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Association between the dietary inflammatory index and common mental health disorders profile scores

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Background & aims: The association between diet and mental health disorders might be mediated by inflammatory properties of the diet. We evaluated the association between the dietary inflammatory index (DII) and the risk of a worsened mental health disorders profile.
Methods: A total of 3363 Iranian adults were included in this cross-sectional study. A mental health disorders profile score was calculated using regression analysis, within the framework of factor analysis, based on anxiety, depression and psychological distress, with a higher scores indicating greater severity of mental problems. Dietary intakes were assessed using a validated dish-based food frequency questionnaire (DFQ). Twenty-seven macro- and micro-nutrients, onions, tea and caffeine were included in the calculation of DII. Each of them received a score based on their inflammatory ability, thus, a greater DII indicated a more pro-inflammatory diet. The odds of being in the highest tertile of mental health disorders profile across the tertiles of DII was assessed using multinomial logistic regression.
Results: Either in the crude or fully-adjusted multinomial logistic regression models, participants in the lowest tertile of DII had a lower risk for being in the top tertile of mental health disorders profile (adjusted model: OR: 0.45; 95% CI: 0.33, 0.60; P trend<0.001). In a stratified analysis by sex, similar findings were observed in both genders, although there was only a trend for the associations to be significant in men (men: OR: 0.53; 95% CI: 0.31, 0.90; P trend = 0.070; women: OR: 0.40; 95% CI: 0.27, 0.58; P trend<0.0001).
Conclusions: Our findings suggest a direct association between the pro-inflammatory properties of the diet and an increased risk of higher mental health disorders profile scores. Prospective dietary intervention studies and observational prospective cohorts are required to confirm these findings.

1. Introduction

Mental health disorders affect ~450 million persons worldwide [1] and, due to their high prevalence, their onset in the early years of life and their chronicity, they are predicted to be the leading cause of disability and early mortality [2,3]. The bidirectional association between mental disorders [4], particularly depression, and chronic diseases, such as obesity, diabetes and other metabolic disorders, may be explained by some common mechanism(s), such as chronic low-grade inflammation [5]. Increased production of pro-inflammatory cytokines may adversely influence neurotransmitters and endothelial function, which lead to impaired expression of brain-derived neurotrophic factor (BDNF) [6]. There is some

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evidence about risk factors for mental health disorders [7], such as excess adiposity [8], sedentary lifestyle [9] and unhealthy diet [8], can induce low-grade inflammation.

In studies assessing the association between dietary patterns and depression, the consumption of foods with presumed anti-inflammatory properties, e.g. beans, fruits and vegetables, has been associated with a lower risk of anxiety [10,11] or depression [9,12]. In contrast, a Western dietary pattern [11], nutrients or foods with presumed pro-inflammatory effects, e.g. a high dietary glycemic index [13], trans or saturated fatty acids [12,14], have been associated with a higher risk of depression, anxiety or psychological distress. Therefore, it could be hypothesized that certain nutrients and foods may influence mental health by their effects on inflammatory processes. However, nutrients and foods are consumed as part of dietary patterns, and not usually in isolation, and therefore, biologic interactions and co-linearity among them may alter their individual effects. A dietary index ('dietary inflammatory index' (DII)) that reflects the inflammatory potential of the diet was developed by Cavicchia et al. [15] in which some dietary components were weighted based on a systematic review of the available literature studying the effect of diet on inflammatory biomarkers. To date, only a few studies have examined the association between the DII with depression [16–21]. Although most of these studies found a positive association between a pro-inflammatory diet and the risk of depression [18–21], some failed to find significant association [16,17]. For example, a 12-year prospective study did not reveal any significant association in either the total study sample or in women, but observed a significant direct association in men [16]. In contrast, a follow-up study indicated that a pro-inflammatory diet was associated with greater risk of recurrent depressive symptoms in women, but not in men [17]. Moreover, most earlier studies only investigated the risk of depression, whilst other mental health measures, such as psychological distress and anxiety, have been poorly investigated [18,22]. In a cross-sectional study, Bergmans et al. indicated that a pro-inflammatory diet was associated with increased risk of psychological distress, but not anxiety [18]. Another cross-sectional study among Iranian adolescent girls suggested that a pro-inflammatory diet is associated with higher levels of stress [22].

Considering that differences may exist in the risk factors for mental disorders as well as dietary intakes in different populations, associations between mental disorders and dietary patterns are likely to vary from one population to another. Therefore, in the current study, we aimed to investigate whether greater inflammatory properties of a diet (reflected in higher DII scores) are associated with higher levels of common mental health disorders profile scores, derived by combining depression, psychological distress and anxiety in a population of Iranian adults. In addition, we also examined whether associations would differ in men and women. We hypothesized that pro-inflammatory properties of the diet would be associated with a higher risk of having mental health disorders. To our knowledge, this is the first study to provide data about the relationship between DII and mental health disorders in a Middle-Eastern population, in whom dietary intakes and the prevalence of mental health disorders may vary from Western countries.

2. Materials and methods

2.1. Study population

The present study was conducted within the framework of the Study on the Epidemiology of Psychological, Alimentary Health and Nutrition (SEPAHAN) project. The SEPAHAN project, which is a cross-sectional study, was designed to examine the association between prevalent gastrointestinal disorders and lifestyle factors, such as dietary intakes and mental health disorders. The methodology for the SEPAHAN project has been described elsewhere in details [23]. In short, non-academic members of staff of Isfahan University of Medical Sciences (IUMS), Isfahan, Iran, who were working in hospitals, university campus and health centers affiliated with IUMS were invited to take part in this project. To increase accuracy of data and response rate, data were collected in two separate waves. The first wave was run in April 2010, and the second wave in mid-May 2010, and participants returned completed questionnaires within 7 days. In the first wave, 8691 out of 10087 distributed questionnaires were returned (response rate: 86.16%). Data regarding gastrointestinal and mental health disorders were collected in the second phase (response rate: 64.6%). Finally, 4763 questionnaires obtained in wave 2 were matched with their corresponding questionnaires in wave 1. For the purpose of the current analysis, after excluding individuals with implausible daily energy intakes (>4200 or <800 kcal/d) [24], statistical analysis was run on the data of 3363 persons, for whom we had complete information about both dietary intakes and mental health disorders. Written informed consent was provided by all study participants prior to their inclusion in the study. The study protocol was approved by the Regional Bioethics Committee of IUMS (#189069, #189082, and #189086).

2.2. Dietary intake assessment

Data on dietary intakes in the preceding year were collected using an Iranian validated 106-item dish-based food frequency questionnaire (DFQ), which was designed according to the Willett-format food frequency questionnaire [25]. Details regarding the design, food categories and reliability and validity of DFQ have been described elsewhere [26]. In short, 5 main parts were considered in the DFQ: 1) mixed dishes, including cooked or canned foods (n = 29); 2) potatoes and grain-based foods (n = 10); 3) dairy products, including milk and other dairy foods, e.g. butter and cream (n = 9); 4) fruit and vegetables (n = 22); and 5) miscellaneous foods and beverages, such as sweets, fast foods, prepared meals, nuts, desserts and beverages (n = 36). Participants were asked to indicate the amount of food consumed for each item by providing natural portion sizes (i.e. 1 orange). There were nine possible options to choose for each food item, from "never or less than once a month" to "12 or more times per day". Using household measures, including spoon, plate, bowl and glass [27], all food items were converted to grams/d. Daily energy and nutrient intakes of each person were estimated based on the USDA food composition database.

2.3. Calculation of dietary inflammatory index (DII)

To reduce between-subject variation, in the process of computing the DII, dietary intakes were adjusted for individual energy intakes using a residual method, as suggested by Willett and Stampfer [28]. Then individual dietary intake information was associated to its regionally representative database, which presents an estimate of global mean intake for each component, along with its standard deviation provided in the DII definition [29]. To calculate an individual's exposure relative to the "standard global mean", given standard means were then subtracted from these values and divided by the corresponding standard deviation. The z scores derived in this way were converted to percentiles and doubled, and then "1" was subtracted. Finally, the centered percentiles for each parameter were multiplied by their corresponding overall inflammatory effect scores, and all derived values were added to create the overall DII. Some components of the DII were not included in the calculation of DII in the present study, because they are not used in the Iranians diet (e.g. ethanol), or data were not available (e.g. some spices). Thus, in the current study, the DII was calculated based on 27 nutrients, onions, tea and caffeine, as derived from the DFQ.

2.4. Assessment of mental health disorders

In SEPAHAN, information about mental health disorders, including depression, anxiety and psychological distress, was obtained from the validated Iranian version of the Hospital Anxiety and Depression Scale (HADS) [30] and General Health Questionnaire-12 (GHQ-12) [31], respectively. HADS includes two discrete parts assessing the severity of anxiety and depression, each consisting of 7 questions with a four-point rating scale (i.e. 0–3), thus, total scores for each part range from 0 to 21. Higher scores reflect a greater severity of anxiety or depression. According to an earlier study assessing the validity and reliability of HADS in Iranians [29], scores of 8 or higher in either part were considered to indicate the presence of anxiety or depression, while scores of 7 or less were considered normal. The GHQ included 12 questions regarding psychological distress [31], with a four-point rating scale, i.e. less than usual, no more than usual, rather more than usual, or much more than usual. Distress scores were calculated using the bimodal scoring method (0-0-1-1), with the first two choices (less than usual, no more than usual) scored ‘0’, and the second two choices (rather more than usual, or much more than usual) ‘1’. Thus, the maximum score could be 12, and higher scores demonstrate an elevated level of distress. In the present study, participants were considered to have psychological distress if they scored higher than the mean GHQ score in a sample of Iranians ≥4 [31].

Because of a high incidence of comorbid, or co-occurring of, psychological problems [32], we used a confirmatory factor analysis for constructing a combined variable of the three disorders i.e. depression, anxiety and psychological distress, to represent an overall and comprehensive assessment of status of mental health disorders. One factor loaded by all three mental health disorders (loadings were as: 0.91 for anxiety, 0.90 for depression and 0.86 for psychological distress) was constructed and named “mental health disorders profile”, and scores were calculated using a regression method within the framework of factor analysis. Higher scores of mental health disorders profile indicate a greater severity of mental disorders. In our proposed model, mental health disorders profile as a latent response was regressed on DII as predictor. Such a framework provides a comprehensive and integrative assessment of the association between two proposed variables. The tertiles of factor scores were used in the association analyses.

2.5. Covariates

Data about body weight and height, demographic characteristics and lifestyle variables (dietary intakes, physical activity) were obtained using pretested self-administered questionnaires [33]. BMI was calculated as weight (kg) divided by height squared (m^2). Because of a close relationship between gastrointestinal disorders and mental health, we considered functional gastrointestinal disorders (FGIDs) as an important covariate in our analysis. Suffering from gastrointestinal disorders was assessed using a valid and modified Iranian version of the ROME III questionnaire [34]. FGIDs were defined as suffering from at least one of the following main gastrointestinal disorders: gastroesophageal reflux, dyspepsia, irritable bowel syndrome and constipation.

2.6. Statistical analysis

First, participants were categorized into separate tertiles based on DII and mental health disorders profile scores. General characteristics of participants in tertiles of DII and mental health disorders profile scores were expressed as means and standard error (SE) or percentages for continuous and categorical variables, respectively. Analysis of variance (ANOVA) was used for comparing continuous demographic variables and chi-square test for categorical variables across tertiles of mental health disorders and DII. To examine the mean differences of nutrient intakes across tertiles of DII, we used analysis of covariance (ANCOVA), in which adjustment was made for age, sex and total energy intake (kcal/d). Total calorie intake of participants adjusted for age and sex was compared among tertiles of DII in the same manner.

Binary logistic regression was performed to assess the risk of depression, anxiety and psychological distress across the tertiles of DII in a crude model and an adjusted model for age, sex, education (less than 12 years, 12–16 years and more than 16 years) and marital status (married, single, divorced, widowed), smoking (non- and ex-smokers vs. current smokers), physical activity (moderately active and active vs. moderately inactive and inactive), BMI, gastrointestinal disorders (yes/no) and anti-psychotropic medicine consumption (yes/no). We used multinomial logistic regression, as the main statistical method, to estimate the odds ratios (OR) (95% confidence interval) for having higher scores of mental health disorders profile by decreasing DII in crude and multivariable-adjusted models. Lower DII scores indicate lower inflammatory potential of the diet. In adjusted models (model 2), we adjusted the confounding effects of age, sex, marital status and education. Further adjustment was made for BMI, smoking and physical activity in model 3. Model 4 was additionally adjusted for use of anti-psychotropic medicines and gastrointestinal disorders. All confounders were included in the statistical analysis as covariates. *P* for linear trends was determined by Mantel-Hanszel extension of chi-square test. We also performed stratified analyses, applying the above-mentioned models, by sex and BMI (<25 and ≥ 25 kg/m^2) to evaluate potential modifying effects of sex and BMI related to mental health status. In the stratified analyses, the adjusted models were also controlled for the same potential confounders, outlined above. All statistical analyses were done using Statistical Package for Social Sciences (SPSS, Inc., Chicago IL, USA; version 20). $P < 0.05$ was considered significant in all statistical analyses.

3. Results

Table 1 shows the general characteristics of the study population according to the mental health disorders profile scores categorized in tertiles. Participants in the highest tertile of mental health disorders profile scores were less likely to be men, highly educated and physically active compared with those in the lowest tertile. Smoking, using anti-psychotropic medicines and suffering from functional gastrointestinal disorders were significantly more prevalent among participants in the top tertile.

Mean (SD) and range of DII were −1.97 (1.31) and −5.55 to 4.61 in our study population. General characteristics of participants across the tertiles of DII are shown in Table 2. Participants in the highest tertile were younger and had significantly higher scores of all three mental health disorders. They were less likely to be physically active and while more likely to be overweight or obese, but more likely to be male or current smoker.

Table 3 shows the age-, sex- and energy-adjusted dietary intakes of participants across tertiles of DII. Participants in the highest tertile of DII consumed lower amounts of carbohydrate, protein, fiber, folate, vitamin B6, magnesium, fruit, vegetables, legumes and nuts, white and red meats and whole grains, but greater amounts of energy, fat, caffeine, hydrogenated vegetable oils and refined grains compared with those in the first tertile.

The associations between DII and mental health disorders profile are presented in Table 4. In the crude multinomial logistic

Table 1
General characteristics of study participants across tertiles of mental health disorders profile[a].

Variables	Tertiles of mental health disorders profile scores			P value[b]
	1	2	3	
Dietary inflammatory index	−2.13 ± 0.04	−2.02 ± 0.04	−1.75 ± 0.04	<0.0001
Age (years)	36.08 ± 0.28	36.50 ± 0.27	35.89 ± 0.27	0.268
BMI (kg/m^2)	25.02 ± 0.14	24.97 ± 0.16	25.01 ± 0.16	0.970
Depression score	3.08 ± 0.04	5.69 ± 0.05	9.39 ± 0.10	<0.0001
Anxiety score	0.68 ± 0.29	2.61 ± 0.05	7.18 ± 0.12	<0.0001
Psychological distress score	0.20 ± 0.01	1.21 ± 0.04	4.75 ± 0.10	<0.0001
Male (%)	51.0	40.6	29.9	<0.0001
Married (%)	80.7	81.2	80.2	0.198
Educational level (%)				0.008
≤12 yr	8.5	10.1	13.9	
12–16 yr	82.1	82.4	79.0	
>16 yr	9.5	7.5	7.1	
Physically active (%)	53.0	45.6	39.9	<0.0001
Anti-psychotropic medicines use[4] (%)	2.0	3.0	11.0	<0.0001
FGID[c] (yes) (%)	30.9	51.7	73.0	<0.0001
Current smokers (%)	10.9	13.8	15.2	0.023
Overweight or obese[c] (%)	46.2	45.1	47.1	0.720

[a] Values are Mean ± SE unless otherwise indicated. BMI: body mass index. FGID: functional gastrointestinal disorders.
[b] Resulted from one-way ANOVA and χ^2 test for continuous and categorical variables, respectively.
[c] FGID defined as suffering from at least one of the following gastrointestinal disorders: gastroesophageal reflux, dyspepsia, irritable bowel syndrome and constipation. Overweight was defined as BMI greater than or equal to 25 and less than or equal to 29.99 kg/m^2 and obese was defined as BMI≥30 kg/m^2.

regression model, participants in the lowest tertile of DII had a lower risk of being in the highest tertile of mental health disorders profile scores than those subjects in the highest tertile (model 1) (OR:0.42; 95% CI:0.32, 0.55; P trend< 0.0001). These associations remained significant after adjustment for demographic covariates (model 2) (OR: 0.43; 95% CI: 0.33, 0.56; P trend< 0.0001), lifestyle confounders (model 3) (OR: 0.44; 95% CI: 0.33, 0.58; P trend< 0.0001), and anti-psychotropic medicines use and gastro-intestinal disorders (model 4) (OR: 0.45; 95% CI: 0.33, 0.60; P trend< 0.0001).

The associations of DII and mental health disorders profile stratified by sex are shown in Table 5. After adjustment for potential covariates, females in the lowest tertile of DII had a lower risk of being in the third tertile of mental health disorders profile (OR: 0.40; 95% CI: 0.27, 0.58; P trend<0.0001). In the fully-adjusted model, male in the lowest tertile of DII tended to have lower, marginally significant, risk of being in the highest tertile of mental health disorders profile (OR: 0.53; 95% CI: 0.31, 0.90; P trend = 0.070).

In the stratified analysis by BMI (<25 and ≥ 25 kg/m^2), participants with normal weight or overweight had a lower risk of being in the highest tertile of mental health disorders profile by decreasing DII. Associations were similar in both normal and overweight subjects (data not shown).

We also investigated the association of DII levels with all three mental health disorders separately considering them each as a binary dependent variable. Binary logistic regression analysis revealed significant direct associations between DII and depression and psychological distress risk in both the crude and fully-adjusted models. In the crude model, a lower risk of depression (T1: OR = 0.70; 95% CI: 0.57, 0.86 and T2: OR = 0.83; 95% CI: 0.68, 1.01; P = 0.001) and psychological distress (T1: OR = 0.60; 95% CI: 0.48, 0.74 and T2: OR = 0.83; 95% CI: 0.68, 1.03; P < 0.0001) was observed in the lowest tertiles of DII compared with the highest tertile. After adjustment for the impacts of confounders, the associations became slightly stronger (for depression: T1: OR = 0.62; 95% CI: 0.48, 0.80 and T2: OR = 0.85; 95% CI: 0.66, 1.08; P < 0.0001; for

Table 2
General characteristics of study participants across tertiles of adopted dietary inflammatory index[a].

Variables	Tertiles of dietary inflammatory index			P value[b]
	1	2	3	
Subjects (n)				
Age (years)	37.63 ± 0.27	36.02 ± 0.27	35.38 ± 0.27	<0.0001
BMI (kg/m^2)	25.55 ± 0.17	24.88 ± 0.13	24.75 ± 0.15	<0.0001
Depression score	5.70 ± 0.10	6.00 ± 0.10	6.48 ± 0.12	<0.0001
Anxiety score	3.20 ± 0.12	3.37 ± 0.11	3.87 ± 0.13	<0.0001
Psychological distress score	1.75 ± 0.08	2.04 ± 0.09	2.36 ± 0.09	<0.0001
Male (%)	34.0	40.7	48.1	<0.0001
Married (%)	83.3	81.2	78.5	0.121
Educational level (%)				0.888
≤12 yr	11.6	10.0	10.3	
12–16 yr	80.3	82.1	81.2	
>16 yr	8.1	7.8	8.4	
Physically active (%)	52.4	44.9	41.2	<0.0001
Anti-psychotropic medicines use[4] (%)	6.7	4.7	5.0	0.116
FGID[c] (yes) (%)	50.1	49.6	55.2	0.027
Current smokers (%)	13.5	12.4	14.1	0.020
Overweight or obese[c] (%)	51.3	45.2	43.8	0.003

[a] Values are Mean ± SE unless otherwise indicated. BMI: body mass index. FGID: functional gastrointestinal disorders.
[b] Resulted from one-way ANOVA and χ^2 test for continuous and categorical variables, respectively.
[c] FGID defined as suffering from at least one of the following gastrointestinal disorders: gastroesophageal reflux, dyspepsia, irritable bowel syndrome and constipation. Overweight was defined as BMI greater than or equal to 25 and less than or equal to 29.99 kg/m^2 and obese was defined as BMI≥30 kg/m^2.

Table 3
Dietary intakes of participants across tertiles of adopted dietary inflammatory index[a].

Variables	Tertiles of dietary inflammatory index			P value[b]
	1	2	3	
Energy (kcal/d)	2040.02 ± 25.94	2273.71 ± 25.67	2844.32 ± 26.05	<0.0001
Carbohydrate (% of total daily energy)	50.64 ± 0.28	48.41 ± 0.27	48.42 ± 0.29	<0.0001
Fat (% of total daily energy)	36.30 ± 0.23	38.07 ± 0.22	38.18 ± 0.24	<0.0001
Protein (% of total daily energy)	15.29 ± 0.08	14.93 ± 0.08	14.22 ± 0.08	<0.0001
Fiber (g/d)	27.12 ± 0.16	22.96 ± 0.16	17.67 ± 0.17	<0.0001
Caffeine (mg/d)	88.37 ± 3.27	96.49 ± 3.14	112.97 ± 3.37	<0.0001
Total folate intake (μg/d)	604.36 ± 4.28	569.21 ± 4.11	549.68 ± 4.41	<0.0001
Vitamin B6 (mg/d)	2.24 ± 0.01	2.01 ± 0.01	1.69 ± 0.01	<0.0001
Vitamin B12 (μg/d)	2.99 ± 0.04	3.00 ± 0.04	2.90 ± 0.04	0.101
Mg (mg/d)	366.34 ± 1.68	333.74 ± 1.61	284.99 ± 1.73	<0.0001
Omega-3 fatty acids (g/d)	2.28 ± 0.04	2.25 ± 0.04	2.23 ± 0.04	0.648
Food groups				
Fruit (g/d)	452.98 ± 7.53	311.71 ± 7.23	196.13 ± 7.76	<0.0001
Vegetables (g/d)	322.29 ± 3.74	235.29 ± 3.59	161.13 ± 3.85	<0.0001
Nuts, legumes and soy (g/d)	65.72 ± 1.24	58.79 ± 1.19	43.07 ± 1.27	<0.0001
White meat (g/d)	66.27 ± 1.55	64.54 ± 1.48	60.46 ± 1.59	0.039
Red meat (g/d)	83.02 ± 1.40	82.09 ± 1.35	69.79 ± 1.44	<0.0001
Hydrogenated vegetable oil (g/d)	9.67 ± 0.38	10.52 ± 0.37	11.36 ± 0.39	0.014
Refined grains (g/d)	338.03 ± 5.67	375.38 ± 5.44	460.88 ± 5.84	<0.0001
Whole grains (g/d)	57.00 ± 2.69	51.73 ± 2.58	23.19 ± 2.77	<0.0001

[a] Values are Mean ± SE. Nutrients were adjusted for age, sex and total energy intake (kcal). Energy intake was adjusted for age and sex.
[b] From analysis of covariance (ANCOVA) and energy was considered as the absolute amount per day. For all nutrients except energy, adjustment was made for age, sex and energy while for energy only for age and sex.

psychological distress: T1: OR = 0.55; 95% CI: 0.42, 0.73 and T2: OR = 0.91; 95% CI: 0.71, 1.17; P < 0.0001). The association for anxiety was significant only in the crude model (T1: OR = 0.77; 95% CI: 0.59, 0.999 and T2: OR = 0.61; 95% CI: 0.46, 0.80; P = 0.04), but not in the fully-adjusted model (T1: OR = 0.80; 95% CI: 0.57, 1.11 and T2: OR = 0.65; 95% CI: 0.46, 0.91; P = 0.169).

4. Discussion

Our study showed that low DII (representing an anti-inflammatory diet) was associated with a lower risk of being in the top tertile of mental health disorders profile (representing lower mental well-being, as it includes a combined measure of depression, anxiety and psychological distress) in a large sample of Iranian adults. In a stratified analysis by sex, these associations were attenuated in men and became marginally significant in the fully-adjusted model, but remained strongly significant in women. This association was also observed for each anxiety, depression and psychological distress, when separately examined, although the significance disappeared for anxiety after statistical adjustments.

Our findings regarding the direct association between a pro-inflammatory diet and worsened mental health disorders profile are consistent with earlier studies' findings. In a prospective study in a Mediterranean population, a pro-inflammatory diet was associated with an over two-fold greater risk of having depression [20]. In another 12-year prospective study, a pro-inflammatory dietary pattern, identified by reduced-rank regression, was associated with increased levels of inflammatory biomarkers (CRP, IL-6 and TNF-α) and higher depression risk [19]. In a cross-sectional study in a representative sample of US adults, a pro-inflammatory diet was associated with a two-fold increase in the risk of depression and an 81% increase in the risk of frequent distress, but no

Table 4
Multivariable-adjusted odds ratio and 95% confidence interval for the association of mental health disorders profile's scores and dietary inflammatory index[a].

Tertiles of mental health disorders profile	Tertiles of dietary inflammatory index			P trend
	1	2	3	
Model 1				<0.0001
Lowest tertile	1 (reference)	1 (reference)	1 (reference)	
Intermediate tertile	0.73 (0.57, 0.94)	0.88 (0.68, 1.13)	1 (reference)	
Highest tertile	0.42 (0.32, 0.55)	0.70 (0.54, 0.90)	1 (reference)	
Model 2				<0.0001
Lowest tertile	1 (reference)	1 (reference)	1 (reference)	
Intermediate tertile	0.74 (0.56, 0.96)	0.85 (0.66, 1.11)	1 (reference)	
Highest tertile	0.43 (0.33, 0.56)	0.68 (0.52, 0.88)	1 (reference)	
Model 3				<0.0001
Lowest tertile	1 (reference)	1 (reference)	1 (reference)	
Intermediate tertile	0.76 (0.58, 0.99)	0.85 (0.65, 1.12)	1 (reference)	
Highest tertile	0.44 (0.33, 0.58)	0.66 (0.51, 0.87)	1 (reference)	
Model 4				<0.0001
Lowest tertile	1 (reference)	1 (reference)	1 (reference)	
Intermediate tertile	0.77 (0.59, 1.02)	0.89 (0.68, 1.17)	1 (reference)	
Highest tertile	0.45 (0.33, 0.60)	0.74 (0.56, 0.99)	1 (reference)	

Model 1: Crude model. Model 2: adjustment was made for age, sex, marital status and education. Model 3: additional adjustment was made for BMI, smoking and physical activity. Model 4: anti-psychotropic medicines use and suffering from gastrointestinal disorders were additionally adjusted.
[a] Multinomial logistic regression model was used.

Table 5
Multivariable-adjusted odds ratio and 95% confidence interval for the association of mental health disorders profile and dietary inflammatory index stratified by sex[a].

Tertiles of mental health disorders profile	Tertiles of dietary inflammatory index			P trend
	1	2	3	
Men				
Model 1				0.008
Lowest tertile	1 (reference)	1 (reference)	1 (reference)	
Intermediate tertile	0.93 (0.66, 1.30)	1.07 (0.77, 1.48)	1 (reference)	
Highest tertile	0.51 (0.35, 0.76)	0.73 (0.51, 1.03)	1 (reference)	
Model 2				0.011
Lowest tertile	1 (reference)	1 (reference)	1 (reference)	
Intermediate tertile	0.96 (0.65, 1.41)	1.01 (0.70, 1.45)	1 (reference)	
Highest tertile	0.46 (0.29, 0.73)	0.76 (0.51, 1.12)	1 (reference)	
Model 3				0.049
Lowest tertile	1 (reference)	1 (reference)	1 (reference)	
Intermediate tertile	1.06 (0.70, 1.62)	0.94 (0.63, 1.39)	1 (reference)	
Highest tertile	0.53 (0.32, 0.87)	0.67 (0.44, 1.04)	1 (reference)	
Model 4				0.070
Lowest tertile	1 (reference)	1 (reference)	1 (reference)	
Intermediate tertile	1.09 (0.71, 1.67)	0.95 (0.63, 1.42)	1 (reference)	
Highest tertile	0.53 (0.31, 0.90)	0.72 (0.46, 1.14)	1 (reference)	
Women				
Model 1				<0.0001
Lowest tertile	1 (reference)	1 (reference)	1 (reference)	
Intermediate tertile	0.58 (0.42, 0.80)	0.74 (0.53, 1.04)	1 (reference)	
Highest tertile	0.40 (0.29, 0.54)	0.63 (0.46, 0.87)	1 (reference)	
Model 2				<0.0001
Lowest tertile	1 (reference)	1 (reference)	1 (reference)	
Intermediate tertile	0.59 (0.42, 0.83)	0.75 (0.52, 1.06)	1 (reference)	
Highest tertile	0.38 (0.27, 0.53)	0.63 (0.45, 0.88)	1 (reference)	
Model 3				<0.0001
Lowest tertile	1 (reference)	1 (reference)	1 (reference)	
Intermediate tertile	0.58 (0.40, 0.84)	0.74 (0.51, 1.09)	1 (reference)	
Highest tertile	0.39 (0.27, 0.55)	0.63 (0.44, 0.91)	1 (reference)	
Model 4				<0.0001
Lowest tertile	1 (reference)	1 (reference)	1 (reference)	
Intermediate tertile	0.60 (0.41, 0.86)	0.78 (0.54, 1.15)	1 (reference)	
Highest tertile	0.40 (0.27, 0.58)	0.72 (0.49, 1.05)	1 (reference)	

Model 1: Crude model. Model 2: Age, marital status and education were adjusted. Model 3: Additional adjustments were done for BMI, smoking and physical activity. Model 4: Further controls were done for anti-psychotropic medicines use and suffering from gastrointestinal disorders.
[a] Multinomial logistic regression model was used.

association was observed for anxiety [18]. Nevertheless, a direct cross–sectional association was found between a pro-inflammatory diet and anxiety among Iranian adolescent girls [22].

Our findings stratified by sex demonstrated that after adjusting for various confounders, associations were significant only among women, whilst the risk of having mental health disorders tended to be lower in the first tertile of DII. This finding is in line with the results of NHANES, which showed DII is associated with a higher risk of depression in shift workers [35]. Nevertheless, the results of the SUN project showed a greater risk of depression in both men and women who were in the highest quintile of a pro-inflammatory diet [20]. While that study [20] found a greater risk among men, we observed stronger associations in women and marginally significant association among men. This discrepancy may be due to our different approach; we assessed mental health disorders more broadly, and not only depression. Several studies have shown a higher prevalence of anxiety and psychological distress in women than in men [36,37]. In addition, diet may also be a more relevant factor in the development of mental health disorders in women, whereas factors other than diet might be more prominent in men. Adjusting for confounding factors confirmed this hypothesis, since the associations became stronger in men, but remained relatively unchanged in women. Another reason for a stronger association among women in our study might be attributable to the age of participants. Our study population was younger than the participants of previous studies [16,20]. Mental health disorders may differ by age as it has been reported that particularly anxiety and psychological distress are more prevalent in younger than older ages [38].

DII is not only associated with the risk of mental health problems, but also metabolic abnormalities, such as obesity, insulin resistance and diabetes [39]. There is a bidirectional association between obesity, insulin resistance and mental disorders [4]. Therefore, it is likely that a lower DII ameliorates mental health by affecting metabolic health. This hypothesis has been supported by the results obtained in both epidemiological studies [20,40] and clinical trials [41]. The results of the SUN project have revealed that a pro-inflammatory diet could be a more detrimental factor for the incidence of depression in individuals who suffer from cardiometabolic diseases, diabetes and obesity than in healthy subjects [20]. Although the interactions were not significant in the SUN project, the authors concluded that, due to the magnitude of findings, they are likely to be biologically relevant [20]. Nevertheless, mental health problems are multifactorial and complex conditions that may be caused by various potential mechanisms, such as oxidative stress, inflammation and disturbed neurotransmitter synthesis. Several lines of evidence support the association between inflammatory cytokines and mental health problems. Inflammatory markers, such as interferon-alpha (IFN-α) may affect neurogenesis [42] and neuroplasticity [43] and the activity of various systems involved in mental disorders, such as serotonergic [44], dopaminergic [45] and brain-derived neurotrophic factor

(BDNF) [46] systems. Results of a meta-analysis have shown that serum levels of total antioxidant capacity and paraxonase were lower in depressed patients compared with non-depressed, whereas the levels of serum free radical and oxidative damage products were higher [47]. Oxidant-antioxidant imbalance is associated with elevated levels of reactive oxygen and nitrogen species, which increases DNA damage and, consequently, mitochondrial dysfunction [48]. Such damage may underlie the relationship between DII and mental health disorders [48,49].

Some limitations of our study should be recognized. First, the cross-sectional design of our study does not allow conclusions regarding causality. On the other hand, because an 'unhealthy' eating style is more prevalent among people with depression [50], it is possible that the association between DII and mental health disorders is bidirectional. Second, the external validity of our findings might be limited to non-academic university staff only, although this is unlikely. Broadening the socio-economic background of the study population may increase the variability in covariates, thus, increasing the external validity of our findings. Third, in spite of excellent consistency between our findings and earlier studies, it should be kept in mind that the nutrient assessment in our study was done using the USDA food composition database. This might influence the observed associations because the same foods grown in different parts of the world may not have the same nutrient levels. Fourth, the use of self-administered questionnaires may limit the accuracy of our findings; also, because of BMI- or sex-differences, we performed subgroup analysis based on sex and BMI to minimize their impacts. Fifth, some dietary components in the calculation of DII could not be used in our study because they were not considered in our FFQ, however, because they are consumed infrequently (e.g. certain spices) their intake variation will not be substantial. Sixth, DII has some limitations, for example, the DII is based on literature, which determined the effect of specific dietary components on inflammation, which might lead to weaker association when compared with the diet as a whole. In addition, DII does not take into account any recommended value for human dietary intakes and does not measure any health outcome.

The study also has a number of strengths. Our analysis carefully took into account the potential effects of various confounders. Moreover, dietary intakes were assessed using a validated dish-based food frequency questionnaire which provides more precise information than a classic FFQ. This is the first study that examined the relationship between DII and mental health disorders in a Middle-Eastern country where dietary intakes and the prevalence of mental health disorders may vary from Western countries. Although the overall mean of DII in our study population was similar to that in a Western population [16,51], the contribution of food parameters in different populations may vary.

In conclusion, our results from on a study in a large sample of Iranian adults indicate that an anti-inflammatory diet may be associated with lower risk of mental health disorders, particularly among women. More studies utilizing a prospective design are warranted to confirm our findings in other populations; furthermore, the hypothesis that changes in DII could prevent or ameliorate mental health disorders warrants examination in intervention studies.

Authors' contributions

PA, AE, AHK, HA, contributed to SEPAHAN study concepts and design, data collection and drafting of the manuscript; AF and FH contributed to statistical analysis, data interpretation and manuscript drafting; CHFB, contributed in manuscript drafting and interpretation of findings. AF supervised the current secondary study. All authors read and approved the final version of the manuscript.

Conflict of interest

None of the authors had any personal or financial conflicts of interest.

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