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Dietary methyl donor micronutrients intake in relation to psychological disorders in adults

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Abstract

Previous investigations have mostly studied an individual methyl donor nutrient in relation to psychological disorders and the findings were inconsistent. We investigated the association of methyl donor micronutrients (folate, B_6, B_{12}, choline, betaine and methionine) with psychological disorders in Iranian adults. In this cross-sectional study, dietary intakes of 3299 adults were collected using a validated food frequency questionnaire. Methyl donor micronutrient score (MDMS) was calculated based on energy-adjusted deciles of each nutrient. Hospital Anxiety and Depression Scale (HADS) and General Health Questionnaire (GHQ), validated for Iranians, have been applied to assess depression, anxiety and psychological distress. Participants had a mean age of 36·3 ± 7·9 years, of whom 58·5 % were women. After considering potential confounders, adults in the top quartile of MDMS, compared to the bottom one, had decreased odds of anxiety (OR: 0·53, 95 % CI: 0·37, 0·75), depression (OR: 0·75, 95 % CI: 0·58, 0·97) and psychological distress (OR: 0·61, 95 % CI: 0·46, 0·80). Among women, the top quartile of MDMS was protectively associated with anxiety (OR: 0·60, 95 % CI: 0·40, 0·90), depression (OR: 0·68, 95 % CI: 0·50, 0·93) and psychological distress (OR: 0·53, 95 % CI: 0·38, 0·74). Overweight and obese subjects in the highest quartile of MDMS had a 67 %, 35 % and 53 % lower odds of anxiety (95 % CI: 0·20, 0·56), depression (95 % CI: 0·44, 0·94) and psychological distress (95 % CI: 0·31, 0·70), respectively. We found that high consumption of methyl donor micronutrients was related to a reduced odds of psychological disorders, especially in women and overweight or obese individuals.

Key words: **Methyl donor micronutrients: Psychological distress: Anxiety: Depression: Psychological disorders**

The prevalence of mental disorders including depression, anxiety and psychological distress, which correlated with low quality of life as well as mortality, is increasing drastically[1–3]. Mental disorders may have also detrimental effects on other chronic conditions[4]. Depression and anxiety have, respectively, a global prevalence of 4·7 % and 7·3 %[5,6]. Iranian national survey demonstrated that depression and anxiety affect 20·8 and 20·0 % of adults, respectively[7].

Along with genetic, lifestyle behaviors, including diet, might have roles in the incidence of anxiety and depression[8]. Earlier studies demonstrated the association between consumption of dairy products, vegetables, fruits, olive oil and phytochemicals and lower risk of depression[9–12]. Moreover, inadequate intake of micronutrients including Mg, K, Zn and B vitamins was positively associated with depression[13–15]. The association of these micronutrients with mental health might be explained by their contribution

Abbreviations: HADS, Hospital Anxiety and Depression Scale; MDMS, methyl donor micronutrient score; SEPAHAN, Studying the Epidemiology of Psycho-Alimentary Health and Nutrition.

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to neural function and synthesis of several neurotransmitters[16–18]. It seems that methyl donor nutrients play important roles in this process[19–22]. These nutrients including B_6, folate and B_{12} may be associated with mental disorders by their role in converting homocysteine to methionine, which is a precursor of S-adenosylmethionine[20]. It has been shown that S-adenosylmethionine is involved in the synthesis of key neurotransmitters including dopamine, serotonin and norepinephrine[20,23]. Moreover, increased levels of homocysteine in folate and cobalamin deficiency have also been associated with severe forms of depression[23,24]. However, data on the link between methyl donor nutrients and mental health are inconsistent. For instance, dietary folate intake was observed to be inversely related to a lower risk of depression in men, but not in women[22]. While intake of vitamin B_{12} was linked to depression in females, but not in males[22]. In the mentioned study, no evidence was found to link dietary B_6 consumption to depression both in men and women[22]. Conversely, a longitudinal study in Canadian adults demonstrated an inverse association between higher intakes of B_6 in women and B_{12} in men and odds of depression; however, no significant association was observed about folate intake[19]. Some other investigations have also revealed no substantial association between dietary consumption of B_6, folate and B_{12} and risk of depression[20,25]. In addition to B-vitamins, dietary choline and betaine as methyl donors have been inversely associated with inflammation[26], an underlying factor in depression and anxiety[27]. In a cross-sectional analysis, serum concentrations of choline was linked to a lower risk of anxiety, while no substantial relation was observed with depression[28].

The association between methyl donor micronutrients and common psychological disorders has primarily been investigated in western populations, with only a few studies performed in Asian countries. On the other hand, earlier studies have mostly investigated an individual methyl donor nutrient in relation to mental disorders and we are aware of no study linking the total score of these nutrients with psychological health. In addition, no study has yet explored the link between dietary consumption of choline, betaine and methionine, as methyl donor micronutrients and mental disorders. Furthermore, data regarding the association between methyl donor micronutrients and anxiety and psychological distress are insufficient. The current study was therefore aimed to investigate the association of methyl donor micronutrients (folate, B_6, B_{12}, choline, betaine and methionine) with psychological disorders (depression, anxiety and psychological distress) in Iranian adults.

Material and methods

Participants

The current cross-sectional study was performed on data from SEPAHAN (Studying the Epidemiology of Psycho-Alimentary Health and Nutrition) project. The original project was conducted on Iranian adults, who were working in fifty different health centres affiliated to Isfahan University of Medical Sciences. The main objective of SEPAHAN was to assess the prevalence of functional gastrointestinal disorders in relation to psychological disorders and lifestyle factors. The methodology of SEPAHAN project with complete information on characteristics of participants, study design and methods used to collect data was previously published[29–31]. Overall, the study was done in two different phases. Data about demographic characteristics as well as dietary intakes of individuals were collected in the first phase on a sample of 10 087; of them, 8691 people returned the completed questionnaires (response rate: 86·16 %). Detailed information on mental health and psychological disorders was gathered in the second phase, on 6239 adults (response rate: 61·85 %). Finally, after combining data from the two phases, full details on 4669 individuals were available. Participants who reported values outside the normal range of 800–4200 kcal/d for total energy intakes as well as those with missing data on dietary data or psychological characteristics were excluded from the current analysis. Therefore, data for 3299 adults (1368 men and 1931 women) were available for the present analysis. Each participant signed an informed written consent form. The SEPAHAN project was ethically approved by the Bioethics Committee of Isfahan University of Medical Sciences[29]. The present study was also approved by the Bioethics Committee of Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.MEDICINE.REC.1399·828).

Dietary intake assessment

Regular dietary intakes were evaluated through a validated Willet-format Dish-based 106-item semi-quantitative Food Frequency Questionnaire (DS-FFQ) which was specifically designed for Iranian adults[32]. Complete details about this questionnaire, including its validity has been described elsewhere[32]. The questionnaire included five different categories of foods and dishes: (1) mixed dishes (cooked or canned, twenty-nine items); (2) dairy products (dairies, cream and butter, nine items); (3) vegetables and fruits (twenty-two items); (4) grains and grain products (different types of bread, potato, biscuits and cakes, ten items) and (5) miscellaneous food items and beverages (including nuts, fast foods, sweets, beverages and desserts, thirty-six items). The questionnaire was completed by a self-administered method. Each questionnaire included a one-page written guideline for participants about completing the questionnaire. The study participants were asked to determine their dietary intakes of foods and mixed dishes in the preceding year based on nine multiple choice frequency response categories varying from 'never or less than once a month' to '12 or more times per day'. Considering the portion size given for each food and dish in the questionnaire and the reported frequency of that item, all foods and dishes were computed on a daily basis and trained nutritionists converted them to grams per day using household measures[33]. Then, all these items were entered to Nutritionist IV software to compute the daily intake of nutrients[34].

In a validation study of the applied DS-FFQ, a sample of 200 randomly selected subjects were asked to complete DS-FFQ at baseline and 6 months later[32]. Furthermore, three detailed dietary records were collected for each participant as a gold standard. Based on the information from this small validation study, we found that DS-FFQ is reasonably valid and reliable. For

instance, carbohydrate intake of participants from the DS-FFQ was correlated well with the average of 3-d dietary records ($r = 0{\cdot}81$). Also, our previous studies showed that the applied DS-FFQ has reasonable validity and reliability for assessment of foods and food patterns[35–37].

Calculation of methyl donor micronutrients intake

Dietary intake of individual methyl donor micronutrients including vitamin B_6, folate, vitamin B_{12}, betaine, choline and methionine was calculated using Nutritionist IV software. To construct a methyl donor micronutrient score (MDMS), individuals were categorised into energy-adjusted deciles of dietary consumption of each above-mentioned micronutrients. Then, participants received a score of 1 for each micronutrient if they were in the first decile and the score of 10 if they were in the last decile. Other deciles received the corresponding scores. Overall MDMS was calculated by summing up the scores each participant received for all methyl donor micronutrient. Therefore, the final MDMS varied from 6 to 60 for each participant.

Assessment of psychological disorders

Depression and anxiety were defined by using the Iranian validated version of Hospital Anxiety and Depression Scale (HADS)[38]. HADS is a fourteen-item scale that consists of two subscales: anxiety and depression. Each item includes a four-point scale; higher scores indicate higher level of anxiety and depression. Anxiety and depression score ranges between 0 and 21. Values of 8 or more for each subscale were defined as psychological disorders, and scores of 0–7 were considered as 'normal' in the current study[38]. A study performed among 167 Iranian adults revealed reasonable validity of the translated version of HADS for measurement of mental health[38].

Furthermore, psychological distress was screened by using the Iranian validated version of General Health Questionnaire (GHQ) that contained twelve items[39]. A four-point rating scale (less than usual, no more than usual, rather more than usual or much more than usual) belongs to each item. To calculate the psychological distress score for each subject, bimodal method was used in the current study (0–0–1–1). This method results in a range of 0 to 12 for General Health Questionnaire scores; higher scores are related to higher degree of psychological distress[39]. In the present study, having a score of 4 or more was defined as high psychological distress. The validity of General Health Questionnaire-12 was reasonable based on a preliminary study on 748 Iranian adults[40].

Assessment of covariates

Information on confounders including gender, age, education (non-university/university graduated), marital status (single/married), smoking status (current smoker/former smoker/non-smoker), house possession (non-owner/owner), family size (≤ 4/> 4 members), history of diabetes, use of anti-psychotic medications (including fluoxetine, imipramine or amitriptyline, nortriptyline, sertraline, fluvoxamine and citalopram) and dietary supplements (including intake of vitamins, Ca, Fe and other dietary supplements) was collected using a self-administered questionnaire. A simple and valid questionnaire named General Practice Physical Activity Questionnaire was applied to assess physical activity level of participants. This questionnaire categorises participants into two groups: physically active ($\geq$ 1 h/week) and physically inactive ($<$ 1 h/week). Data on anthropometric indices including height, weight and waist circumference (WC) were gathered using a self-administered questionnaire. BMI was calculated by dividing weight (kg) to height (m^2). A pilot study on 200 subjects examined the validity of self-reported anthropometric measures. The correlation coefficients for self-reported weight, height, WC and BMI *v.* measured values were 0·95 ($P < 0{\cdot}001$), 0·83 ($P < 0{\cdot}001$), 0·60 ($P < 0{\cdot}001$) and 0·70 ($P < 0{\cdot}001$), respectively[41].

Statistical methods

First, energy-adjusted intakes of each methyl donor micronutrient were calculated based on residual method. After constructing an MDMS, subjects were classified according to quartile cut-off points of MDMS. Then, data on socio-demographic variables were reported as means ± SDS and percentages for continuous and categorical variables, respectively. The differences across quartiles of MDMS were assessed using ANOVA and χ^2 test. To examine subjects' dietary intakes across quartiles of MDMS, we applied ANCOVA. Crude and multivariable-adjusted models were considered to evaluate the relationship between MDMS and psychological health. Age (continuous), gender (male/female), energy intake (continuous), physical activity ($<$ 1 h/week/$\geq$ 1 h/week), education (under diploma/diploma/above diploma/bachelors and above), house possession (yes/no), history of diabetes (yes/no) and use of anti-psychotic medications (yes/no) were adjusted in the first model. Further adjustment was done for dietary intakes of thiamin (continuous), Fe (continuous), fat (continuous) and BMI (continuous). All OR were obtained by considering the first quartile of MDMS as the reference. The quartiles of MDMS were considered as an ordinal variable in the logistic regression models to estimate the trend of odds ratios across these quartiles. A similar analysis was performed while we considered each unit increase in MDMS as the exposure. We also performed a sensitivity analysis by excluding subjects who were taking anti-psychotic medications. Moreover, to minimise the impact of reverse causality, we excluded participants with the highest 10 % scores of psychological disorders and repeated the analyses. Significant interactions between sex and BMI-groups and prevalence of psychological disorders were seen ($P < 0{\cdot}05$). Therefore, stratified analyses were done to obtain OR for psychological disorders in different categories of sex (male/female) and BMI ($<$ 25/$\geq$ 25 kg/m^2). In addition, we applied linear regression analysis in which MDMS and psychological disorders scores were treated as continuous variables. All statistical analyses were carried on using SPSS software (version 20; SPSS Inc). $P < 0{\cdot}05$ was considered as significant level.

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Table 1. General characteristics of study participants across quartiles of methyl donor intake (Number and percentages, mean values and standard deviations, *n* 3299)*

	Quartiles of energy-adjusted MDMS												
	Q_1 (*n* 890)			Q_2 (*n* 772)			Q_3 (*n* 804)			Q_4 (*n* 833)			
	%	Mean	SD	%	Mean	SD	%	Mean	SD	%	Mean	SD	*P*†
Age (years)		35·4	7·50		36·3	8·14		36·1	7·76		37·4	8·00	< 0·001
Weight (kg)		66·8	12·21		68·4	13·06		69·2	13·00		70·3	14·21	< 0·001
Body mass index (kg/m^2)		24·4	3·68		24·9	3·92		25·1	3·74		25·3	3·89	< 0·001
Female (%)	61·4			60·9			57·0			53·8			0·01
Married (%)	77·9			78·4			82·0			81·9			0·05
Education (%)(> diploma)	66·3			64·2			56·6			51·2			< 0·001
Family size (%)(> 4)	13·2			11·8			11·7			14·0			0·42
House possession (%)	54·2			58·1			58·2			62·8			0·01
Diabetes (%)	1·2			1·1			1·5			3·3			0·01
Anti-psychotic medications‡ (%)	6·0			5·0			6·3			4·9			0·50
Dietary supplements use§ (%)	32·0			30·5			31·0			26·5			0·06
Smokers (%)	12·7			12·6			14·3			15·5			0·25
Physically active (%)(≥ 1 h/week)	10·7			12·3			11·5			18·1			< 0·001
Overweight/Obese‖ (%)	41·2			46			48·9			50·6			0·01

* All values are means ± standard deviation (SD), unless indicated.
† Obtained from ANOVA for continuous variables and chi-square test for categorical variables.
‡ Anti-psychotic medications included the intake of fluoxetine, imipramine or amitriptyline, nortriptyline, sertraline, fluvoxamine and citalopram.
§ Dietary supplements included the intake of vitamins, calcium, iron and other dietary supplements.
‖ BMI ≥ 25.

Results

The study sample included 3299 individuals with a mean weight of 68·7 ± 13·18 kg and age range of 19–70 years; 58·5 % of study subjects were females. Table 1 indicates general characteristics of study participants according to energy-adjusted quartiles of methyl donor intake. Compared with the first quartile, individuals in the last quartile of MDMS had higher age, weight and BMI values. Also, those in the fourth quartile were less likely to be females, educated and being dietary supplement users, compared with individuals in the reference quartile. In contrast, participants in the top quartile were more likely to be married and house owners, as well as to have diabetes and high levels of physical activity compared with the bottom quartile.

Dietary intakes of selected nutrients and food groups of study participants across energy-adjusted categories of methyl donor intake are indicated in Table 2. Individuals in the last quartile of MDMS had lower intakes of energy, carbohydrates, thiamin and refined grains, compared with people in the first quartile. In contrast, they had higher consumption of proteins, fats, *n*-3 fatty acids, dietary fibre, Fe, red meat, vegetables, low-fat dairy and nut, soya and legumes.

As shown in Fig. 1, subjects in the top category of MDMS compared with the bottom level had a lower prevalence of anxiety (10·4 % *v.* 15·6 %; $P = 0·01$) and distress (18·6 % *v.* 26·9 %; $P < 0·001$), while the prevalence of depression was not significantly different across quartiles of MDMS ($P = 0·17$).

Multivariable-adjusted OR for anxiety, depression and distress across quartiles of methyl donor intake are reported in Table 3. Compared with the lowest quartile, subjects in the highest quartile of MDMS had 47 % decreased odds of anxiety, after adjusting for all of potential confounders (OR: 0·53, 95 % CI: 0·37, 0·75). The risk of depression was not significantly associated with MDMS categories in the crude model (OR: 0·82, 95 % CI: 0·67, 1·02). However, after controlling all potential confounders including dietary factors and BMI in the last model, those in the fourth category of MDMS had 25 % lower odds of depression (OR: 0·75, 95 % CI: 0·58, 0·97), in comparison with individuals in the first category. Subjects in the fourth quartile of MDMS, compared with reference level, had a decreased odds of distress both in the crude (OR: 0·62, 95 % CI: 0·49, 0·78) and fully adjusted model (OR: 0·61, 95 % CI: 0·46, 0·80). A significant trend was seen for all psychological disorders across quartiles of MDMS in fully adjusted model. Furthermore, each unit increase in MDMS was associated with a 3, 2 and 3 % decreased odds of anxiety (OR: 0·97, 95 % CI: 0·95, 0·98), depression (OR: 0·98, 95 % CI: 0·97, 0·99) and psychological distress (OR: 0·97, 95 % CI: 0·96, 0·98), respectively. When we excluded participants who were taking antipsychotic medications (*n* 187), findings did not significantly change for anxiety (OR for Q4 *v.* Q1:0·47, 95 % CI: 0·32, 0·68), depression (OR for Q4 *v.* Q1:0·73, 95 % CI: 0·56, 0·96) and psychological distress (OR for Q4 *v.* Q1:0·58, 95 % CI: 0·43, 0·77). Again, each unit increase in MDMS was significantly associated with a reduced odds of anxiety (OR: 0·96, 95 % CI: 0·95, 0·98), depression (OR: 0·98, 95 % CI: 0·97, 0·99) and distress (OR: 0·97, 95 % CI: 0·96, 0·98). After excluding participants in the top 10 % of each outcome score, findings remained significant for psychological distress, but they disappeared for anxiety and depression (online Supplemental Table 1).

Multivariable-adjusted OR for psychological disorders across different categories of methyl donor intake, stratified by gender, are presented in Table 4. After controlling confounding variables, the highest level of MDMS, compared with the lowest level, was significantly linked to 68 % reduced odds of anxiety in males (OR: 0·32, 95 % CI: 0·15, 0·68). However, no relation was observed between MDMS and depression or distress among male participants Women in the highest quartile of MDMS, compared with those in the lowest quartile, had 40, 32 and 47 %

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Table 2. Multivariable-adjusted intakes of selected nutrients and food groups of study participants across quartiles of methyl donor intake (Mean values and standard errors, *n* 3299)*

	Quartiles of energy-adjusted MDMS								
	Q_1 (*n* 890)		Q_2 (*n* 772)		Q_3 (*n* 804)		Q_4 (*n* 833)		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	*P*†
Energy (Kcal/d)	2585·5	28·52	2332·3	30·44	2242·6	29·82	2349·1	29·48	< 0·001
Methyl donor nutrients:									
Vitamin B_6 (mg/d)	1·7	0·01	2·0	0·01	2·1	0·01	2·3	0·01	< 0·001
Folate (mcg/d)	586·4	4·29	582·5	4·54	563·1	4·46	569·4	4·40	< 0·001
Vitamin B_{12} (mcg/d)	2·1	0·03	2·7	0·03	3·2	0·03	3·8	0·03	< 0·001
Methionine (mg/d)	1·1	0·01	1·4	0·01	1·5	0·01	1·7	0·01	< 0·001
Choline (mg/d)	211·3	2·06	262·3	2·19	299·3	2·15	346·7	2·12	< 0·001
Betaine (mg/d)	136·1	4·76	126·9	5·05	105·7	4·96	99·0	4·89	< 0·001
Other nutrients:									
Proteins (% of energy)	12·8	0·06	14·4	0·07	15·5	0·07	16·8	0·06	< 0·001
Fats (% of energy)	34·7	0·22	36·6	0·23	38·9	0·23	39·9	0·22	< 0·001
Carbohydrates (% of energy)	53·8	0·25	50·5	0·26	47·2	0·26	44·9	0·25	< 0·001
Dietary fibre (g/d)	21·3	0·20	22·9	0·21	22·9	0·21	23·5	0·21	< 0·001
n-3 fatty acids (g/d)	1·7	0·03	1·8	0·03	1·8	0·03	1·8	0·03	0·01
Vitamin B_1 (mg/d)	2·0	0·02	1·9	0·02	1·8	0·02	1·7	0·02	< 0·001
Fe (mg/d)	18·0	0·12	17·9	0·12	17·4	0·12	17·2	0·12	< 0·001
Food groups:									
Red meat (g/d)	57·7	1·34	74·7	1·42	88·9	1·39	94·3	1·37	< 0·001
Whole grains (g/d)	45·3	2·68	45·6	2·84	42·8	2·79	36·7	2·75	0·08
Refined grains (g/d)	457·7	5·60	406·8	5·93	369·3	5·83	333·8	5·74	< 0·001
Fruit (g/d)	308·5	8·07	333·1	8·55	315·6	8·40	315·6	8·28	0·20
Vegetables (g/d)	183·7	3·88	224·2	4·11	252·2	4·04	300·1	3·98	< 0·001
Nuts, soya and legumes (g/d)	45·8	1·24	53·6	1·31	59·4	1·29	70·8	1·27	< 0·001
Low-fat dairy (g/d)	220·5	8·54	288·0	9·04	356·0	8·89	477·0	8·76	< 0·001
High-fat dairy (g/d)	14·8	0·61	15·0	0·65	15·2	0·64	13·9	0·63	0·44

* All values are means ± standard error (SE); energy intake is adjusted for age and gender; all other values are adjusted for age, gender and energy intake.
† Obtained from ANCOVA.

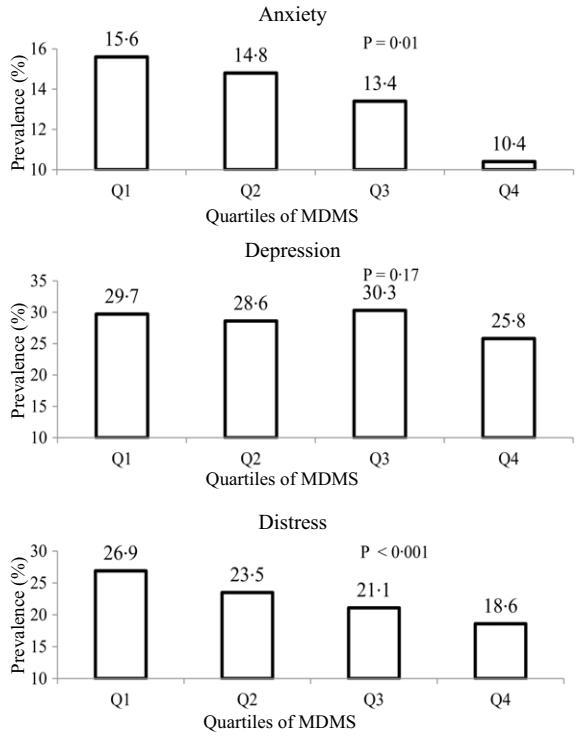

Fig. 1. The prevalence of anxiety, depression and distress in study participants across quartiles of MDMS.

decreased odds of anxiety (OR: 0·60, 95 %CI: 0·40–0·90), depression (OR: 0·68, 95 % CI: 0·50, 0·93) and psychological distress (OR: 0·53, 95 % CI: 0·38, 0·74), respectively.

Multivariable-adjusted OR for psychological disorders across different categories of methyl donor intake, stratified by BMI status, are reported in Table 5. Among normal-weight subjects (BMI < 25 kg/m^2), anxiety, depression and distress were not significantly associated with MDMS in multivariable-adjusted model. In participants with overweight and obesity (BMI ≥ 25 kg/m^2), the top quartile of MDMS compared with the bottom quartile was respectively associated with 67, 35 and 53 % lower odds of anxiety (OR: 0·33, 95 % CI: 0·20, 0·56), depression (OR: 0·65, 95 % CI: 0·44, 0·94) and distress (OR: 0·47, 95 % CI: 0·31, 0·70) in the multivariable-adjusted model.

Based on linear regression analysis, inverse significant associations were observed between each unit increase in MDMS, as a continuous variable, and score of all psychological disorders (Table 6). Similar results were found when we considered MDMS quartiles as the exposure of interest.

Discussion

The current cross-sectional study showed that consumption of methyl donor micronutrients was inversely linked to psychological disorders in Iranian adults. These associations were independent of several potential confounders. Stratified analysis by

Table 3. Multivariable- adjusted odds ratio for anxiety, depression and distress across quartiles of methyl donor intake* (Odd ratios and 95 % confidence intervals)

	Quartiles of energy-adjusted MDMS							Per unit increase in MDMS	
	Q_1	Q_2		Q_3		Q_4			
	OR	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}	OR	95 % CI
Whole population										
Anxiety										
Participants (*n*)/Cases (*n*)	890/139	772/114		804/108		833/87				
Crude	1·00	0·94	0·72, 1·23	0·84	0·64, 1·10	0·63	0·47, 0·84	< 0·001	0·98	0·97, 0·99
Model 1	1·00	0·87	0·65, 1·18	0·75	0·55, 1·02	0·57	0·41, 0·79	< 0·001	0·97	0·96, 0·99
Model 2	1·00	0·83	0·61, 1·14	0·74	0·54, 1·02	0·53	0·37, 0·75	< 0·001	0·97	0·95, 0·98
Depression										
Participants (*n*)/Cases (*n*)	890/264	772/221		804/244		831/214				
Crude	1·00	0·95	0·77, 1·18	1·03)	0·84, 1·27	0·82	0·67, 1·02	0·15	0·99	0·98, 1·00
Model 1	1·00	0·98	0·78, 1·24	1·07)	0·85, 1·35	0·82	0·65, 1·05	0·21	0·99	0·98, 1·00
Model 2	1·00	0·96	0·75, 1·22	0·99	0·78, 1·27	0·75	0·58, 0·97	0·05	0·98	0·97, 0·99
Distress										
Participants (*n*)/Cases (*n*)	903/243	786/185		823/174		850/158				
Crude	1·00	0·84	0·67, 1·04	0·73	0·58, 0·91	0·62	0·49, 0·78	< 0·001	0·98	0·97, 0·99
Model 1	1·00	0·88	0·69, 1·12	0·71	0·55, 0·91	0·68	0·53, 0·88	0·001	0·98	0·97, 0·99
Model 2	1·00	0·86	0·67, 1·11	0·69	0·53, 0·89	0·61	0·46, 0·80	< 0·001	0·97	0·96, 0·98
After excluding anti-psychotic medication users†										
Anxiety										
Participants (*n*)/Cases (*n*)	837/120	735/100		752/91		792/67				
Crude	1·00	0·94	0·71, 1·25	0·82	0·61, 1·10	0·55	0·40, 0·76	< 0·001	0·98	0·96, 0·99
Model 1	1·00	0·89	0·65, 1·21	0·77	0·56, 1·07	0·49	0·34, 0·70	< 0·001	0·97	0·95, 0·98
Model 2	1·00	0·88	0·63, 1·22	0·78	0·56, 1·10	0·47	0·32, 0·68	< 0·001	0·96	0·95, 0·98
Depression										
Participants (*n*)/Cases (*n*)	837/234	735/200		753/213		790/190				
Crude	1·00	0·96	0·77, 1·20	1·02	0·82, 1·27	0·82	0·65, 1·02	0·13	0·99	0·98, 1·00
Model 1	1·00	0·98	0·77, 1·25	1·07	0·84, 1·37	0·81	0·63, 1·04	0·19	0·99	0·98, 1·00
Model 2	1·00	0·96	0·74, 1·23	0·99	0·77, 1·28	0·73	0·56, 0·96	0·04	0·98	0·97, 0·99
Distress										
Participants (*n*)/Cases (*n*)	849/214	747/164		771/150		808/137				
Crude	1·00	0·84	0·66, 1·05	0·72	0·57, 0·91	0·61	0·48, 0·77	< 0·001	0·98	0·96, 0·99
Model 1	1·00	0·86	0·66, 1·10	0·70	0·54, 0·91	0·65	0·50, 0·84	< 0·001	0·98	0·96, 0·99
Model 2	1·00	0·85	0·65, 1·10	0·70	0·51, 0·88	0·58	0·43, 0·77	< 0·001	0·97	0·96, 0·98

* All values are OR and 95 % CI. Model 1: Adjusted for age, gender, energy intake, education, house possession, physical activity, diabetes and intake of anti-psychotic medications. Model 2: More adjustments for dietary intakes of Fe, thiamin, fat and BMI.
† Intake of anti-psychotic medications was not included in the models.

gender revealed that methyl donor micronutrients intake was linked with anxiety, depression and psychological distress in females. However, no association was found between methyl donor micronutrients intake with depression and psychological distress in males after considering confounding variables. We also found a significant inverse relationship in overweight or obese individuals; but not in normal-weight participants. To the best of our knowledge, we were the first to explore the association between a total dietary score of methyl donor micronutrients and psychological disorders in adults.

The prevalence of psychological disorders, especially depression and anxiety, has drastically increased worldwide[1,3]. These mental disorders have become global health challenges along with other chronic conditions such as diabetes[42], CVD[43], obesity[44] and cancers[45]. In addition, dietary intake as an important approach to prevent psychological disorders has a great interest. In the present investigation, we found methyl donor micronutrients intake to be inversely associated with psychological disorders, especially in women and in overweight and obese subjects. Therefore, consuming dietary sources of these nutrients could be an efficient recommendation to reduce psychological disorders.

Methyl donor micronutrients are widely distributed across foods. For instance, animal foods such as meats (including red meat, white meat and fish), eggs and dairy products are primary sources of vitamin B_6, B_{12}, methionine and choline[46–48]. Furthermore, fresh fruits and green leafy vegetables and legumes are rich in folate[49]. Betaine is highly found in wheat bran, wheat germ, spinach and wheat bread[46]. Other foods might also contain some amounts of these nutrients; so, the overall intake of these nutrients came from the whole diet. In this case, when the exposure is a combination of several nutrients, adjustment for other nutrients might help exploring the independent associations between methyl donor micronutrients and psychological disorders, but including the overall diet quality in the multivariable-adjusted models might result in over-adjustment. This is why we did adjustments for nutrients (thiamin, iron and fats), but not for foods or overall diet quality in our analysis.

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Table 4. Multivariable- adjusted odds ratio for anxiety, depression and distress across quartiles of methyl donor intake, stratified by gender* (Odd ratios and 95 % confidence intervals)

	Quartiles of energy-adjusted MDMS							
	Q_1	Q_2		Q_3		Q_4		
	OR	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}
Men								
Anxiety								
Participants (*n*)/Cases (*n*)	341/35	301/32		341/31		385/19		
Crude	1·00	1·04	0·63, 1·73	0·87	0·53, 1·45	0·45	0·25, 0·81	0·01
Multivariable-adjusted†	1·00	1·00	0·54, 1·87	0·63	0·32, 1·21	0·32	0·15, 0·68	0·002
Depression								
Participants (*n*)/Cases (*n*)	341/70	300/61		341/78		385/76		
Crude	1·00	0·99	0·67, 1·45	1·15	0·80, 1·65	0·95	0·66, 1·37	0·98
Multivariable-adjusted†	1·00	1·06	0·66, 1·71	1·21	0·76, 1·93	0·87	0·54, 1·41	0·66
Distress								
Participants (*n*)/Cases (*n*)	349/64	307/60		354/54		393/55		
Crude	1·00	1·08	0·73, 1·60	0·80	0·54, 1·19	0·73	0·49, 1·07	0·05
Multivariable-adjusted†	1·00	1·41	0·87, 2·28	0·82	0·49, 1·38	0·82	0·49, 1·37	0·17
Women								
Anxiety								
Participants (n)/Cases (*n*)	549/104	471/82		463/77		448/68		
Crude	1·00	0·90	0·66, 1·24	0·85	0·62, 1·18	0·77	0·55, 1·07	0·11
Multivariable-adjusted†	1·00	0·78	0·54, 1·12	0·75	0·52, 1·10	0·60	0·40, 0·90	0·02
Depression								
Participants (*n*)/Cases (*n*)	549/194	472/160		463/166		446/138		
Crude	1·00	0·94	0·72, 1·22	1·02	0·79, 1·32	0·82	0·63, 1·07	0·26
Multivariable-adjusted†	1·00	0·92	0·69, 1·23	0·89	0·66, 1·20	0·68	0·50, 0·93	0·02
Distress								
Participants (*n*)/Cases (*n*)	554/179	479/125		469/120		457/103		
Crude	1·00	0·74	0·56, 0·97	0·72	0·55, 0·95	0·61	0·46, 0·81	0·001
Multivariable-adjusted†	1·00	0·71	0·52, 0·96	0·62	0·46, 0·85	0·53	0·38, 0·74	< 0·001

* All values are OR and 95 % CI.
† Adjusted for age, energy intake, education, house possession, physical activity, diabetes, intake of anti-psychotic medications, dietary intakes of Fe, thiamin, fat and BMI.

Based on our findings, a higher intake of methyl donor micronutrients was protectively related to odds of depression, especially in females. Similarly, a cross-sectional study revealed a reduced odds of depression in relation to the highest consumption of vitamin B_{12} only in women[22]. It might be due to female gonadal hormones, which could alter the monoamines' activity in the brain[50]. A longitudinal study revealed that high consumption of vitamin B_6 and B_{12} was related to a lower possibility of depression in males and females, respectively[19]. On the other hand, another longitudinal study revealed that dietary intakes of folate, vitamin B_6 and B_{12} were not associated with depression in older adults in both genders[25]. However, considering combined dietary and supplemental intakes, 2 % decreased risk of depression was found by each 10 mg and 10 mcg increment intake of vitamin B_6 and B_{12}, respectively[25]. A cohort study on Finnish adults has also revealed an inverse association between folate intake and depression, while no significant relation was seen for vitamin B_{12} in this regard[51]. Moreover, a cross-sectional investigation reported no significant link for plasma concentrations of choline and odds of depression[28]. A meta-analysis of randomised controlled trials has additionally revealed that folate and vitamin B_{12} supplementation diminished depressive symptoms severity in long-term treatments[52].

Few previous studies have examined the association between dietary intakes of each methyl donor micronutrient with anxiety. We documented that methyl donor micronutrients intake was significantly associated with anxiety in both genders. This association was stronger in men. This might be explained by higher smoking prevalence among men, which is responsible for a decline in bioavailability of B vitamins[53]. In accordance with our findings, a cross-sectional study on a general adult population in Norway revealed that low plasma levels of choline were linked with 33 % greater odds of anxiety[28]. Conversely, Mozaffari *et al.* in their cross-sectional investigation found no association between dietary consumption of vitamin B_6, folate and cobalamin and possibility of anxiety in women[54].

Evidence regarding the association between methyl donors and psychological distress is scarce. Our investigation showed that higher methyl donor micronutrient intake was inversely associated with high psychological distress. However, after stratified analysis by sex, this association remained significant only in women. A cohort study showed a significant linkage between lower dietary intake of vitamin B_{12} and increased risk of psychological distress at the age of 53 years[21]. However, other B vitamins were not associated with psychological distress in this study[21]. A cross-sectional study on Iranian women found that higher intake of vitamin B_{12} could double the odds of psychological distress[54].

The current discrepancies among findings of previous studies could be a result of differences in studied populations, study designs, measurement tools, as well as different confounders that have been considered in the analyses. General characteristics of studied participants in prior reports were widely varied. Some studies were conducted in

Table 5. Multivariable- adjusted odds ratio for anxiety, depression and distress across quartiles of methyl donor intake, stratified by BMI* (Odd ratios and 95 % confidence intervals)

	Quartiles of energy-adjusted MDMS							
	Q_1	Q_2		Q_3		Q_4		
	OR	OR	95 % CI	OR	95 % CI	OR	95 % CI	P_{trend}
BMI < 25 (kg/m^2)								
Anxiety								
Participants (*n*)/Cases (*n*)	508/71	398/52		400/48		397/48		
Crude	1·00	0·93	0·63, 1·36	0·84	0·57, 1·24	0·85	0·57, 1·25	0·34
Multivariable-adjusted†	1·00	0·94	0·61, 1·45	0·79	0·50, 1·23	0·78	0·49, 1·24	0·21
Depression								
Participants (*n*)/Cases (*n*)	508/152	399/118		399/113		395/104		
Crude	1·00	0·98	0·74, 1·31	0·93	0·69, 1·24	0·84	0·62, 1·12	0·22
Multivariable-adjusted†	1·00	1·10	0·79, 1·52	0·96	0·68, 1·34	0·83	0·59, 1·19	0·26
Distress								
Participants (*n*)/Cases (*n*)	515/135	404/99		406/88		404/81		
Crude	1·00	0·91	0·68, 1·23	0·78	0·57, 1·06	0·71	0·52, 0·97	0·02
Multivariable-adjusted†	1·00	0·94	0·67, 1·32	0·70	0·49, 1·00	0·72	0·50, 1·05	0·03
BMI ≥ 25 (kg/m^2)								
Anxiety								
Participants (*n*)/Cases (*n*)	357/63	337/54		375/58		403/36		
Crude	1·00	0·89	0·60, 1·33	0·85	0·58, 1·26	0·46	0·30, 0·71	0·001
Multivariable-adjusted†	1·00	0·66	0·42, 1·05	0·62	0·39, 0·98	0·33	0·20, 0·56	< 0·001
Depression								
Participants (*n*)/Cases (*n*)	357/105	336/94		376/125		403/103		
Crude	1·00	0·93	0·67, 1·30	1·20	0·87, 1·63	0·82	0·60, 1·13	0·50
Multivariable-adjusted†	1·00	0·78	0·53, 1·13	1·00	0·70, 1·45	0·65	0·44, 0·94	0·07
Distress								
Participants (*n*)/Cases (*n*)	361/100	344/79		388/81		413/67		
Crude	1·00	0·78	0·55, 1·09	0·69	0·49, 0·96	0·51	0·36, 0·73	< 0·001
Multivariable-adjusted†	1·00	0·72	0·49, 1·06	0·61	0·41, 0·91	0·47	0·31, 0·70	< 0·001

* All values are OR and 95 % CI.
† Adjusted for age, energy intake, education, house possession, physical activity, diabetes, intake of anti-psychotic medications, dietary intakes of Fe, thiamin and fat.

Table 6. Linear association of methyl donor intake (as a continuous variable) with anxiety, depression and distress scores (as continuous variables)* (Coefficient values and 95 % confidence intervals)

	Per 1 unit of MDMS†				Per 1 quartile of MDMS‡			
	β	95 % CI	*P*	R^2	β	95 % CI	*P*	R^2
Anxiety score								
Crude	–0·03	–0·05, –0·02	< 0·001	0·005	–0·18	–0·29, –0·07	0·001	0·003
Model 1	–0·03	–0·05, –0·02	< 0·001	0·10	–0·17	–0·28, –0·06	0·004	0·09
Model 2	–0·05	–0·06, –0·03	< 0·001	0·10	–0·24	–0·36, –0·12	< 0·001	0·10
Depression score								
Crude	–0·03	–0·04, –0·01	< 0·001	0·004	–0·15	–0·25, –0·05	0·004	0·003
Model 1	–0·03	–0·05, –0·02	< 0·001	0·10	–0·15	–0·25, –0·05	0·004	0·10
Model 2	–0·04	–0·06, –0·02	< 0·001	0·11	–0·20	–0·32, –0·09	< 0·001	0·11
Distress score								
Crude	–0·03	–0·04, –0·02	< 0·001	0·007	–0·18	–0·27, –0·10	< 0·001	0·006
Model 1	–0·02	–0·04, –0·01	< 0·001	0·07	–0·15	–0·24, –0·06	0·001	0·07
Model 2	–0·03	–0·05, –0·02	< 0·001	0·08	–0·18	–0·28, –0·09	< 0·001	0·07

* Model 1: Adjusted for age, energy intake, education, house possession, physical activity, diabetes, intake of anti-psychotic medications. Model 2: More adjustments for dietary intakes of Fe, thiamin, fat and BMI.
† MDMS was considered as a continuous variable.
‡ Quartiles of MDMS were considered as an ordinal variable.

elders[19,25], which have poor vitamin B_{12} absorption and thus lower blood levels than younger adults[55]. It has been hypothesised that the association between folate, B_{12} and B_6 and depression could be stronger when study participants had deficiency or insufficiency of these vitamins[22,51,56,57]. For instance, Finnish adults have low consumption of folate sources (i.e. vegetables) and higher dietary proportions of dairy and meat, as rich sources of vitamin B_{12}[51]; therefore, only folate found to be associated with depression in this population[51]. It is also worth mentioning that folate status (intake or serum level) was associated with depression mostly in the nations that flour fortification was not mandatory[19]. Furthermore, once folate levels attain suboptimal levels, additional intakes do not obtain further benefits[22].

Reverse causation is a possible concern in epidemiologic studies, in particular when the study design is cross-sectional. This should be taken into account when interpreting the findings. The reverse causation hypothesises that the association might be in the reverse direction, for which the study is conducted[58]. For instance, depressive symptoms might cause a change in the dietary intakes. Few studies explored the role of reverse causation for the association between dietary intakes and mental disorders. A longitudinal study confirmed bidirectional relations between food group intakes and depression[59]. It has been shown that depressive symptoms are linked to changes in meat, dairy product and vegetable consumption[59]. A cohort study has also revealed that low blood levels of folate were in relation to depression at baseline, but no association was indicated with the incidence of depression after 2 years of follow-up[60]. However, another cohort study did not observe major changes in B-vitamin intake and thus did not support the reverse causality hypothesis[61]. Given that depressed or anxious individuals might change their dietary intake, we excluded severe cases, i.e. those in the top 10 % of each outcome score, from the analysis to minimise the possible impact of reverse causality. After this exclusion, our results indicated that methyl donor micronutrients intake was inversely associated with psychological distress, but not with anxiety and depression. A plausible explanation for this finding might be a few number of remaining cases with anxiety and depression in the analysis that would result in wide confidence intervals and thus non-significant associations.

Several mechanisms could clarify the inverse association between methyl donor micronutrients intake and mental disorders. Vitamin B_6 and B_{12} are key cofactors for converting homocysteine to cysteine and then methionine[20]. Methionine is a precursor of S-adenosylmethionine, which is a crucial co-substrate in the methylation process and synthesis of neurotransmitters including dopamine, serotonin and norepinephrine[62]. Therefore, pyridoxine and cobalamin deficiency might result in reduced production of these neurotransmitters, as well as accumulation of homocysteine in the body. These consequences could in turn lead to development of psychological disorders[63,64]. Hyperhomocysteinemia might alter neurotransmitters' activity by inhibiting one-carbon methylation, which may result in depression[65]. In additional, homocysteine accumulation in the body might result in mitochondrial dysfunction, apoptosis of dopaminergic neurons and oxidative stress; which in turn could lead to depression[66]. Furthermore, choline acts as a precursor in the synthesis of brain acetylcholine, which contributes to the better cognitive function[67]. Impaired cognition might make daily task hard to do, which sequentially leads to the manifestation of anxiety symptoms[68].

The present study has several strengths and weaknesses. This was the first study evaluating the relation between dietary intake of a combination of methyl donor micronutrients and mental disorders. Also, a large population of adults was studied through the use of validated questionnaires for assessment of dietary intakes, psychological disorders and physical activity. Several potential confounders were also considered in the analysis. Nevertheless, some limitations should be acknowledged when interpreting our findings. We cannot infer a causal relationship between methyl donor micronutrients intake and psychological disorders due to the cross-sectional design of our study. Therefore, further prospective cohort studies are needed to establish causality. Since we applied a self-administered FFQ, measurement errors and misclassification of participants were inevitable, although a validated FFQ was used and this method of data collection could facilitate study performance and increase response rate. Finally, the study was conducted on non-academic staff of a medical university with a wide range of socio-economic status; so, extrapolation of our findings to general population should be made with cautious.

In conclusion, high intake of methyl donor micronutrients was found to be associated with a reduced odds of psychological disorders, especially in women and overweight or obese individuals. Therefore, more consumption of dietary sources of methyl donor micronutrients could be an approach to prevent psychological disorders. Further prospective studies are required to affirm these findings.

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Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114521003081

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