively measured under standardized conditions.

Finally, inflammatory biomarker levels, such as C-reactive protein, interleukin-6, growth differentiation factor-15, troponin T, and pro-brain natriuretic peptide, were obtained from biological blood samples to assess whether higher DII was associated with high-grade inflammation.

2.3. Statistical analysis

The following analyses were performed separately in each cohort's database. First, we described the baseline characteristics of cohort participants according to the quartiles of DII. Second, bivariate correlation coefficients were calculated to examine the baseline relationship between the DII scores and the following covariates: sex, age, household economy, education level, marital status, smoking, BMI, physical activity, time watching TV, night's sleep duration, chronic conditions, loneliness, and depressive symptoms. In addition, bivariate correlations were calculated to analyse the baseline association between DII scores and the level of some inflammatory biomarkers available in each database. Third, logistic binary regression models were used to estimate the odds ratio (OR) (as estimators of the relative risk) and the 95% confidence interval (95% CI) for the association between the overall baseline quartiles of the DII score and the incidence of self-reported physician diagnosis of depression or mild-to-major symptoms of depression over the follow-up period. We built three models: model 1, a crude model; model 2, adjusted for sex, age, household economy, education level, marital status, smoking status, BMI, physical activity, time watching TV and night-time sleep duration; and model 3, additionally adjusted for loneliness (only for the SE-II cohort), functional disability (only for the SE-II cohort), diabetes mellitus, cardiovascular disease, hypertension, chronic respiratory disease, cancer at any site, musculoskeletal disorder and neurodegenerative disease. To explore possible multicollinearity between independent variables such as physical activity, time spent watching TV, and BMI, bivariate correlations were computed. Potential multicollinearity involving two variables was considered if the correlation coefficient was >0.70 [37].

Stratified analyses were performed to identify potential modifiers of the study association, and *p* values were calculated using the log-likelihood ratio test to assess interactions between the main covariates (i.e., sex, age, physical activity, loneliness/poor social network, and morbidity) and DII scores on self-reported diagnosis or mild-to-major symptoms of depression. Additionally, to test the robustness of our results, sensitivity analyses were performed using an alternative cut-off value ($\geq$5) in the GDS-10 score that specifies only major depressive symptoms [26] for the SE-II cohort. The Kolmogorov–Smirnov test was applied to the GDS-10 score and confirmed that its distribution did not deviate from normality in the analytical sample ($p = 0.376$). Furthermore, the relationship between the continuous DII score and the number of incident depressive symptoms (GDS-10 score) was summarized with β coefficients (95% CI) obtained from linear regression models for the SE-II cohort.

Finally, we combined the fully adjusted OR (95% CI) of each cohort to estimate the pooled OR with a DerSimonian and Laird random effects model [38]. Heterogeneity was measured using the I^2 statistic and was considered not important ($I^2 < 40\%$), substantial (I^2: 30%–60%), important (I^2: 50%–90%), or considerable ($I^2 > 75\%$) [39].

Statistical analyses were performed using STATA SE software, version 15 (StataCorp, College Station, TX, USA).

3. Results

A total of 1627 participants (mean age 71.5 ± 5.5, 53.1% female) from the SE-I cohort and 1579 participants (mean age 71.4 ± 4.2, 46.7% female) from the SE-II cohort were included in the analyses.

Slightly more than 55% of the individuals included had no studies or primary education level, 31% were single, widowed or separated, 66% were less physically active, and 49% had two or more chronic diseases. Tables 1, 2 and S1 present the main baseline characteristics of the study participants in the SE-I and SE-II cohorts, respectively. Bivariate correlations showed that the DII score was directly correlated with female sex, age, difficult household economy, education level (no studies or primary studies), marital status (single, widowed or separated), less physical activity and

Table 1
Baseline characteristics of the SE-I study sample by Dietary Inflammatory Index quartiles.

Baseline characteristics	Total (n = 1627)	Quartiles of Dietary Inflammatory Index			
		Q1: anti-inflammatory diet (n = 407)	Q2 (n = 407)	Q3 (n = 407)	Q4: proinflammatory diet (n = 406)
Dietary Inflammatory Index, score	0.8 ± 1.9	−1.7 ± 0.8	0.1 ± 0.4	1.5 ± 0.4	3.2 ± 0.7
Female, *n* (%)	864 (53.1)	170 (41.8)	198 (48.6)	225 (55.3)	271 (66.7)
Age, years	71.5 ± 5.5	70.9 ± 5.2	71.2 ± 5.4	71.5 ± 5.4	72.2 ± 6.0
Difficult to make ends meet, *n* (%)	23 (1.5)	5 (1.3)	1 (0.3)	5 (1.4)	12 (3.2)
No studies/primary education, *n* (%)	934 (57.4)	213 (52.3)	228 (56.0)	231 (56.8)	262 (64.5)
Single/widowed/separated, *n* (%)	504 (31.4)	102 (25.3)	102 (25.1)	133 (33.1)	167 (42.2)
Current smoking status, *n* (%)	159 (9.8)	37 (9.1)	39 (9.6)	41 (10.1)	42 (10.3)
C-Reactive Protein, mg/L	3.8 ± 7.1	3.3 ± 4.9	3.6 ± 6.9	3.6 ± 4.7	4.8 ± 1.0
Body Mass Index, kg/m^2	28.6 ± 4.3	28.6 ± 4.6	28.5 ± 3.9	28.4 ± 4.2	29.1 ± 4.3
Less physical active, *n* (%)	1308 (80.4)	308 (75.7)	328 (80.6)	324 (79.6)	348 (85.7)
Time watching TV, h/wk	19.1 ± 11.6	18.0 ± 10.7	18.6 ± 6.5	19.1 ± 11.1	20.9 ± 13.6
Night's sleep duration, h/d	6.8 ± 1.4	6.9 ± 1.4	6.9 ± 1.3	6.8 ± 1.4	6.9 ± 1.5
One or more chronic conditions[a], *n* (%)	1486 (94.6)	372 (94.7)	378 (95.2)	371 (93.9)	365 (94.6)

Values are means ± standard deviations or *n* (%). Abbreviations: **Q**, quartile; **SE**, Seniors-ENRICA. The numbers of participants who were missing data were as follows: 137 for household economy, 20 for marital status, 1 for alcohol intake, 1 for total energy intake, 6 for C-reactive protein, 24 for body mass index, 21 for physical activity, 13 for time watching TV, 19 for night's sleep duration, 14 for diabetes, 8 for cardiovascular disease, 17 for hypertension, 3 for neurodegenerative disease, and 16 for musculoskeletal disorder.

[a] Chronic condition diagnosed by a physician includes diabetes mellitus, cardiovascular disease (ischemic heart disease, stroke, or heart failure), hypertension, chronic respiratory disease (asthma or chronic bronchitis), cancer at any site, musculoskeletal disorder (osteoarthritis, rheumatoid arthritis, or hip fracture), and neurodegenerative disease (Parkinson or dementia/Alzheimer).

Table 2
Baseline characteristics of the SE-II study sample by Dietary Inflammatory Index quartiles.

Baseline characteristics	Total (n = 1579)	Quartiles of Dietary Inflammatory Index			
		Q1: anti-inflammatory diet (n = 395)	Q2 (n = 395)	Q3 (n = 395)	Q4: proinflammatory diet (n = 394)
Dietary Inflammatory Index, *score*	0.3 ± 1.6	−1.7 ± 0.7	−0.3 ± 0.3	0.9 ± 0.3	2.5 ± 0.7
Female, *n* (%)	738 (46.7)	153 (38.7)	164 (41.5)	201 (50.9)	220 (55.8)
Age, years	71.4 ± 4.2	70.8 ± 4.2	71.6 ± 4.2	71.1 ± 4.1	72.2 ± 4.4
Difficult to make ends meet, *n* (%)	181 (11.5)	34 (8.6)	46 (11.7)	45 (11.4)	56 (14.2)
No studies/primary education, *n* (%)	929 (58.9)	212 (53.7)	226 (57.2)	234 (59.2)	257 (65.4)
Single/widowed/separated, *n* (%)	485 (30.7)	115 (29.1)	110 (27.8)	108 (27.4)	152 (38.6)
Current smoking status, *n* (%)	138 (8.7)	27 (6.8)	28 (7.1)	37 (9.4)	46 (11.7)
Interleukin-6, pg/ml	3.3 ± 5.0	3.4 ± 7.4	3.0 ± 2.7	3.3 ± 4.4	3.5 ± 4.1
Growth Differentiation Factor-15, pg/ml	1336.4 ± 782.5	1236.8 ± 575.6	1307.3 ± 755.5	1324.2 ± 677.6	1481.5 ± 1036.7
Troponin T, pg/ml	10.49 ± 5.3	10.4 ± 4.7	10.4 ± 4.6	10.2 ± 5.0	10.9 ± 6.9
Pro-Brain Natriuretic Peptide, pg/ml	111.9 ± 138.9	112.0 ± 133.2	105.5 ± 140.8	107.4 ± 104.2	123.1 ± 170.2
Body Mass Index, kg/m^2	27.7 ± 4.3	28.0 ± 4.6	27.6 ± 4.2	27.6 ± 4.1	27.7 ± 4.3
Less physical active, n (%)	817 (52.4)	185 (47.3)	207 (52.8)	202 (52.1)	223 (57.6)
Time watching TV, h/wk	21.9 ± 10.5	20.7 ± 9.6	21.8 ± 10.2	22.6 ± 10.9	22.2 ± 11.2
Night's sleep duration, h/d	6.8 ± 1.3	6.9 ± 1.2	6.9 ± 1.2	6.8 ± 1.4	6.8 ± 1.3
One or more chronic conditions[a], *n* (%)	1221 (77.3)	299 (75.7)	320 (81.0)	292 (73.9)	310 (78.7)
Loneliness, scale score	3.4 ± 1.1	3.3 ± 0.9	3.4 ± 1.0	3.4 ± 1.0	3.6 ± 1.3
Depressive symptoms, GDS-10	0.3 ± 0.5	0.2 ± 0.5	0.3 ± 0.5	0.3 ± 0.6	0.4 ± 0.6

Values are means ± standard deviations or *n* (%). Abbreviations: **Q**, quartile; **GDS-10**, 10-item Geriatric Depression Scale; **SE**, Seniors-ENRICA. The numbers of participants who were missing data were as follows: 2 for household economy, 1 for education level, 1 for marital status, 3 for alcohol intake, 101 for interleukin-6, 100 for growth differentiation factor-15, troponin T and pro-brain natriuretic peptide, 6 for body mass index, 21 for physical activity, 9 for time watching TV, 2 for cardiovascular disease, 160 for hypertension, 1 for chronic respiratory disease, 43 for musculoskeletal disorder disease, 3 for functional disability, and 128 for depressive symptoms.

[a] Chronic condition diagnosed by a physician includes diabetes mellitus, cardiovascular disease (ischemic heart disease, stroke, or heart failure), hypertension, chronic respiratory disease (asthma or chronic bronchitis), cancer at any site, musculoskeletal disorder (osteoarthritis, rheumatoid arthritis, or hip fracture), neurodegenerative disease (Parkinson or dementia/Alzheimer), and functional disability (Katz scale).

time watching TV in the two baseline samples, and with current smoking status, loneliness and depressive symptoms in the SE-II sample. Moreover, the DII score was directly correlated with C-reactive protein ($r = 0.080$) in the SE-I sample and with growth differentiation factor-15 in the SE-II sample ($r = 0.090$). None of the covariates used in the logistic models had coefficient correlation with other independent variables higher than 0.2, meaning that there would be no multicollinearity in entering them simultaneously in the models.

The associations between DII and the incidence of self-reported physician diagnosis of depression and mild-to-major symptoms of depression are presented in Table 3. The overall incidence of self-reported diagnosed depression was 5.3% ($n = 86$) in the 3.2-year follow-up for SE-I. The overall incidence of self-reported diagnosis

Table 3
Prospective associations between a proinflammatory diet and the incidence of depression (diagnosed or ≥3 symptoms) in the SE-I and SE-II cohorts.

	Quartiles of Dietary Inflammatory Index				*p-for-trend*[a]
	Q1: anti-inflammatory diet	Q2	Q3	Q4: proinflammatory diet	
SE-I, *n*	407	407	407	406	
DII, score range	−4.562, −0.641	−0.629, 0.816	0.817, 2.231	2.233, 5.404	
Incidence of depression[b], *n* (%)	10 (0.6)	18 (1.1)	25 (1.5)	33 (2.0)	
Model 1 – crude model	1.00 (ref)	1.84 (0.84, 4.03)	2.60 (1.23, 5.48)*	3.51 (1.71, 7.23)*	**<0.001**
Model 2 – adjusted model	1.00 (ref)	1.22 (0.52, 2.83)	2.11 (0.97, 4.57)	2.27 (1.06, 4.84)*	**0.015**
Model 3 – adjusted model	1.00 (ref)	1.37 (0.57, 3.29)	2.24 (0.99, 5.08)	2.76 (1.25, 6.08)*	**0.005**
SE-II, *n*	395	395	395	394	
DII, score range	−4.403, −0.839	−0.838, 0.286	0.293, 1.501	1.503, 4.860	
Incidence of depression[c], *n* (%)	24 (6.1)	27 (6.8)	39 (9.9)	50 (12.7)	
Model 1 – crude model	1.00 (ref)	1.13 (0.64, 2.00)	1.69 (0.99, 2.87)	2.25 (1.35, 3.73)*	**<0.001**
Model 2 – adjusted model	1.00 (ref)	1.01 (0.55, 1.85)	1.58 (0.90, 2.75)	1.83 (1.06, 3.14)*	**0.007**
Model 3a – adjusted model	1.00 (ref)	0.95 (0.49, 1.87)	1.38 (0.74, 2.58)	1.90 (1.04, 3.40)*	**0.005**
Pooled cohorts					
Model 1 – crude model	1.00 (ref)	1.09 (0.45, 1.73)	1.84 (0.98, 2.70)	2.45 (1.35, 3.54)*	
Model 2 – adjusted model	1.00 (ref)	1.06 (0.49, 1.63)	1.69 (0.87, 2.51)	1.93 (1.02, 2.84)*	
Model 3 – adjusted model	1.00 (ref)	1.04 (0.42, 1.65)	1.52 (0.69, 2.36)	2.07 (1.01, 3.13)*	

Values are odds ratios (95% CI) for logistic regression models. * $p < 0.05$. Abbreviations: **DII**, Dietary Inflammatory Index; **Q**, quartile; **SE**, Seniors-ENRICA.
Model 2: adjusted for sex (female, male), age (y), household economy (difficult to make ends meet or easy to make ends meet), education level (no studies/primary or secondary/university), marital status (married or single/widowed/separated), smoking status (never/former or current), body mass index (kg/m^2), physical activity (less active or more active), time watching TV (h/wk), and night's sleep duration (h/d); Model 3: Model 2 adjusted for chronic conditions diagnosed by a physician, including diabetes mellitus (yes, no), cardiovascular disease (yes, no), hypertension (yes, no), chronic respiratory disease (yes, no), cancer at any site (yes, no), musculoskeletal disorder (yes, no), and neurodegenerative disease (yes, no). Model 3a: Model 3 adjusted for functional disability (yes, no) and loneliness (scale score). All covariates were from baseline.

[a] *p* value for linear association between the continuous score of the Dietary Inflammatory Index (main independent variable) and incidence of depression (dependent variable).

[b] Incident cases of depression were defined as those participants free of depression at baseline assessment and who self-reported physician-diagnosed depression during the 3.2-year follow-up.

[c] Incident cases of depression were defined as those participants free of depression at baseline assessment and who self-reported physician-diagnosed depression or ≥3 symptoms in the Geriatric Depression Scale-10 during the 2.3-year follow-up.

or mild/major symptoms of depression was 8.9% ($n = 140$) at the 2.3-year follow-up for SE-II. Of the 226 individuals who developed depression during follow-up in both cohorts, 72.6% ($n = 164$) were female. In crude regression models (model 1), direct associations between the highest versus the lowest quartile of DII and incidence of self-reported diagnosis or symptoms of depression were observed both in the SE-I (OR = 3.51; 95% CI: 1.71–7.23, *p-for-trend* < 0.001) and in the SE-II (OR = 2.25; 95% CI: 1.35–3.73, *p-for-trend* < 0.001). When covariates were added to the adjusted models, the association remained statistically significant (SE-I model 3, OR = 2.76; 95% CI: 1.25–6.08, *p-for-trend* = 0.005; SE-II model 3, OR = 1.90; 95% CI: 1.04–3.40, *p-for-trend* = 0.005). Finally, when combining the results of both cohorts, the pooled fully adjusted OR for the association between the highest versus the lowest quartile of DII and incidence of self-reported diagnosis or symptoms of depression was 2.07 (95% CI: 1.01–3.13; I^2: 0%, $p = 0.53$) (Table 3). Additionally, in the pooled cohorts, the results were consistent across strata defined by sex, age, loneliness, and morbidity (all first-order interaction coefficients were $p > 0.05$) (Fig. S1).

Additionally, sensitivity analysis using ≥5 depressive symptoms as the cut-off value (major depressive symptomatology) on the GDS-10 score for the SE-II cohort showed similar results (4th quartile compared with 1st quartile, OR = 2.01; 95% CI: 1.03–3.93, *p-for-trend* = 0.002) to the main analysis in the fully adjusted model (Table S2). Last, an increasing DII score was associated with an increasing number of incident depressive symptoms in the unadjusted and adjusted models for the SE-II cohort (Table S3).

4. Discussion

This study analysed the prospective association between the potential inflammatory effects of diet and the risk of self-reported diagnosis or symptoms of depression in national (SE-I) and regional (SE-II, region of Madrid) representative samples of Spanish older adults. The main finding was that in both cohorts, the individuals in the highest quartile of the DII score (indicating a high proinflammatory diet) at baseline had a greater incidence of self-reported diagnosis or symptoms of depression than those in the lowest quartile (indicating an anti-inflammatory diet) over a mean of 3.2- (SE-I) and 2.3-year (SE-II) follow-up. These associations remained significant after adjustment for several key confounders, such as socioeconomic factors, lifestyle habits and chronic diseases. The prospective results of both SE-I and SE-II cohorts were synthesized and confirmed in a pooled analysis. Specifically, older adults in the highest quartile of DII were twice as likely to develop self-reported diagnosis or symptoms of depression than those in the lowest quartile after two to three years of follow-up. Our results emphasize the key role of diet in the inflammatory pathway that may lead to depression in older adults.

Previous prospective cohort studies specifically in older adults [19] or analysing older population subgroups are scarce [16,17]. Of these, studies reporting the number of incident cases of depression showed similar (i.e., 8%) [16] or slightly higher (i.e., 13%) [17] results to ours; however, the number of incident cases of depressive symptoms was not reported specifically for older adults. In one study, French individuals ≥60 years in the highest quartile of DII did not have a significantly increased risk of developing depressive symptoms (OR: 1.22, 95% CI: 0.91 to 1.64) during ~5-year follow-up [16]. In another study with Australian participants ≥65 years, no significant association was observed across quartiles of DII and the risk of depressive symptoms during ~5-year follow-up [17]. Moreover, no significant association was found between higher inflammatory dietary patterns and depressive symptoms in Italian subjects ≥65 years over a period of nine years [19]. Conversely, the results from both the SE-I and SE-II cohorts showed that older adults consuming a highly inflammatory diet were more prone to develop self-reported diagnosis or symptoms of depression than those with the lowest inflammatory diet score. Several differences could be behind these apparently inconsistent findings. First, the other studies analysed changes in depressive symptoms. Our study used a more comprehensive definition of depression, including self-reported physician-diagnosed depression or many (≥3 or ≥5) depressive symptoms. Second, the longitudinal studies were adjusted for socioeconomic and lifestyle factors, but their analyses did not consider the role of some relevant confounders, such as loneliness [16,17,19], functional disability [16,17] or a broad range of morbidities [16,17,19]. Last, our study adjusted for these main risk factors for depression and examined its influence on the association between the highest proinflammatory diet and the incidence of self-reported depression.

Several mechanisms underlying the potential damaging role of a proinflammatory diet in the risk of depression in older ages can be suggested, such as oxidative stress, alterations in brain immune and neuronal function, and the crosstalk between the gut microbiome and brain health [31,40–42]. Moreover, chronic inflammation in older adults is influenced by a complex process of cellular senescence, which is characterized by the detention of cell proliferation and the development of a multifaceted senescence-associated secretory phenotype [43]. This senescent phenotype turns senescent fibroblasts into proinflammatory cells (secretion of proinflammatory cytokines, chemokines and other proinflammatory molecules) [42,43], with its clinical consequences, including an increased risk of depression [44]. From the nonendogenous contributors, diet has been conceived as a major component in increasing inflammatory response system activation in older adults [45]. Evidence suggests that the activation of the innate immune system through proinflammatory nutrients releases proinflammatory cytokines, promoting depressive-like behaviours [46]. Furthermore, the impact of the highest proinflammatory diet on the risk of depression may be based on the synergistic combination of certain main risk factors for depression, including health conditions (obesity, chronic status) [32], poor social network (loneliness) [47], individual determinants (sex, age) [30], and lifestyle-related behaviours (physical activity) [48]. However, in this study, there were no consistent findings to establish which specific components significantly influenced this association. Further investigations assessing the multifactorial nature of the mechanisms by which diet-related inflammatory activity is associated with the risk of depression are needed for a deeper understanding.

The increased frequency of depression in older age and its clinical, economical, and socioemotional implications represent a crucial public health challenge. The results of this study, which include longitudinal prospective analyses of two cohorts of Spanish older adults and a pooled-analysis approach, have significant clinical and public health implications. A healthy diet aiming to disrupt the depression–inflammation cycle should consider the favourable nutrient intake and the anti-inflammatory dietary components, such as high contents of polyunsaturated fatty acids, carotenoids, dietary fibre, vitamins, and minerals, mostly reported in this study with Spanish older adults. These nutrients and foods have been consistently associated with major pathophysiologic pathways of depression, such as oxidative stress, inflammation, and the gut microbiome [27,44]. Therefore, limiting a proinflammatory diet (e.g., lowering the intake of carbohydrates, cholesterol, total fat, saturated fat, and *trans*-fat) and promoting an anti-inflammatory diet (e.g., increasing the intake of fibre, *n*-3 fatty acids, *n*-6 fatty acids, vitamins A, B, C, D and E, and minerals such as selenium and zinc) should be considered among the preventive and non-pharmacological intervention approaches for depression in older adults.

Our study has some limitations that should be noted. First, dietary variables were collected through a questionnaire, which might have some degree of measurement errors due to recall and information biases. Second, although the DII score was calculated with a larger number of food parameters (32 of the 45 proposed), compared to previous studies [13–15,17,18], the unavailability of data on the remaining 13 food components may be a potential limitation. Third, due to the small number of participants in the prospective stratified analyses, we were unable to report consistent findings in the association between the proinflammatory diet and the risk of depressive disorder. Fourth, although individuals with depression at baseline were excluded, we cannot rule out the possibility that emerging depressive symptoms themselves could alter the food choices of participants. Previous studies [49,50] indicated that depressive symptoms may lead to increased inflammatory diet choices. Therefore, since a bidirectional association between DII and depressive symptoms may exist, well-designed, long-term clinical trials are needed to demonstrate consistent causal relationships. Fifth, this study did not assess depression as a structured clinical diagnostic interview conducted by a physician, which may affect prevalence and incidence estimates. Finally, unmeasured factors related to the association between diet and depression, such as xenobiotic exposure or early-life stress [42], might have led to potential residual confounding.

5. Conclusions

Our findings indicate that Spanish older adults consuming a high proinflammatory diet (i.e., a higher Dietary Inflammatory Index score) are more likely to develop self-reported diagnosis or symptoms of depression than those with an anti-inflammatory dietary pattern. Since diet is a modifiable lifestyle factor, future long-term clinical trials should test whether reducing the intake of proinflammatory foods (e.g., ultra-processed meat products or pastries) and nutrients (e.g., cholesterol or saturated fat) and encouraging an anti-inflammatory diet (rich in unsaturated fatty acids or dietary fibre) is an effective strategy to prevent depression in older ages. Moreover, additional prospective studies are needed to provide evidence on the biological and environmental mechanisms underlying the association between the potential inflammatory effect of diet and the risk of depression in older adults.

Funding statement

This research was funded by FIS grants (19/319 and 19/665, State Secretary of R + D + I and FEDER/FSE), the REACT EU Program, Community of Madrid, and the European Regional Development Fund- European Union: FACINGLCOVID-CM project, and FEDER funds from the European Union (CB16/10/00477). This work was also supported by the National Agency for Research and Innovation (POS_EXT_2020_20_1_165371). B.B.-P. was supported by a grant from the Universidad de Castilla-La Mancha co-financed by the European Social Fund (2020-PREDUCLM-16746). R.F.-R. was supported by a grant from the Spanish Ministry of Education, Culture and Sport (FPU 19/00167). Dr. Mesas is financially supported by a 'Beatriz Galindo' contract (BEAGAL18/00093) from the Spanish Ministry of Education, Culture and Sport. The funders played no role in the study design, the data collection or analysis, the decision to publish, or the preparation of the manuscript.

Author contributions

B.B.-P.: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. R.O.: Data curation, Methodology, Writing – review & editing. V.M.-V: Funding acquisition, Methodology, Writing – review & editing, Supervision. F.R.-A.: Data curation, Funding acquisition, Methodology, Writing – review & editing, Supervision. R.F.-R.: Formal analysis, Writing – review & editing. J.R. B.: Data curation, Funding acquisition, Writing – review & editing. E.L.-G.: Data curation, Methodology, Writing – review & editing. A.E.M.: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing, Supervision.

Data availability statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgments

We thank all participants in the Seniors-ENRICA study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.10.007.

References

[1] GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatr 2022;9(2):137–50. https://doi.org/10.1016/S2215-0366(21)00395-3.

[2] Institute of Health Metrics and Evaluation. Global health data exchange (GHDx). 2019. http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/d780dffbe8a381b25e1416884959e88b. Accessed March 9, 2022.

[3] Santomauro DF, Mantilla Herrera AM, Shadid J, Zheng P, Ashbaugh C, Pigott DM, et al. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet 2021;398(10312):1700–12. https://doi.org/10.1016/S0140-6736(21)02143-7.

[4] Patel V, Chisholm D, Parikh R, Charlson FJ, Degenhardt L, Dua T, et al. Addressing the burden of mental, neurological, and substance use disorders: key messages from Disease Control Priorities, 3rd edition. Lancet 2016;387(10028):1672–85. https://doi.org/10.1016/S0140-6736(15)00390-6.

[5] Black CN, Bot M, Scheffer PG, Cuijpers P, Penninx BWJH. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. Psychoneuroendocrinology 2015;51:164–75. https://doi.org/10.1016/J.PSYNEUEN.2014.09.025.

[6] Yang L, Zhao Y, Wang Y, Liu L, Zhang X, Li B, et al. The effects of psychological stress on depression. Curr Neuropharmacol 2015;13(4):494–504. https://doi.org/10.2174/1570159X1304150831150507.

[7] Schuch FB, Vancampfort D, Firth J, Rosenbaum S, Ward PB, Silva ES, et al. Physical activity and incident depression: a meta-analysis of prospective cohort studies. Am J Psychiatr 2018;175(7):631–48. https://doi.org/10.1176/APPI.AJP.2018.17111194.

[8] Marx W, Moseley G, Berk M, Jacka F. Nutritional psychiatry: the present state of the evidence. Proc Nutr Soc 2017;76(4):427–36. https://doi.org/10.1017/S0029665117002026.

[9] Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol 2015;16(1):22–34. https://doi.org/10.1038/nri.2015.5.

[10] Sarris J, Logan AC, Akbaraly TN, Paul Amminger G, Balanzá-Martínez V, Freeman MP, et al. International Society for Nutritional Psychiatry Research consensus position statement: nutritional medicine in modern psychiatry. World Psychiatr 2015;14(3):370–1. https://doi.org/10.1002/WPS.20223.

[11] Papier K, Hartman L, Tong TYN, Key TJ, Knuppel A. Higher meat intake is associated with higher inflammatory markers, mostly due to adiposity: results from UK biobank. J Nutr 2022;152(1):183–9. https://doi.org/10.1093/JN/NXAB314.

[12] Yu Z, Malik VS, Keum NN, Hu FB, Giovannucci EL, Stampfer MJ, et al. Associations between nut consumption and inflammatory biomarkers. Am J Clin Nutr 2016;104(3):722–8. https://doi.org/10.3945/AJCN.116.134205.

[13] Sánchez-Villegas A, Ruíz-Canela M, De La Fuente-Arrillaga C, Gea A, Shivappa N, Hébert JR, et al. Dietary inflammatory index, cardiometabolic conditions and depression in the Seguimiento Universidad de Navarra cohort study. Br J Nutr 2015;114(9):1471–9. https://doi.org/10.1017/S0007114515003074.
[14] Lucas M, Chocano-Bedoya P, Shulze MB, Mirzaei F, ÉJ O'Reilly, Okereke OI, et al. Inflammatory dietary pattern and risk of depression among women. Brain Behav Immun 2014;36:46–53. https://doi.org/10.1016/J.BBI.2013.09.014.
[15] Shivappa N, Hébert JR, Veronese N, Caruso MG, Notarnicola M, Maggi S, et al. The relationship between the dietary inflammatory index (DII ®) and incident depressive symptoms: a longitudinal cohort study. J Affect Disord 2018;235:39–44. https://doi.org/10.1016/J.JAD.2018.04.014.
[16] Adjibade M, Lemogne C, Touvier M, Hercberg S, Galan P, Assmann KE, et al. The inflammatory potential of the diet is directly associated with incident depressive symptoms among French adults. J Nutr 2019;149(7):1198–207. https://doi.org/10.1093/JN/NXZ045.
[17] Shakya PR, Melaku YA, Shivappa N, Hébert JR, Adams RJ, Page AJ, et al. Dietary inflammatory index (DII®) and the risk of depression symptoms in adults. Clin Nutr 2021;40(5):3631–42. https://doi.org/10.1016/J.CLNU.2020.12.031.
[18] Ma Y, Li R, Zhan W, Huang X, Zhang Z, Lv S, et al. Role of BMI in the relationship between dietary inflammatory index and depression: an intermediary analysis. Front Med 2021;8. https://doi.org/10.3389/fmed.2021.748788.
[19] Vermeulen E, Brouwer IA, Stronks K, Bandinelli S, Ferrucci L, Visser M, et al. Inflammatory dietary patterns and depressive symptoms in Italian older adults. Brain Behav Immun 2018;67:290–8. https://doi.org/10.1016/J.BBI.2017.09.005.
[20] Rodríguez-Artalejo F, Graciani A, Guallar-Castillón P, León-Muñoz LM, Zuluaga MC, López-García E, et al. Rationale and methods of the study on nutrition and cardiovascular risk in Spain (ENRICA). Rev Española Cardiol 2011;64(10):876–82. https://doi.org/10.1016/J.REC.2011.05.023.
[21] Cabanas-Sánchez V, Esteban-Cornejo I, García-Esquinas E, Ortolá R, Ara I, Rodríguez-Gómez I, et al. Cross-sectional and prospective associations of sleep, sedentary and active behaviors with mental health in older people: a compositional data analysis from the Seniors-ENRICA-2 study. Int J Behav Nutr Phys Activ 2021;18(1). https://doi.org/10.1186/S12966-021-01194-9.
[22] Struijk EA, Guallar-Castillón P, Rodríguez-Artalejo F, López-García E. Mediterranean dietary patterns and impaired physical function in older adults. J Gerontol A Biol Sci Med Sci 2018;73(3):333–9. https://doi.org/10.1093/GERONA/GLW208.
[23] Ortolá R, García-Esquinas E, Buño-Soto A, Cabanas-Sánchez V, Martínez-Gómez D, Sotos-Prieto M, et al. Associations of device-measured sleep, sedentariness and physical activity with growth differentiation factor 15 in older adults. J Cachexia Sarcopenia Muscle 2022;13(2):1003. https://doi.org/10.1002/JCSM.12924.
[24] Guallar-Castillón P, Sagardui-Villamor J, Balboa-Castillo T, Sala-Vila A, Astolfi MJA, Pelous MDS, et al. Validity and reproducibility of a Spanish dietary history. PLoS One 2014;9(1):e86074. https://doi.org/10.1371/JOURNAL.PONE.0086074.
[25] Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Publ Health Nutr 2014;17(8):1689–96. https://doi.org/10.1017/S1368980013002115.
[26] Shah A, Herbert R, Lewis S, Mahendran R, Platt J, Bhattacharyya B. Screening for depression among acutely ill geriatric inpatients with a short Geriatric Depression Scale. Age Ageing 1997;26(3):217–21. https://doi.org/10.1093/AGEING/26.3.217.
[27] Marx W, Lane M, Hockey M, Aslam H, Berk M, Walder K, et al. Diet and depression: exploring the biological mechanisms of action. Mol Psychiatr 2020;26(1):134–50. https://doi.org/10.1038/s41380-020-00925-x.
[28] Kandola AA, del Pozo Cruz B, Osborn DPJ, Stubbs B, Choi KW, Hayes JF. Impact of replacing sedentary behaviour with other movement behaviours on depression and anxiety symptoms: a prospective cohort study in the UK Biobank. BMC Med 2021;19(1):1–12. https://doi.org/10.1186/S12916-021-02007-3.
[29] Freeman A, Tyrovolas S, Koyanagi A, Chatterji S, Leonardi M, Ayuso-Mateos JL, et al. The role of socio-economic status in depression: results from the COURAGE (aging survey in Europe). BMC Publ Health 2016;16(1). https://doi.org/10.1186/S12889-016-3638-0.
[30] Buckman JEJ, Saunders R, Stott J, Arundell LL, O'Driscoll C, Davies MR, et al. Role of age, gender and marital status in prognosis for adults with depression: an individual patient data meta-analysis. Epidemiol Psychiatr Sci 2021;30:e42. https://doi.org/10.1017/S2045796021000342.
[31] Li R, Zhan W, Huang X, Zhang L, Sun Y, Zhang Z, et al. Investigating associations between depressive symptoms and anti-/pro-inflammatory nutrients in an elderly population in Northern China: a bayesian Kernel machine regression approach. J Inflamm Res 2021;14:5201. https://doi.org/10.2147/JIR.S330300.
[32] Ma Y, Xiang Q, Yan C, Liao H, Wang J. Relationship between chronic diseases and depression: the mediating effect of pain. BMC Psychiatr 2021;21(1):1–11. https://doi.org/10.1186/s12888-021-03428-3.
[33] Haftenberger M, Schuit A, Tormo M, Boeing H, Wareham N, Bueno-de-Mesquita H, et al. Physical activity of subjects aged 50-64 years involved in the European prospective investigation into cancer and nutrition (EPIC). Publ Health Nutr 2002;5(6B):1163–77. https://doi.org/10.1079/PHN2002397.
[34] Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, et al. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Publ Health Nutr 2003;6(4):407–13. https://doi.org/10.1079/PHN2002439.
[35] Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. J Am Geriatr Soc 1983;31(12):721–7. https://doi.org/10.1111/J.1532-5415.1983.TB03391.X.
[36] Hughes ME, Waite LJ, Hawkley LC, Cacioppo JT. A short scale for measuring loneliness in large surveys: results from two population-based studies. Res Aging 2004;26(6):655–72. https://doi.org/10.1177/0164027504268574.
[37] Tabachnick BG, Fidell LS. Using multivariate statistics. 6th ed. Boston, MA: Pearson; 2013.
[38] DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015;45(Pt A):139–45. https://doi.org/10.1016/J.CCT.2015.09.002.
[39] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions version 6.2 (updated February 2021). Cochrane. 2021.
[40] Liu FH, Liu C, Gong TT, Gao S, Sun H, Jiang YT, et al. Dietary inflammatory index and health outcomes: an umbrella review of systematic review and meta-analyses of observational studies. Front Nutr 2021;8:647122. https://doi.org/10.3389/fnut.2021.647122.
[41] Cernackova A, Durackova Z, Trebaticka J, Mravec B. Neuroinflammation and depressive disorder: the role of the hypothalamus. J Clin Neurosci 2020;75:5–10. https://doi.org/10.1016/J.JOCN.2020.03.005.
[42] Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med 2019;25(12):1822–32. https://doi.org/10.1038/s41591-019-0675-0.
[43] Coppé JP, Desprez PY, Krtolica A, Campisi J. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol 2010;5:99. https://doi.org/10.1146/annurev-pathol-121808-102144.
[44] Tolkien K, Bradburn S, Murgatroyd C. An anti-inflammatory diet as a potential intervention for depressive disorders: a systematic review and meta-analysis. Clin Nutr 2019;38(5):2045–52. https://doi.org/10.1016/j.clnu.2018.11.007.
[45] Zitvogel L, Pietrocola F, Kroemer G. Nutrition, inflammation and cancer. Nat Immunol 2017;18(8):843–50. https://doi.org/10.1038/NI.3754.
[46] Firth J, Veronese N, Cotter J, Shivappa N, Hebert JR, Ee C, et al. What is the role of dietary inflammation in severe mental illness? A review of observational and experimental findings. Front Psychiatr 2019;10(350). https://doi.org/10.3389/fpsyt.2019.00350.
[47] Lee SL, Pearce E, Ajnakina O, Johnson S, Lewis G, Mann F, et al. The association between loneliness and depressive symptoms among adults aged 50 years and older: a 12-year population-based cohort study. Lancet Psychiatr 2021;8(1):48–57. https://doi.org/10.1016/S2215-0366(20)30383-7.
[48] Dishman RK, McDowell CP, Herring MP. Customary physical activity and odds of depression: a systematic review and meta-analysis of 111 prospective cohort studies. Br J Sports Med 2021;55(16):926–34. https://doi.org/10.1136/BJSPORTS-2020-103140.
[49] Payne ME, Steck SE, George RR, Steffens DC. Fruit, vegetable, and antioxidant intakes are lower in older adults with depression. J Acad Nutr Diet 2012;112(12):2022–7. https://doi.org/10.1016/J.JAND.2012.08.026.
[50] Jacka FN, Cherbuin N, Anstey KJ, Butterworth P. Does reverse causality explain the relationship between diet and depression? J Affect Disord 2015;175:248–50. https://doi.org/10.1016/J.JAD.2015.01.007.