



Association of Dietary Acid Load and Depression among Iranian Women: A Case-Control Study

Mina Darand: PhD¹, Moloud Ghorbani: MSc², Vahid Arabi, MSc^{3,4}; Maryam Khosravi: PhD² & Mahdieh Hosseinzadeh, PhD^{*5,6}

¹ Cardiovascular Research Center, Rajaei Cardiovascular Institute, Tehran, Iran; ² Department of Nutrition, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; ³ Department of Community Nutrition, School of Nutrition and Food Science, Nutrition and Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran; ⁴ Students Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran; ⁵ Research Center for Food Hygiene and Safety, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; ⁶ Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran,

ARTICLE INFO

ORIGINAL ARTICLE

Article history:

Received: 2 Jul 2025

Revised: 7 Jun 2026

Accepted: 21 Jun 2026

*Corresponding author:

hoseinzade.mahdie@gmail.com
Department of Nutrition, School
of Public Health, Shahid
Sadoughi University of Medical
Sciences, Yazd, Iran.

Postal code: 8915173160

Tel: +98 35 38203232

Keywords:

Depression; Depressive
disorder; Acid-base
equilibrium; Dietary acid
load; Potential renal acid
load; Net endogenous acid
production.

ABSTRACT

Background: The present study aimed to investigate the association between dietary acid load and depression among Iranian women. **Methods:** This case-control study was conducted on 110 women with depression and 220 healthy controls recruited from two psychiatric clinics in Tehran, Iran. Dietary intake over the previous 12 months was assessed using a validated semi-quantitative food frequency questionnaire (FFQ) consisting of 168 items. Dietary acid load was calculated using two established indices: Potential Renal Acid Load (PRAL) and Net Endogenous Acid Production (NEAP). The association between dietary acid load and depression was evaluated using multivariate logistic regression models in crude and adjusted analyses. The adjusted model was controlled for potential confounders, including energy, physical activity, history of depression, smoking status, periods of unemployment, occupational status, and body mass index (BMI). **Results:** Participants in the highest quartile of PRAL and NEAP had significantly higher odds of depression compared to those in the lowest quartile. In the fully adjusted model, the odds ratio (OR) for depression was 3.52 (95% CI: 1.64–7.54; P for trend <0.001) for PRAL and 4.07 (95% CI: 1.86–8.89; P for trend <0.001) for NEAP. **Conclusion:** Higher dietary acid load, as measured by PRAL and NEAP, was associated with increased odds of depression in women. However, due to the case-control design, causal inferences cannot be established. Further prospective studies are warranted to confirm these findings.

Introduction

Psychological disorders, particularly depression, have increased at an alarming rate worldwide in recent years (Depression, 2017). It is

estimated that approximately 4.4% of the global population (5.1% of females and 3.6% of males) are affected by depressive disorders, with a notably

This paper should be cited as: Darand M, Ghorbani M, Arabi V, Hosseinzadeh M, Khosravi M. Association of Dietary Acid Load and Depression among Iranian Women: A Case-Control Study. Journal of Nutrition and Food Security (JNFS), 2026; 11(4): 457-468.

higher prevalence of approximately 21% reported among the adult population in Iran (Depression, 2017, Noorbala *et al.*, 2004).

The etiology of mental disorders is multifactorial, involving genetic predisposition as well as environmental and social determinants (Lange *et al.*, 2017, Sarris *et al.*, 2016, Saveanu and Nemeroff, 2012). Recently, growing evidence has highlighted the critical role of nutrition and overall dietary patterns in the prevention and management of mental health disorders (Abshirini *et al.*, 2019, Murakami and Sasaki, 2010, Rao *et al.*, 2008). Notably, examining dietary patterns rather than isolated food items provides more robust and reliable insights, as it accounts for the synergistic and interactive effects of various dietary components (Mozaffari *et al.*, 2018). Dietary acid load has emerged as a comprehensive indicator for evaluating the acidifying or alkalizing potential of an individual's diet (Scialla and Anderson, 2013). Established indices such as net endogenous acid production (NEAP) and potential renal acid load (PRAL) are widely used, valid, and practical approaches for estimating dietary acid load based on nutrient composition (Frassetto *et al.*, 1998, Remer and Manz, 1994).

A growing body of literature suggests that diets characterized by a high acid load - typically rich in animal-based products - may be associated with an increased risk of mental health disorders, including depression (Bahari *et al.*, 2023). In contrast, dietary patterns rich in fruits and vegetables, such as Mediterranean and plant-based diets, which exert a more alkalizing effect, have been associated with a reduced risk of these conditions (Molendijk *et al.*, 2018, Rahmani *et al.*, 2018, Saghafian *et al.*, 2018).

From a mechanistic perspective, it has been proposed that a high dietary acid load may stimulate the secretion of glucocorticoids, particularly cortisol, thereby influencing psychological well-being (Buehlmeier *et al.*, 2016, Esche *et al.*, 2016). Elevated glucocorticoid levels can induce structural and functional alterations in key regions of the limbic system, including the hippocampus and amygdala, ultimately contributing to changes in emotional regulation

and behavior (Dedovic *et al.*, 2009, Mora *et al.*, 2012). Given these inconsistencies, further well-designed studies are warranted, particularly in regions such as West Asia and North Africa, where the intake of alkalizing foods is low and the prevalence of psychological disorders is high. Therefore, the present study was designed to comprehensively investigate the association between dietary acid load and depression.

Materials and Methods

Study population

This case-control study was conducted among 110 depressed women and 220 control participants. Patients with depression were diagnosed by psychiatrists according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (Gonçalves *et al.*, 2008), validated for the Iranian population. Participants were recruited from two psychiatric clinics in Tehran using a convenience sampling method (Shooshtari *et al.*, 2007). The control group had no evidence of major depressive disorder based on the Beck Depression Inventory-II (BDI-II) (Whisman *et al.*, 2000) validated for the Iranian population (Ghassemzadeh *et al.*, 2005). In addition, participants in both groups had no history of depression during the previous year. Cases and controls were individually matched according to sex, age, and residential area. Each patient with depression was matched with two control subjects within a 10-year age range. Moreover, eligible control subjects were recruited from the patients' residential areas by trained interviewers. The inclusion criteria included age 18–65 years, residence in Tehran, Iran, and a diagnosis of major depressive disorder; only recent-onset cases were included. The exclusion criteria included the presence of cognitive or psychotic disorders diagnosed by a psychiatrist, current use of antidepressant medications or other psychiatric treatments, hormonal disorders, chronic diseases such as diabetes, cardiovascular diseases, and cancer, history of trauma resulting in unconsciousness or hospitalization within the past 3 months, acute or chronic infectious diseases,

alcohol or drug use at the time of the study or within the past 3 months, body mass index (BMI) ≥ 40 kg/m², pregnancy or lactation at the time of the study or within the past year, adherence to any special diet within the past year, and unwillingness to participate in the study (FÚart *et al.*, 2009, Samieri *et al.*, 2008). A written informed consent form was completed by the subjects. This study has been approved by the Ethics Committee of Tehran University of Medical Sciences.

Sample size calculation

The sample size was calculated using OpenEpi software for an unmatched case-control study with a case-to-control ratio of 1:2 (110 depressed women and 220 healthy controls). The calculation was based on a two-sided 95% confidence level, 80% statistical power, and the expected proportion of exposure in controls and odds ratio from previous studies.

Assessment of dietary intake

A validated semi-quantitative food frequency questionnaire consisting of 168 items was used to assess food consumption in the previous 12 months (Mirmiran *et al.*, 2010). Data from the questionnaire was converted into grams per day. The conversion of food portion sizes to grams was also conducted via household measures (Ghaffarpour *et al.*, 1999). Then, the registered foods were assessed using the upgraded Nutritionist IV software (First Databank, San Bruno, CA, USA) specifically designed for Iranian foods. Finally, the FFQs were administered by an expert dietitian.

Calculation of dietary acid load indices

The dietary acid load was calculated using the relevant data with 2 validated methods: PRAL and NEAP. PRAL was calculated using the method explained by Remer and Manz (Remer and Manz, 1994):

$$\text{PRAL (mEq/day)} = (0.4888 \times \text{protein intake [g/day]}) + (0.0366 \times \text{phosphorus [mg/day]}) - (0.0205 \times \text{potassium [mg/day]}) - (0.0125 \times \text{calcium [mg/day]}) - (0.0263 \times \text{magnesium [mg/day]}).$$

NEAP was computed by the algorithm illustrated by Frassetto *et al.* (Frassetto *et al.*, 1998) as follows:

$$\text{NEAP (mEq/day)} = (54.5 \times \text{protein intake [g/day]}) / \text{potassium intake [mEq/day]} - 10.2.$$

Assessment of other variables

General information and data on drug use were collected through a general questionnaire. For all participants, weight and height were measured, and BMI was calculated. A categorized physical activity questionnaire, based on the metabolic equivalent hours per day (MET-h/day), was applied. This questionnaire includes nine levels of activity, from rest and sleep (MET=0.9) to severe activity (MET ≥ 6). The validity and reliability of this questionnaire have been affirmed by Kelishadi *et al.* in Iran (Kelishadi *et al.*, 2001).

Ethical considerations

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Shahid Sadoughi University of Medical Sciences (IR.SSU.SPH.REC.1405.028). Written informed consent was obtained from all subjects/patients.

Data analysis

Qualitative and quantitative variables were compared between the case and control groups using a chi-square test and independent t-test, respectively. Also, the comparison of quantitative variables and dietary intakes of the participants across quartiles of PRAL was made using a one-way ANOVA test. The association between depression and PRAL and NEAP was investigated using multivariate logistic regression in crude and adjusted models. Model I was adjusted for energy intake. In model II, physical activity, history of depression, smoking status, periods of unemployment, job, and BMI were additionally adjusted. Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 26.0). P-values < 0.05 were considered statistically significant.

Results

General characteristics of the study population

The general characteristics of women with and without depression, as well as across PRAL quartiles, are presented in **Table 1**. As shown in the table, physical activity, history of depression, periods of unemployment, and job differed

significantly between the case and control groups ($P<0.05$). With increasing PRAL scores, the

number of smokers and individuals with a history of depression also increased significantly ($P<0.05$).

Table 1. Characteristics of study participants according to the patients and controls and quartiles of the PRAL score.

Variables	Health status			PRAL quartiles				P-value ^b
	Control	Case	P-value ^a	Q1	Q2	Q3	Q4	
Body mass index (kg/m ²)	26.43±5.51	26.45±5.13	0.98	27.25±5.72	27.14±6.02	25.69±4.71	25.63±4.79	0.08
Physical activity (MET-h/week)	38.58±4.93	36.94±5.45	0.006	38.75±4.38	37.72±5.57	38.81±6.02	38.88±4.28	0.05
Years of education	12.20±4.56	11.24±4.27	0.070	12.16±4.32	11.37±4.61	11.95±4.68	12.07±4.34	0.67
History of depression	22(10)	33(30)	<0.001	22(10)	33(30)	22(10)	33(30)	<0.001
Marital status								
Single	67(30.3)	32(29.1)	0.24	21(26.5)	20(24.1)	26(31.3)	32(36.6)	0.45
Married	143(64.7)	67(60.9)		56(68.3)	58(69.9)	51(61.4)	45(54.2)	
Divorced or widowed	11(5)	11(10)		5(6.1)	5(6)	6(7.2)	6(7.2)	
Smoking status								
Non smoker	209(94.6)	98(89.9)	0.11	80(76.6)	79(95.2)	75(90.4)	73(89)	<0.001
Smoker	12(5.4)	11(10.1)		2(2.4)	4(4.8)	8(9.6)	9(11)	
Periods of unemployment								
House worker ≤6 months in the last 5 years	98(44.3)	65(59.1)	0.007	44(53.7)	46(55.4)	39(47)	34(41)	0.23
More than 6 months in the last 5 years	104(47.1)	32(29.1)		6(7.3)	9(10.8)	5(6)	12(14.5)	
More than 6 months in the last 5 years	19(8.6)	13(11.8)		32(39)	28(33.7)	39(47)	37(44.6)	
Job								
Employee	42(19.4)	12(11.3)	0.014	18(22)	13(16.3)	11(13.6)	12(15.2)	0.10
Self-employed	32(14.8)	16(15.1)		8(9.8)	12(15)	11(13.6)	17(21.5)	
Students	38(17.6)	9(8.5)		7(8.5)	8(10)	17(21)	15(19)	
House worker & retired	104(48.1)	69(65.1)		49(59.8)	47(58.8)	42(51.9)	35(44.3)	

As characteristics are very similar according to the NEAP score, baseline characteristics are only presented according to the PRAL score quartiles; ^a: Obtained from Chi-squared test and independent t-test for categorical and continuous variables, respectively; ^b: Chi-squared test for qualitative variables and ANOVA test for quantitative variables. Continuous and categorical data are presented as mean ± SD and frequency (percentage), respectively.

Dietary intakes of participants

Table 2 presented the energy and dietary intakes of study participants based on PRAL quartiles. Individuals in the highest PRAL quartiles had significantly greater intakes of energy, protein, cholesterol, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, magnesium, zinc, and phosphorus ($P<0.05$), but significantly lower intakes of carbohydrates, fiber, calcium, potassium, vitamin A, vitamin C, vitamin B6, and vitamin B12 ($P<0.05$). Intake of fat ($P=0.36$) and sodium ($P=0.13$) did not differ

significantly across PRAL quartiles. Based on food group intake, participants with higher PRAL scores had significantly lower intakes of fruits and vegetables ($P<0.001$), whereas they had higher intakes of red meat ($P=0.008$) and refined grains ($P<0.001$). There were no significant differences in the intake of fish ($P=0.23$), dairy products ($P=0.08$), whole grains ($P=0.13$), legumes and nuts ($P=0.15$), sugars ($P=0.65$), sugar-sweetened beverages ($P=0.28$), or tea and coffee ($P=0.28$) across PRAL quartiles.

Table 2. Dietary daily intakes (mean±SD) of participants according to the PRAL quartiles.

Variables	Q1(N=82)	Q2(N=83)	Q3(N=83)	Q4(N=83)	P-value ^a
PRAL (mEq/d)	-49.73 ± 23.53	-19.45 ± 3.79	-7.49 ± 4.60	19.95 ± 25.29	<0.001
NEAP (mEq/d)	22.30 ± 5.15	29.70 ± 3.89	36.58 ± 3.44	51.20 ± 10.34	<0.001
Energy intake(kcal)	2872.6 ± 1209.5	2411.8 ± 843.5	2530 ± 953.6	3060.6 ± 1216.5	<0.001
Carbohydrate(g)	63.42 ± 0.08	61.57 ± 0.06	61.42 ± 0.07	58.85 ± 0.09	0.003
Protein(g)	13.70 ± 0.02	13.97 ± 0.02	14.35± 0.02	16.13± 0.09	0.01
Fat(g)	25.86 ± 0.07	26.87 ± 0.06	28.08 ± 0.07	27.78± 0.09	0.36
Fibre (g/d)	38.42 ± 14.72	24.98 ± 7.86	23.87 ± 8.14	26.02 ± 21.83	<0.001
Cholesterol (mg/d)	281.22 ± 171.87	258.84 ± 140.79	247.23 ± 116.19	327.09 ± 283.77	<0.001
SFA (mg/d)	24.48 ± 13.42	21.53 ± 8.97	22.04 ± 12.27	27.91 ± 17.57	0.009
MUFA (mg/d)	26.46 ± 16.19	23.49 ± 12.08	23.97 ± 13.51	29.56 ± 16.43	0.031
PUFA (mg/d)	21.97 ± 17.89	18.81 ± 10.84	18.97 ± 11.24	24.64 ± 15.54	0.024
Zinc (mg/d)	13.22 ± 5.39	11.24 ± 4.26	11.80 ± 4.23	16.10 ± 8.36	<0.001
Phosphorus (mg/d)	1774.75 ± 734.91	1498.32 ± 561.61	1559.73 ± 549.76	2050.12 ± 1008.65	<0.001
Potassium (mg/d)	6317.21 ± 2521.29	4374.48 ± 1343.74	4041.48 ± 1349.23	4084.45 ± 1608.45	<0.001
Calcium (mg/d)	1286.86 ± 463.54	1051.15 ± 390.96	1054.02 ± 435.91	1156.88 ± 483.75	0.002
Magnesium (mg/d)	508.32 ± 218.18	397.07 ± 137.06	403.56 ± 143.23	515.09 ± 364.49	<0.001
Sodium (mg/d)	3927.35 ± 1909.09	3801.80 ± 2013.87	3725.79 ± 2141.43	4444.20 ± 2542.79	0.13
Vitamin A (RAE/d)	2758.91± 2105.37	1523.93 ± 771.45	1536.64 ± 911.56	1349.35 ± 767.60	<0.001
Vitamin C (mg/d)	388.59± 196.43	218.65 ± 76.35	188.94 ± 91.10	146.90 ± 78.15	<0.001
Vitamin B6 (mg/d)	3.17 ± 2.02	2.16± 0.76	2.15 ± 0.75	2.42 ± 1.20	<0.001
Folate (µg/d)	710.06 ± 290.59	549.04 ± 204.30	559.02 ± 222.31	654.40 ± 307.98	<0.001
Vitamin B12 (mg/d)	8.57 ± 39.17	3.91 ± 3.18	3.80 ± 2.47	5.26 ± 5.29	0.37
Food groups (g/1000 kcal)					
Fruits	944.69 ± 448.73	520.66 ± 202.64	478.13 ± 258.63	362.74 ± 209.21	<0.001
Vegetables	537.38 ± 259.33	368.82 ± 166.08	313.59 ± 152.43	231.08 ± 128.01	<0.001
Red meat	24.66 ± 72.22	19.79 ± 17.54	25.17 ± 17.88	39.72 ± 65.03	0.008
Fish	8.45 ± 8.68	6.65 ± 9.70	10.13 ± 16.36	10.56 ± 17.10	0.23
Dairy	492.98 ± 249.22	408.29 ± 226.20	406.67 ± 297.79	405.43 ± 261.12	0.08
Legumes and nuts	81.17 ± 57.78	67.73 ± 49.17	65.94 ± 52.73	29.78 ± 25.53a	0.15
Whole grains	70.11 ± 97.49	64.05 ± 70.97	78.86 ± 107.67	102.34 ± 154.29	0.13
Refined grains	362.15 ± 28.76	380.67 ± 222.67	446.84 ± 244.37	608.40 ± 322.87	<0.001
Sugars	22.45 ± 66.25b	23.32 ± 19.02	22.36 ± 20.79	19.35 ± 15.72	0.65
Sugar-sweetened beverages (ml/day)	37.47 ± 61.09	66.46 ± 129.02	56.41 ± 120.89	62.16 ± 86.94	0.28
Tea and coffee	859.19 ± 510.70	887.20 ± 498	730.91 ± 598.87	656.59 ± 482.61	0.28

PRAL: Potential renal acid load; **NEAP:** net endogenous acid production; **SFA:** Saturated fatty acid; **MUFA:** Monounsaturated fatty acid; **PUFA:** Polyunsaturated fatty acid; As characteristics are very similar according to the NEAP score, baseline characteristics are only presented according to the PRAL score quartiles; ^a: ANOVA test was used.

Association between PRAL and NEAP and odds of depression

Crude and multivariate-adjusted odds ratios for the association between PRAL, NEAP, and depression are presented in **Table 3**. In the crude model, participants in the highest quartiles of PRAL and NEAP had 4.11- and 4.43-times higher odds of depression, respectively, compared with those in the lowest quartiles. This association remained significant after adjustment for energy intake, physical activity, history of depression, smoking status, periods of

unemployment, job, and BMI (Odds Ratio (OR)_{PRAL}: 3.52; 95%, CI:1.64 to 7.54, *P* for trend: <0.001) and OR_{NEAP}: 4.07; 95%, CI:1.86 to 8.89, *P* for trend: <0.001).

Discussion

The findings showed that higher dietary acid load indices (PRAL and NEAP) are associated with higher odds of depression in women. Furthermore, the authors observed that participants in the highest quartile of dietary acid load compared to the lowest quartile had a significantly

higher intake of red meat and refined grains. Also, fruit and vegetable consumption were significantly

lower in the highest quartile of dietary acid load versus the lowest quartile.

Table 3. The OR (95%CI) of depression across quartiles of PRAL and NEAP.

Dietary acid load score	Cases (N)	Crude	Model I	Model II
PRAL (mEq/day)				
<-27.2	27	1	1	1
-27.2 to -13.6	20	1.21 (0.58-2.52)	1.31 (0.62-2.77)	0.95 (0.42-2.14)
-13.5 to 1.61	30	2.16 (1.07-4.34)	2.30 (1.13-4.67)	2.59 (1.19-5.60)
≥2.21	43	4.11 (2.07-8.16)	4.03 (2.02-8.03)	3.52 (1.64-7.54)
<i>P-trend</i>		<0.001	<0.001	<0.001
NEAP (mEq/day)				
<27.2	16	1	1	1
27.2 to 27.9	20	1.31 (0.62-2.75)	1.33 (0.63-2.81)	1.14 (0.51-2.55)
34.4 to 37.7	31	2.45 (1.21-4.97)	2.38 (1.17-4.84)	2.12 (0.96-4.66)
≥42.9	43	4.43 (2.21-8.88)	4.23 (2.10-8.52)	4.07 (1.86-8.89)
<i>P-trend</i>		<0.001	<0.001	<0.001

PRAL: Potential renal acid load; **NEAP:** **OR:** Odds ratio; **NEAP:** Net endogenous acid production; **Model I:** Adjusted for energy intake; **Model II:** Model I + adjusted for physical activity, history of depression, smoking status, periods of unemployment, job and BMI; Logistic regression was used.

Few studies have investigated the relationship between dietary acid load and depression. A cross-sectional study on women in the age range of 20-50 showed that individuals who had higher dietary acid load scores had greater odds for stress, anxiety, and depression compared to lower scores (Mozaffari *et al.*, 2020). Results from Ausimmune longitudinal study (AusLong study) with a 10-year follow-up indicated that a higher dietary acid load in multiple sclerosis patients increased depression levels but not anxiety (Saul *et al.*, 2023). Wu *et al.* in a longitudinal study among breast cancer survivors demonstrated that women in the highest quartile of PRAL had a greater risk of depression versus women in the lowest quartile (Wu *et al.*, 2020). Findings from a study on 4378 persons (1909 male and 2469 female) reported that subjects in the highest category of the dietary acid load had a higher risk of anxiety and depression compared to those in the lowest (Milajerdi *et al.*, 2020). However, another research did not show a significant relationship between the intake of acidic foods and the risk of depression (Jans *et al.*, 2018). The results from a cohort study demonstrated that adherence to a high-protein diet might be a protective factor against depression in men while having a detrimental role in women (Wolfe *et al.*,

2011). The fact was that these disagreement results were related to differences in the sources of consumed proteins. It is suggested that a higher intake of animal proteins, as opposed to plant-based protein sources, is a major contributor to psychological disorders such as depression (Hosseinzadeh *et al.*, 2016).

The results demonstrated that women in the highest quartile of dietary acid load versus the lowest quartile had a significantly higher intake of red meat and refined grains. In a cross-sectional study on 3172 adults (18–55 years old), women in the highest quartile of refined grains intake compared with the first quartile, had higher odds of anxiety and depression (Sadeghi *et al.*, 2019). In a study by Mofrad *et al.* women in the highest quartile of red meat consumption compared with those in the lowest quartile had the highest prevalence of depressive symptoms, anxiety and stress (Mofrad *et al.*, 2021). In contrast, the results of a study published in 2021, showed no association between red meat consumption and mental disorders in women (Kazemi *et al.*, 2021). Moreover, Chi *et al.* in a prospective study, did not find any relationship between red meat and poultry consumption and the risk of depression in postmenopausal women (Chi *et al.*, 2016). Also,

the authors observed that fruit and vegetable consumption were significantly lower in the highest quartile of dietary acid load compared to the lowest quartile. Findings from the Taiwan Longitudinal Survey on Aging (TLSA) showed that fruit and vegetable consumption combined with physical activity was inversely related to the risk of depression (Fann *et al.*, 2022). Grases *et al.* in an observational retrospective study indicated no consumption of legumes, and low intake of fruit and vegetable were significantly correlated with depression (Grases *et al.*, 2019). Results of a study on women by 15 years of follow up showed that a higher consumption of fruit (≥ 4 servings) and vegetable (≥ 5 servings) was associated with lower odds of depression symptoms (Dharmayani *et al.*, 2022). The Australian Diabetes, Obesity and Lifestyle Study (AusDiab study) after 12 years of follow up, demonstrated that a diet rich in fruits and vegetables, especially yellow/orange/red and leafy green vegetables, lowered the odds of depressive symptoms (Radavelli-Bagatini *et al.*, 2021). Moreover, other cross-sectional studies on Finnish population and university students from 16 countries found no association between fruit and vegetable intake and depression (Allgöwer *et al.*, 2001, Hintikka *et al.*, 2005). Different findings might be due to diversity in the study population, using different measurement tools for the evaluation of psychopathy, and lack of adjusting some special dietary intakes (such as fiber and omega-3) as confounders (Crichton *et al.*, 2013, Jacka *et al.*, 2010).

Several pathways have been suggested to describe the positive association between dietary acid load and psychopathy: First, there is an acid-sensing ion channel-1a (ASIC1a) expressed in the nervous system, especially in the amygdala, which has a central role in the regulation of mood (Coryell *et al.*, 2007, Rauch *et al.*, 2003). Overexpression of ASIC1a in mice caused the fear condition, while ASIC1a inhibition had anti-anxiety and anti-depressant effects (Wemmie *et al.*, 2008). Therefore, a high dietary acid load produces high PH which might motivate ASIC1a and result in psychological disorders. Second,

metabolic acidosis can elevate the secretion of cortisol (Maurer *et al.*, 2002, Perez *et al.*, 1979). A large number of researches supported a direct relationship between cortisol and psychological disorders (Heinze *et al.*, 2016, Vives *et al.*, 2015, Zorn *et al.*, 2017). In addition, metabolic acidosis can increase the inflammatory parameters level (de Nadai *et al.*, 2013), so oxidative stress might result in higher risk of psychological disorders (Najjar *et al.*, 2013).

Consumption of refined grains augments the risk of inflammation, as a risk factor for psychopathy (Lopez-Garcia *et al.*, 2004). Moreover, refined grains lead to postprandial hyperglycemia and hyperinsulinemia (Bao *et al.*, 2011, Seaquist *et al.*, 2013) and this might reduce blood glucose concentrations to a level that is a threshold for the release of autonomic hormones such as cortisol, adrenaline, growth hormone and glucagon (Ludwig, 2002). Red meat contains a high amount of dietary fat which has contributed to causing depression in animals. In one study conducted on rats, those who had a high-fat diet were more likely to have depression (Abildgaard *et al.*, 2011). Arachidonic acid which is abundant in red meat, produces the inflammatory mediators named eicosanoids. In contrast, eicosapentaenoic acid (EPA) and docosahexaenoic acid (Dharmayani *et al.*) are known due to their anti-inflammatory effects. Therefore, the level of inflammation ascertains through the balance between Arachidonic acid and DHA or EPA. High consumption of red meat by changing the balance toward Arachidonic acid results in inflammation and finally depression (Shibata *et al.*, 2018). In addition, animal protein consumption caused an increase in some gut microbiota like *Bacteroides* entero, which are deemed to have a role in developing depression via the link between the gut and brain (Dash *et al.*, 2015).

The existing findings are focused on the particular nutrients within fruit and vegetables, which affect psychological health (Rooney *et al.*, 2013). B vitamins have effects on single-carbon metabolism and synthesis of neurotransmitters, including serotonin, catecholamines and other

monoamine neurotransmitters (Kennedy, 2016, Stough *et al.*, 2011). Moreover, the vital role of B vitamins in brain function is ascertained via a number of neuropsychiatric signs related to deficiencies in each of the B vitamins, like folate and vitamin B12 (Kennedy, 2016, Rao *et al.*, 2008). A recent investigation showed that the association between dietary patterns and depression is mediated by folate and vitamin B12 serum concentrations. This study reported that an increase in serum folate and vitamin B12 in healthy dietary pattern and a decrease in these two vitamins in unhealthy dietary pattern were associated with depression (Khosravi *et al.*, 2020). Also, fruits and vegetables are rich in antioxidants components and have a promising relationship with psychological well-being (Islam *et al.*, 2020). They lead to decrease oxidative stress and inflammation, potentially via the activation of transcription factors, including nuclear factor erythroid 2-related factor 2 (Nrf2) or nuclear factor κ B (NF κ B) (Kaulmann and Bohn, 2014).

Although this was the first case-control study that examined the relation of dietary acid load scores (PRAL and NEAP) among women, and results were adjusted for energy intake, physical activity, history of depression, smoking status, periods of unemployment, job and BMI; however, this study had some limitations. First, because this study only included women, the results cannot be generalized to both genders. Furthermore, the use of the FFQ questionnaire for participants' dietary assessment is inevitably subject to error. Due to the subjective nature of this method, over- or under-reporting of food intake cannot be predicted, therefore more detailed studies are required.

Conclusion

The results revealed that there is a significant inverse association between dietary acid load scores (PRAL and NEAP) and the odds of depression in women. However, more studies are needed to support these findings in the future.

Acknowledgments

The authors thank all the participants in this research study.

Authors' contributions

Darand M, Hosseinzadeh M and Khosravi M designed the study. Darand M, Ghorbani M, Arabi V and Hosseinzadeh M contributed to the statistical analysis, data interpretation and manuscript drafting. The final version of manuscript for submission was approved by all authors for submission.

Conflicts of interest

There were not any conflicts of interest.

Funding

This research has been supported by Tehran University of Medical Sciences & health Services grant No. 19374-161-03-91.

References

- Abildgaard A, et al. 2011. A high-fat diet exacerbates depressive-like behavior in the Flinders Sensitive Line (FSL) rat, a genetic model of depression. *Psychoneuroendocrinology*. **36** (5): 623-633.
- Abshirini M, et al. 2019. Dietary total antioxidant capacity is inversely associated with depression, anxiety and some oxidative stress biomarkers in postmenopausal women: a cross-sectional study. *Annals of general psychiatry*. **18** (1): 1-9.
- Allgöwer A, Wardle J & Steptoe A 2001. Depressive symptoms, social support, and personal health behaviors in young men and women. *Health psychology*. **20** (3): 223.
- Bahari H, et al. 2023. Dietary acid load, depression, and anxiety: results of a population-based study. *BMC psychiatry*. **23** (1): 679.
- Bao J, Atkinson F, Petocz P, Willett WC & Brand-Miller JC 2011. Prediction of postprandial glycemia and insulinemia in lean, young, healthy adults: glycemic load compared with carbohydrate content alone. *American journal of clinical nutrition*. **93** (5): 984-996.
- Buehlmeier J, Remer T, Frings-Meuthen P, Maser-Gluth C & Heer M 2016. Glucocorticoid activity and metabolism with NaCl-induced low-grade metabolic acidosis and oral alkalization: Results of two randomized controlled trials. *Endocrine*. **52**: 139-147.
- Chi SH, Wang JY & Tsai AC 2016. Combined

association of leisure-time physical activity and fruit and vegetable consumption with depressive symptoms in older Taiwanese: Results of a national cohort study. *Geriatrics & gerontology international*. **16** (2): 244-251.

Coryell MW, et al. 2007. Targeting ASIC1a reduces innate fear and alters neuronal activity in the fear circuit. *Biological psychiatry*. **62** (10): 1140-1148.

Crichton GE, Bryan J, Hodgson JM & Murphy KJ 2013. Mediterranean diet adherence and self-reported psychological functioning in an Australian sample. *Appetite*. **70**: 53-59.

Dash S, Clarke G, Berk M & Jacka FN 2015. The gut microbiome and diet in psychiatry: focus on depression. *Current opinion in psychiatry*. **28** (1): 1-6.

de Nadai TR, et al. 2013. Metabolic acidosis treatment as part of a strategy to curb inflammation. *International journal of inflammation*. **2013** (1): 601424.

Dedovic K, Duchesne A, Andrews J, Engert V & Pruessner JC 2009. The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. *Neuroimage*. **47** (3): 864-871.

Depression W 2017. Other common mental disorders: global health estimates. In *Geneva: World Health Organization*.

Dharmayani PNA, Mishra GD & Miharshahi S 2022. Fruit and vegetable consumption and depression symptoms in young women: results from 1973 to 1978 cohort of the Australian Longitudinal Study on Women's Health. *European journal of nutrition*. **61** (8): 4167-4178.

Esche J, et al. 2016. Higher diet-dependent renal acid load associates with higher glucocorticoid secretion and potentially bioactive free glucocorticoids in healthy children. *Kidney international*. **90** (2): 325-333.

Fann L-Y, et al. 2022. The Synergetic Impact of Physical Activity and Fruit and Vegetable Consumption on the Risk of Depression in Taiwanese Adults. *International journal of environmental research and public health*. **19**

(12): 7300.

Frassetto LA, Todd KM, Morris Jr RC & Sebastian A 1998. Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. *American journal of clinical nutrition*. **68** (3): 576-583.

FÚart C, et al. 2009. Adherence to a Mediterranean diet, cognitive decline, and risk of dementia. *JAMA*. **302** (6): 638-648.

Ghaffarpour M, Houshiar-Rad A & Kianfar H 1999. The manual for household measures, cooking yields factors and edible portion of foods. *Tehran: Nashre Olume Keshavarzy*. **7** (213): 42-58.

Ghassemzadeh H, Mojtabei R, Karamghadiri N & Ebrahimkhani N 2005. Psychometric properties of a Persian-language version of the Beck Depression Inventory-Second edition: BDI-II-PERSIAN. *Depression and anxiety*. **21** (4): 185-192.

Gonçalves DM, Stein AT & Kapczinski F 2008. Performance of the self-reporting questionnaire as a psychiatric screening questionnaire: a comparative study with structured clinical interview for DSM-IV-TR. *Cadernos de saude publica*. **24**: 380-390.

Grases G, Colom M, Sanchis P & Grases F 2019. Possible relation between consumption of different food groups and depression. *BMC psychology*. **7**: 1-6.

Heinze K, Lin A, Reniers RL & Wood SJ 2016. Longer-term increased cortisol levels in young people with mental health problems. *Psychiatry research*. **236**: 98-104.

Hintikka J, et al. 2005. Daily tea drinking is associated with a low level of depressive symptoms in the Finnish general population. *European journal of epidemiology*. **20** (4): 359-363.

Hosseinzadeh M, et al. 2016. Empirically derived dietary patterns in relation to psychological disorders. *Public health nutrition*. **19** (2): 204-217.

Islam MR, et al. 2020. Evaluation of serum amino acids and non-enzymatic antioxidants in drug-naïve first-episode major depressive disorder.

- BMC psychiatry*. **20** (1): 333.
- Jacka FN, et al.** 2010. Association of Western and traditional diets with depression and anxiety in women. *American journal of psychiatry*. **167** (3): 305-311.
- Jans G, et al.** 2018. Depression and anxiety: lack of associations with an inadequate diet in a sample of pregnant women with a history of bariatric surgery - A multicenter prospective controlled cohort study. *Obesity surgery*. **28** (6): 1629-1635.
- Kaulmann A & Bohn T** 2014. Carotenoids, inflammation, and oxidative stress—implications of cellular signaling pathways and relation to chronic disease prevention. *Nutrition research*. **34** (11): 907-929.
- Kazemi S, et al.** 2021. Red and white meat intake in relation to mental disorders in Iranian adults. *Frontiers in nutrition*. **8**: 710555.
- Kelishadi R, et al.** 2001. Assessment of physical activity of adolescents in Isfahan. *Journal of Shahrekord University of Medical Sciences*. **3** (2): 55-66.
- Kennedy DO** 2016. B vitamins and the brain: mechanisms, dose and efficacy—a review. *Nutrients*. **8** (2): 68.
- Khosravi M, et al.** 2020. The relationship between dietary patterns and depression mediated by serum levels of Folate and vitamin B12. *BMC psychiatry*. **20** (1): 63.
- Lange KW, et al.** 2017. The role of nutritional supplements in the treatment of ADHD: what the evidence says. *Current psychiatry reports*. **19** (2): 8.
- Lopez-Garcia E, et al.** 2004. Major dietary patterns are related to plasma concentrations of markers of inflammation and endothelial dysfunction. *American journal of clinical nutrition*. **80** (4): 1029-1035.
- Ludwig DS** 2002. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA*. **287** (18): 2414-2423.
- Maurer M, Muser J, Riesen W, Hulter H & Krapf R** 2002. Alkali-induced neutralization of the acidogenic western diet inhibits bone resorption independent of potassium intake and reduces cortisol secretion in humans. *Journal of the American Society of Nephrology*. **13**: 387A-387A.
- Milajerdi A, et al.** 2020. Dietary acid load in relation to depression and anxiety in adults. *Journal of human nutrition and dietetics*. **33** (1): 48-55.
- Mirmiran P, Esfahani FH, Mehrabi Y, Hedayati M & Azizi F** 2010. Reliability and relative validity of an FFQ for nutrients in the Tehran lipid and glucose study. *Public health nutrition*. **13** (5): 654-662.
- Mofrad MD, Mozaffari H, Sheikhi A, Zamani B & Azadbakht L** 2021. The association of red meat consumption and mental health in women: A cross-sectional study. *Complementary therapies in medicine*. **56**: 102588.
- Molendijk M, Molero P, Sánchez-Pedreño FO, Van der Does W & Martínez-González MA** 2018. Diet quality and depression risk: a systematic review and dose-response meta-analysis of prospective studies. *Journal of affective disorders*. **226**: 346-354.
- Mora F, Segovia G, Del Arco A, de Blas M & Garrido P** 2012. Stress, neurotransmitters, corticosterone and body–brain integration. *Brain research*. **1476**: 71-85.
- Mozaffari H, Daneshzad E, Surkan PJ & Azadbakht L** 2018. Dietary total antioxidant capacity and cardiovascular disease risk factors: a systematic review of observational studies. *Journal of the American College of Nutrition*. **37** (6): 533-545.
- Mozaffari H, Siassi F, Guilani B, Askari M & Azadbakht L** 2020. Association of dietary acid-base load and psychological disorders among Iranian women: a cross-sectional study. *Complementary therapies in medicine*. **53**: 102503.
- Murakami K & Sasaki S** 2010. Dietary intake and depressive symptoms: a systematic review of observational studies. *Molecular nutrition & food research*. **54** (4): 471-488.
- Najjar S, Pearlman DM, Alper K, Najjar A & Devinsky O** 2013. Neuroinflammation and

- psychiatric illness. *Journal of neuroinflammation*. **10** (1): 1-24.
- Noorbala AA, Yazdi SB, Yasamy M & Mohammad K** 2004. Mental health survey of the adult population in Iran. *British journal of psychiatry*. **184** (1): 70-73.
- Perez GO, Oster JR, Katz FH & Vaamonde CA** 1979. The effect of acute metabolic acidosis on plasma cortisol, renin activity and aldosterone. *Hormone research in paediatrics*. **11** (1): 12-21.
- Radavelli-Bagatini S, et al.** 2021. Association of habitual intake of fruits and vegetables with depressive symptoms: the AusDiab study. *European journal of nutrition*. **60**: 3743-3755.
- Rahmani J, Milajerdi A & Dorosty-Motlagh A** 2018. Association of the Alternative Healthy Eating Index (AHEI-2010) with depression, stress and anxiety among Iranian military personnel. *BMJ military health*. **164** (2): 87-91.
- Rao TS, Asha M, Ramesh B & Rao KJ** 2008. Understanding nutrition, depression and mental illnesses. *Indian journal of psychiatry*. **50** (2): 77.
- Rauch SL, Shin LM & Wright CI** 2003. Neuroimaging studies of amygdala function in anxiety disorders. *Annals of the New York Academy of Sciences*. **985** (1): 389-410.
- Remer T & Manz F** 1994. Estimation of the renal net acid excretion by adults consuming diets containing variable amounts of protein. *American journal of clinical nutrition*. **59** (6): 1356-1361.
- Rooney C, McKinley MC & Woodside JV** 2013. The potential role of fruit and vegetables in aspects of psychological well-being: a review of the literature and future directions. *Proceedings of the nutrition society*. **72** (4): 420-432.
- Sadeghi O, Hassanzadeh-Keshteli A, Afshar H, Esmailzadeh A & Adibi P** 2019. The association of whole and refined grains consumption with psychological disorders among Iranian adults. *European journal of nutrition*. **58**: 211-225.
- Saghafian F, et al.** 2018. Fruit and vegetable consumption and risk of depression: accumulative evidence from an updated systematic review and meta-analysis of epidemiological studies. *British journal of nutrition*. **119** (10): 1087-1101.
- Samieri C, et al.** 2008. Dietary patterns derived by hybrid clustering method in older people: association with cognition, mood, and self-rated health. *Journal of the American Dietetic Association*. **108** (9): 1461-1471.
- Sarris J, et al.** 2016. Adjunctive nutraceuticals for depression: a systematic review and meta-analyses. *American journal of psychiatry*. **173** (6): 575-587.
- Saul A, et al.** 2023. Long-term dietary acid load is associated with depression in multiple sclerosis, but less evidence was found with fatigue and anxiety. *Multiple sclerosis and related disorders*. **69**: 104415.
- Saveanu RV & Nemeroff CB** 2012. Etiology of depression: genetic and environmental factors. *Psychiatric clinics*. **35** (1): 51-71.
- Scialla JJ & Anderson CA** 2013. Dietary acid load: a novel nutritional target in chronic kidney disease? *Advances in chronic kidney disease*. **20** (2): 141-149.
- Sequist ER, et al.** 2013. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *Journal of clinical endocrinology & metabolism*. **98** (5): 1845-1859.
- Shibata M, et al.** 2018. Association between the ratio of serum arachidonic acid to eicosapentaenoic acid and the presence of depressive symptoms in a general Japanese population: the Hisayama Study. *Journal of affective disorders*. **237**: 73-79.
- Shooshtari MH, et al.** 2007. Structured clinical interview for DSM-IV (SCID Persian translation and cultural adaptation). *Iranian journal of psychiatry*. **2** (1): 46-48.
- Stough C, et al.** 2011. The effect of 90 day administration of a high dose vitamin B-complex on work stress. *Human psychopharmacology: Clinical and experimental*. **26** (7): 470-476.
- Vives AH, et al.** 2015. The relationship between cortisol, stress and psychiatric illness: New insights using hair analysis. *Journal of psychiatric research*. **70**: 38-49.

- Wemmie JA, Zha X-m & Welsh MJ** 2008. Acid-sensing ion channels (ASICs) and pH in synapse physiology. In *Structural and functional organization of the synapse* (ed. J. Hell and M. Ehlers), pp. 661-681. Springer: Boston.
- Whisman MA, Perez JE & Ramel W** 2000. Factor structure of the Beck Depression Inventory—Second Edition (BDI-ii) in a student sample. *Journal of clinical psychology*. **56** (4): 545-551.
- Wolfe AR, et al.** 2011. Dietary protein and protein-rich food in relation to severely depressed mood: a 10 year follow-up of a national cohort. *Progress in neuro-psychopharmacology and biological psychiatry*. **35** (1): 232-238.
- Wu T, Hsu F-C & Pierce JP** 2020. Acid-producing diet and depressive symptoms among breast cancer survivors: a longitudinal study. *Cancers*. **12** (11): 3183.
- Zorn JV, et al.** 2017. Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology*. **77**: 25-36.