

# The association between dietary acid load and the migraine odds

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## Research article

**Keywords:** Dietary acid load, Headache, Migraine, Nitric oxide, Inflammation

**DOI:** <https://doi.org/10.21203/rs.3.rs-56657/v1>

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# Abstract

**Background:** According to previous evidence, it has been shown that high acidic load in human body could affect inflammatory factors and the nitric oxide pathway. On the other hand, these factors are thought to play a role in initiation of migraine attacks. Therefore, we aimed to explore the association between dietary acid load and the odds of migraine in a case-control study.

**Methods:** The migraine group (n=514, diagnosed according to the ICHDIII criteria) was recruited from a tertiary headache clinic. The controls consisted of 582 sex-matched healthy volunteers who were randomly selected from the general population. For dietary intake assessments, we used a validated 168-item semiquantitative food frequency questionnaire (FFQ). Using three different measures, such as potential renal acid load (PRAL), net endogenous acid production (NEAP), and protein /potassium ratio for estimation of the dietary acid load.

**Results:** According to multivariable logistic regression analysis, in comparison with the lowest tertile, highest tertile of dietary acid load measures including PRAL (OR=7.208, 95% CI 3.33– 15.55), NEAP (OR=4.108, 95% CI 1.924– 8.774), protein/potassium ratio (OR=4.127, 95% CI 1.933– 8.814) were shown to significantly increase odds of migraine (P for trend= <0.001).

**Conclusions:** In this study, it was found that high dietary acid load may be associated with higher odds of migraine. Consequently, restricting dietary acid load could be beneficial in reducing the odds of developing migraine in susceptible subjects.

## Introduction

Migraine is one of the most disabling neurological problems in the world (1). According to report in 2019, The estimated prevalence of migraine is from 12–16% of the general population (2). This disease has been related to other health problems such as anxiety, depression, fibromyalgia, asthma, obesity, stroke, and coronary heart disease (3, 4). Although underlying mechanisms for the onset of migraine are not entirely realized, several abnormal conditions in the body are involved in the pathophysiology of this disorder. Some of these mechanisms include changes in cerebral blood flow, mitochondrial and hormonal dysfunction, genetic factors, obesity, neuroinflammation, in addition to increased levels of a number of neuropeptides especially nitric oxide (NO), and calcitonin gene-related peptide (CGRP) which are thought to be involved in the function of trigeminovascular system. On the other hand, activation of the trigeminovascular system could lead to excretion of substances such as CGRP, substance P and NO (5–8). These agents are associated with inflammation and vasodilation in cranial vessels, which lead to intense pain (5, 6, 8). NO is believed to play an important role in initiating of migraine attacks that perform its functions by NO/cyclic guanosine monophosphate (cGMP) pathway, and its levels are shown to be elevated in people with migraine during and between headache attacks (9, 10). Moreover, cytokines and inflammatory agents around nerves can activate trigeminovascular neurons and increase CGRP release (11). It has been shown that inflammatory factors such as tumor necrosis factor-alpha (TNF- $\alpha$ ), C-

reactive protein (CRP), Interleukin 6 (IL6) increased in people with migraine headache compared to healthy subjects (10, 12–15).

The available evidence suggests that even a slight increase in acidic load may stimulate the expression of induced NO synthases, increase levels of inflammatory factors such as TNF, increase blood flow as well as adiposity measures such as body mass index (BMI) (16–20). High dietary acid load, that is known by high intake of acid precursors including phosphorus and protein containing sulfuric amino acid and low intake of base precursors such as potassium, magnesium and calcium, could shift the acid-base balance towards acidosis (21, 22). This type of diet is rich in meat, dairy, and grain and poor in fruits and vegetables (22). A previous case-control study (23) has addressed that the western diet, which is typically characterized by high consumption of meat and low content of vegetables and fruits, thus may have a high dietary acid load (24), could increase odds of migraine.

High acidic load in the human body could affect inflammation, NO pathways, blood flow and adiposity measures (16–20). On the other hand, these factors are thought to play a role in initiation of migraine attacks (5, 6, 8, 10, 12–15). Thus, it can be hypothesized that higher consumption of acidogenic foods including meat that yield higher dietary acid load might increase the odds of developing migraine in susceptible patients. Therefore, in current study, we aimed to explore the association between dietary acid load and the odds of migraine headache.

## Materials And Methods

### *Study population and design*

In current case-control study migraineurs were recruited from the tertiary headache clinic of Sina University Hospital and a private headache clinic. The data was collected from 2015 to 2018. Detailed information on the study methods has been reported previously (25). Our expert headache-specialist neurologist diagnosed migraine headache (episodic and chronic migraine) according to the international headache classification (ICHDIII criteria, beta version) (26). Due to the fact that episodic migraine patients are less likely to be referred to our tertiary headache clinic, a higher proportion of referred patients were diagnosed with chronic migraine. Based on ICHDIII-beta criteria, chronic migraine is defined as 15 or more headache days per month with at least 8 migraine headache types in the last 3 months and episodic migraine characterised by up to 14 days per month. Controls were consisted of 582 sex-matched healthy volunteers who were randomly selected from the general population. Inclusion criteria for both the patients and control group included: age between 18–60 years, body mass index (BMI) between 18.5 and 35 kg/m<sup>2</sup> and daily energy intake between 800 and 5000 kcal. Exclusion criteria for both groups were: the pregnant or breastfeeding, having a history of chronic diseases such as gastrointestinal, liver or kidney disorders, diabetes mellitus, cardiovascular diseases, malignancy, tuberculosis, sarcoidosis, rheumatoid arthritis, psychiatric disorders and any type of neurological diseases except for migraine including parkinson, alzheimer disease, multiple sclerosis, etc., substance/alcohol- overusing or consistent smoking and following a specific diet over last year. The patients who referred to our tertiary headache clinic

prescribed medications by our expert headache-specialist neurologist. These drugs consisted of: Abortive drugs for acute treatment of headache attack (i.e., nonsteroidal antiinflammatory drugs (NSAIDs), other analgesics (codeine), and triptans), prophylactic medications (i.e., propranolol ( $\beta$ blockers), topiramate and sodium valproate/Depakene (antiepileptic drugs), selective serotonin reuptake inhibitor (SSRIs), and tricyclic antidepressants (TCAs). The research methods and study design was reviewed and approved by ethics committee of vice-chancellor in research affairs (ethics code: IR.TUMS.NI.REC.1398.010). Also, a written informed consent was obtained from all studied subjects.

### ***Assessment of anthropometric measures***

For anthropometric variables, body weight was measured using a seca755 medical scale (weighing accuracy of 0.5 kg), and height was measured by a standard stadiometer (accuracy of 0.1 cm). BMI was calculated as weight (kg) divided by the square of the height (m<sup>2</sup>).

### ***Dietary assessment and calculation of dietary acid load***

Food intake was assessed by a validated 168-item semi-quantitative food frequency questionnaire (FFQ) (27). Trained dietitians completed FFQ for all our participants. The food items were according to the US department of agriculture (USDA) standard serving sizes. Household measures (e.g., beans, 1 tablespoon; chicken meat, 1 leg or wing; rice, 1 large or small plate) were used, when standard serving sizes did not fit (28). By FFQ questionnaire, participants reported their intake of each food item base on daily, weekly, monthly or yearly. Then, data was converted to gram assuming each month equals 30.5 days. Daily macronutrient intake for each individual was measured by use of the Iranian national food composition table. Total macronutrient consumption was measured by summing up macronutrient intake from all consumed foods(29).

In this study, we used three different measures, including potential renal acid load (PRAL), net endogenous acid production (NEAP), and protein/potassium ratio for calculating dietary acid load, which been validated in previous studies (30-32). The algorithms of these measures were as follows: first, PRAL (mEq/day) =  $0.49 \times \text{protein (g/day)} + 0.037 \times \text{phosphorus (mg/day)} - 0.021 \times \text{potassium (mg/day)} - 0.026 \times \text{magnesium (mg/day)} - 0.013 \times \text{calcium (mg/day)}$  (30). Second, NEAP (mEq/d) =  $[54.5 \times \text{protein intake (g/d)} \div \text{potassium intake (mEq/d)}] - 10.2$  (31). Third, protein/potassium ratio =  $\text{total protein (g/d)} / \text{potassium intake (g/d)}$  (32).

### **Statistical method**

Analyses were performed applying the Statistical Package for the Social Sciences (SPSS) software (version 24 (Chicago: SPSS Inc. IBM Corp.)). All dietary variables that aimed to be investigated concerning migraine odds were classified in tertiles. Accordingly, baseline characteristics, anthropometric data, and nutritional intakes were compared through tertiles of PRAL and NEAP. One-way analysis of variance and the chi-squared test were used to compare continuous and categorical variables between PRAL and NEAP tertiles, respectively, and mean (standard deviation, SD) or number (%) were reported as appropriate. To

explore the association between dietary acid load measures and migraine odds, adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were obtained using multivariable logistic regression models following adjustment for age (year, continuous), sex, BMI (kg/m<sup>2</sup>, continuous), total daily energy intake (Kcal/d, continuous) as well as daily intake of carbohydrates (g/d), total fat (g/d), Na (mg/d), and dietary food groups (i.e., total refined grains, whole grains, total sugar, vegetables, fruits, red meat, poultry and egg, processed meat, fish, dairy, and nuts). To test for linear trends across tertiles, the median value of each tertile of dietary acid load measures was considered a continuous variable. All reported P values were two-sided, and p-value less than 0.05 was considered statistical significance level.

## Results

In total, 1096 participants (approximately 94% women) were assessed in this study of which 514 were migraine patients with a mean age of 36.20 (9.78) and 582 were healthy with a mean age of 44.58 (13.84). The mean BMI in migraine patients and healthy subjects was 25.9 (4.75) and 28.1(4.80) kg/m<sup>2</sup>, respectively. Two-hundred seventy-nine patients had chronic migraine, and 235 had episodic migraine.

Individuals in the third tertile of PRAL (median score = 13.06) and NEAP (median score = 71.99) scores were younger and tended to have higher consumption of refined grains, sugar, process meats, total protein, total fat and lower consumption of vegetables, fruits, nuts, dairy, total energy, total carbohydrate, plants protein and sodium in comparison with the first tertile of PRAL (median score=-27.05) and NEAP (median score = 31.11) scores (P value < 0.05). Mean intake of fish, poultry, and eggs were similar across the PRAL and NEAP tertiles (P value > 0.05) (Table 1). Besides, regarding to PRAL score, individuals in the second tertile (median score= -1.53) had greater BMI and higher intake of red meat and animal protein in comparison with the first tertile (median score= -27.05) (P value < 0.05). Regarding NEAP score, subjects in third tertile (median score = 71.99) and second tertile (median score = 49.80) had greater whole grain consumption in comparison with first tertile (median score = 31.11) (P value < 0.05) (Table 1).

Table 1

Baseline characteristics and dietary intakes of study participants according to the tertiles of dietary acid load.

	Dietary PRAL (mEq/d)				Dietary NEAP(mEq/d)			
	T1	T2	T3	p <sup>a</sup>	T1	T2	T3	p <sup>a</sup>
Age <sup>b</sup>	41.79 ± 12.99	41.60 ± 12.86	38.95 ± 12.53*	0.004	42.6 ± 13.19	39.8 ± 12.43 *	39.8 ± 12.76 *	0.004
Body mass index (kg/m <sup>2</sup> )	26.82 ± 4.53	27.66 ± 5.21*	26.80 ± 4.89	0.029	26.8 ± 4.60	27.4 ± 5.14	26.9 ± 4.92	0.217
<b>Nutrient intake</b>								
Total energy (kcal)	2402 ± 716	1970 ± 533 *	2189 ± 514*	< 0.001	2316 ± 744	2087 ± 546 *	2159 ± 526 *	< 0.001
Total carbohydrate (gr)	285.6 ± 111.8	210.5 ± 72.7 *	219.2 ± 73.6*	< 0.001	274.1 ± 117.5	221.3 ± 72.9 *	220.1 ± 74.6 *	< 0.001
Total protein (gr)	92.8 ± 27.5	83 ± 22.8 *	97.1 ± 23.1*	< 0.001	88.4 ± 27.4	89.6 ± 24.0	94.9 ± 23.8 *	0.001
Total animal protein (gr)	41.2 ± 16.4	36.5 ± 13.3*	41.6 ± 15.8	< 0.001	40.4 ± 15.8	39.7 ± 14.4	39.2 ± 16.0	0.610
Total plant protein (gr)	41.1 ± 14.6	33.5 ± 12.5 *	35.8 ± 12.3*	< 0.001	38.6 ± 15.0	36.0 ± 12.9 *	35.9 ± 12.5 *	0.013
Total fat (gr)	94.0 ± 38.2	83.8 ± 48.2	118.7 ± 133.4*	< 0.001	91.6 ± 36.9	90.2 ± 57.0	114.7 ± 131.3 *	< 0.001
Na (mg/d)	1838.1 ± 895.7	1476.6 ± 741.5 *	1506.7 ± 705.8*	< 0.001	1739.8 ± 842.1	1635.3 ± 852.5	1446.8 ± 671.7 *	< 0.001
<b>Food groups</b>								

PRAL; potential renal acid load, NEAP; net endogenous acid production.

\* P value by post hoc analyses when compared with lowest tertiles.

<sup>a</sup> ANODA test for variables.

<sup>b</sup> values are mean ± standard deviation.

	Dietary PRAL (mEq/d)				Dietary NEAP(mEq/d)			
Whole Grains (g/d)	37.4 ± 51.1	44.1 ± 61.6	43.2 ± 63.2	0.252	33.4 ± 46.2	46.4 ± 58.9 *	44.9 ± 68.8 *	0.005
Refined Grains (g/d)	293.4 ± 162.6	333.9 ± 144.7 *	458.6 ± 168.0*	0.000	269.4 ± 151.4	352.0 ± 144.3 *	464.3 ± 166.1 *	< 0.001
total sugar (g/d)	40.8 ± 53.8	53.0 ± 73.1	97.3 ± 115.9 *	< .0001	39.3 ± 53.7	59.9 ± 79.0	91.9 ± 113.5 *	< 0.001
Vegetables (g/d)	463.4 ± 217.9	356.4 ± 155.9 *	236.5 ± 122.1*	< 0.001	454.4 ± 216.1	364.1 ± 166.3 *	238.0 ± 120.8 *	< 0.001
Fruit (g/d)	1047.7 ± 859.4	387.0 ± 178.7 *	247.2 ± 128.6*	< 0.001	1027.6 ± 868.6	410.1 ± 212.7 *	246.0 ± 125.3 *	< 0.001
Nuts(g/d)	18.2 ± 21.8	8.9 ± 16.4 *	6.9 ± 10.4*	< 0.001	18.3 ± 23.3	9.8 ± 15.0 *	6.0 ± 9.0 *	< 0.001
Dairy (g/d)	383.3 ± 233.0	301.6 ± 165.5	281.3 ± 147.3*	< 0.001	385.1 ± 232.0	320.3 ± 166.9 *	261.0 ± 141.0 *	0.000
Red meat (g/d)	30.5 ± 22.5	25.7 ± 21.5*	31.6 ± 25.7	0.002	29.1 ± 22.3	28.3 ± 22.8	30.3 ± 25.1	0.490
Processed meat (g/d)	4.2 ± 8.4	4.4 ± 8.3	11.1 ± 15.2*	< 0.001	3.6 ± 6.8	5.7 ± 10.2 *	10.4 ± 15.0 *	0.000
Fish (g/d)	9.5 ± 12.2	8.4 ± 10.1	9.9 ± 9.8	0.142	8.9 ± 11.7	9.5 ± 10.8	9.3 ± 9.7	0.708
Poultry and Eggs (g/d)	53.0 ± 32.5	48.5 ± 28.7	58.6 ± 37.2	< 0.001	51.8 ± 31.5	52.9 ± 30.5	55.5 ± 37.2	0.311
PRAL; potential renal acid load, NEAP; net endogenous acid production.								
* P value by post hoc analyses when compared with lowest tertiles.								
<sup>a</sup> ANODA test for variables.								
<sup>b</sup> values are mean ± standard deviation.								

The ORs and corresponding 95% CIs for migraine according to tertiles of dietary acid load measures intake are shown in Table 2 and Fig. 1. According to multivariable logistic regression analysis, in comparison with the lowest tertile, individuals in the third tertile of PRAL scores had increased odds of migraine by approximately seven times (OR = 7.208, 95% CI 3.33– 15.55; P for trend = < 0.001). Also, the

subjects in the third tertile of each of NEAP score or protein/potassium ratio were shown to have approximately four-fold elevation in migraine odds when comparing to those in the first tertiles (OR = 4.10, 95% CI 1.92– 8.77; P for trend = < 0.001) (OR = 4.12, 95% CI 1.93– 8.81; P for trend = < 0.001), respectively (Table 2 and Fig. 1).

Table 2  
Odds ratio and 95% confidence interval for migraine according to the tertiles of dietary acid load.

<b>Dietary indexes of acid load</b>				
	T1	T2	T3	P for trend
<b>PRAL (mEq/d)</b>				
Cases/non-cases	197/169	138/227	179/186	
Multivariable model <sup>a</sup>	1.00	2.190 (1.242–3.861)	7.208 (3.339–15.558)	< 0.001
<b>NEAP(mEq/d)</b>				
Cases/non-cases	207/158	142/224	165/200	
Multivariable model	1.00	1.574 (0.910–2.722)	4.108 (1.924–8.774)	< 0.001
<b>protein/potassium ratio</b>				
Cases/non-cases	207/158	141/224	166/200	
Multivariable model	1.00	1.573 (0.910–2.720)	4.127 (1.933–8.814)	< 0.001
PRAL; potential renal acid load, NEAP; net endogenous acid production.				
<sup>a</sup> Multivariable model; adjusted for gender, age, body mass index, Total energy, Total carbohydrate, Total fat, Na, Refined grains, Whole grains, Sugar, Vegetables, Fruit, Red meat, Poultry and Egg, Processed meat, Fish, Dairy, Nuts.				

## Discussion

The result of this large population-observational study showed that high dietary acid load intake had a direct association with odds of migraine. Participants with higher PRAL scores, that had high daily intake of protein as well as phosphorus as acid-producing components and less potassium, magnesium, and calcium consumption per day as base-producing components (30, 33, 34), had approximately seven times increased odds of migraine, compared to those who had the lowest scores. Also, increased scores of NEAP and protein/potassium ratio that shows higher daily consumption of protein divided by potassium (31, 32) were related to about four-fold elevation in migraine odds.

In this study we used different methods for calculating dietary acid load, including PRAL, NEAP, and protein/potassium ratio. These methods are based on protein, potassium, phosphorus, calcium, and magnesium intake, which are acid-base precursors and probably related to PH homeostasis in the human



body (22, 30, 32). The higher value of PRAL, NEAP scores, and protein/potassium ratio are indications of more acidic food, while the lower amount of these measurements are pointing to more basic food consumption. Individuals with high dietary acid load had a lower intake of fruits and vegetables and more meat and protein consumption (22). In the present study, we found that high PRAL, NEAP, and protein/potassium ratio, which might be related to meats, grain, and sugar consumption, have a positive association with odds of migraine. Therefore, these findings demonstrated that a high acidic load in the human body, which could be induced by acidic food intake (21), may have an essential contribution to migraine pathogenesis and developing odds of this disorder.

To our knowledge, the association between the dietary acid load and odds of migraine has not been studied yet. Previous studies have only reported the consumption of single acidic and basic food items with odds of migraine (35, 36). In agreement to our finding, one case-control research showed that odds of migraine decreased by about 50 percent and 70 percent as consumption of vegetables and fruits increased in paediatrics (35). Furthermore, a study reported individual with migraine has a significantly higher frequency of using red meat than individuals without migraine (36). Also, according to the available evidences, individuals with western dietary patterns defined by high intakes of red and processed meat and low intake of fruits and vegetables had higher frequency of migraine attacks (23). Due to the high amount of acidic food items in the western dietary pattern, this type of diet may give an example of a high dietary acid load (24), which at least in part is in line with our findings.

Although protein intake can influence acid-base balance in the human body because of containing sulphuric amino acid (22), a recent study revealed that there were no differences in dietary protein intake among women with and without migraine (37). In the present study, we found that high PRAL, NEAP, and protein/potassium ratio, which significantly associated with high total protein intake, had positive associations with odds of migraine. The observed difference may be related to dietary patterns and dietary habits of the studied population as well as various controlled confounders. Moreover, another explanation for these difference probably due to the fact that dietary acid load measures such as PRAL, NEAP, protein/potassium ratio calculated by comparison between the acid and base precursors intake. Therefore, perhaps total protein intake as acid precursor, in comparison with base precursors have different effects on odds of migraine than consumption of total protein alone.

Chronic consumption of a diet with a high acid load could shift the acid-base balance toward acidosis (21). Besides, with the presence of abnormalities in acid-base balance, the dietary acid load is more likely to induce acidosis in the human body (18). It has been found that people with migraine could have abnormalities in the acid-base balance due to mitochondrial dysfunction (38, 39). Several possible mechanisms have been suggested that a high acidic load may play a role in the onset of migraine attacks or increasing headache attack frequency in migraineurs (16–20); these are explicated as follows. First, animal and human studies have reported that acidosis can cause high inflammation and NO due to its damaging effect on tissues or blood vessels (16–18, 40). The physiological ways to explain this issue is that TNF- $\alpha$ , myeloperoxidase, and NO synthases enzymes may be produced through acidosis condition in the human body (18). Inflammation and factors such as CGRP and NO are believed to play important

roles in migraine attacks initiation (41, 42). On the other hand, cytokines and inflammatory agents around nerves could activate trigeminovascular neurons and increase CGRP release by cellular mechanisms. Due to the existence of the majority of TNF- $\alpha$  receptors in trigeminal ganglion neurons, TNF- $\alpha$ , may increase CGRP gene expression in trigeminal ganglion neurons by increasing intra cellular MAP kinases signaling pathways, which might be attributed to the onset of headache (42–46). Additionally, NO can causes intense pain by increasing dilation and inflammation in cranial vessels through NO-cGMP pathway (9, 10). Therefore, acidosis condition by augmenting inflammation and NO synthesis may have a negative effect on the initiation of migraine attacks.

Second, a high acidic load might cause cortisol augmenting, which might have a negative impact on pain recovery in migraineurs (47). Also, elevated cortisol level, which may be augmented by acidosis, appeared to be associated with high blood flow and BMI in the human body (19, 20). It has been revealed that high blood flow and BMI may play negative roles in the onset of migraine pathogenesis. For example available evidence reported that the odds of migraine is increased in obese individuals (15, 48). Moreover, although there is controversial evidence regarding the association between hypertension and migraine, several findings delineated that long duration and uncontrolled hypertension, especially systolic blood pressure, may have a positive link with migraine with/without aura (49, 50).

Third, gut microbiota could be influenced by dietary acid load due to less intake of fruits and vegetables, which may lead to low microbial diversity in gastrointestinal systems then the adverse effects on human microbiomes (51). Recent shreds of evidence suggested the existence of a link between gut microbiota and migraine (7). Besides, studies have reported that there might be potential beneficial effects following probiotics supplementation in subjects with migraine headache (15, 52, 53).

Therefore, a high acidic load may be contributed with high odds of migraine through increasing inflammatory state, elevating cortisol levels, modifying NO signaling pathway, blood flow, and gut-microbiota, in addition to affecting on body weight and hypertension risk (16–20, 40, 47, 51).

The present study consists of several strengths. Dietary acid load was assessed by various methods such as PRAL, NEAP, protein/potassium ratio that were estimated using a validated FFQ. Another strength was a relatively large population of migraineurs in the case group. Additionally, all migraine patients were diagnosed by our expert neurologist-headache specialist according to the ICHDIII beta criteria. To our knowledge, this was the first study that preformed to explore the association of dietary acid load measures with odds of migraine. However, the limitations of this study are needed to be considered. First, the exact dosage of medications used, and the frequency and intensity of migraine headache attacks were not considered in the calculations. Second, body acid-base balance assessment was based on dietary calculation, and even if urinary and serum pH were available then the result would be more accurate.

## Conclusion

The result of this large population-observational study showed that high dietary acid load intake had a positive association with odds of migraine. Thus, as a strategy to reduce dietary acid load, restricting intake of acidogenic foods such as meat, grains, and sugar that are high in protein and phosphorous and low in basic precursors, may be considered a suggestion for reduction of migraine odds. However, our findings require further confirmation within large sample size cohort studies and well-designed clinical trials to identify the effects of dietary acid load on migraine clinical features and its related health outcomes.

## **Declarations**

### **Acknowledgments**

We thank the participants of the present study. In particular, we extend our gratitude to Ms. Jabbari, and the staff of Sina University Hospital for their kind cooperation. Also, the authors would like to thank Epidemiology and biostatistics of the Research Development Center of Sina Hospital for their technical assistance.

### **Authors' Contributions**

MT and SRJ jointly conceived and designed the study and contributed to the draft. ZGh, PR, BT, PS, AK, MN, FK and MM involved in data gathering and performed the research. MM drafted the manuscript. All authors critically revised the manuscript for important intellectual contents. MT gave final approval of the version to be published.

### **Funding**

This research has been supported by Iranian Center of Neurological Research, Neuroscience Institute, grant number 97-03-54-39214.

### **Availability of data and materials**

All included references in the present review article are available on the Internet.

### **Ethics approval and consent to participate**

The research methods and study design was reviewed and approved by ethics committee of vice-chancellor in research affairs (ethics code: IR.TUMS.NI.REC.1398.010). Also, a written informed consent was obtained from all studied subjects.

### **Consent for publication**

Not applicable.

### **Competing interests**

The authors declare that they have no conflict of interest.

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## Abbreviations

FFQ: food frequency questionnaire; PRAL: potential renal acid load; NEAP: endogenous acid production; NO: nitric oxide; cGMP: cyclic guanosine monophosphate; TNF- $\alpha$ : tumor necrosis factor-alpha; CRP: *C-reactive protein*; IL6: Interleukin 6; BMI: body mass index; ICHDIII: international headache classification III; NSAIDs: nonsteroidal antiinflammatory drugs; SSRIs: selective serotonin reuptake inhibitor; TCAs: tricyclic antidepressants; USDA: US department of agriculture.

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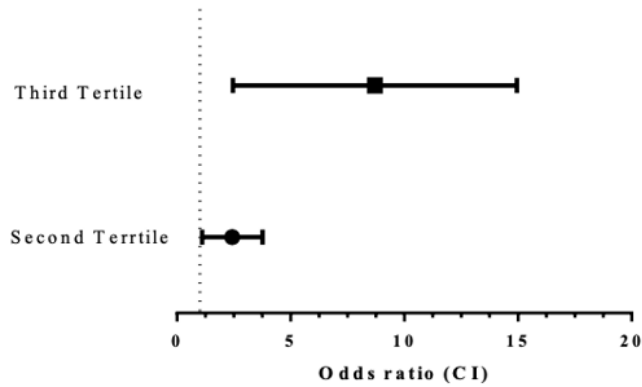
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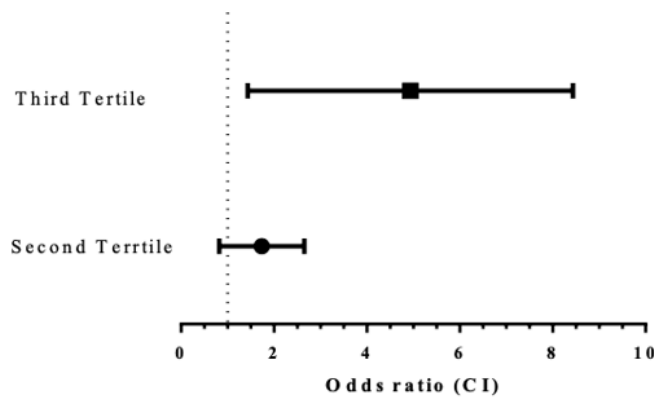
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## Figures

**a. PRAL (mEq/day)**



**b. NEAP (mEq/d)**



**c. Total protein/potassium ratio**

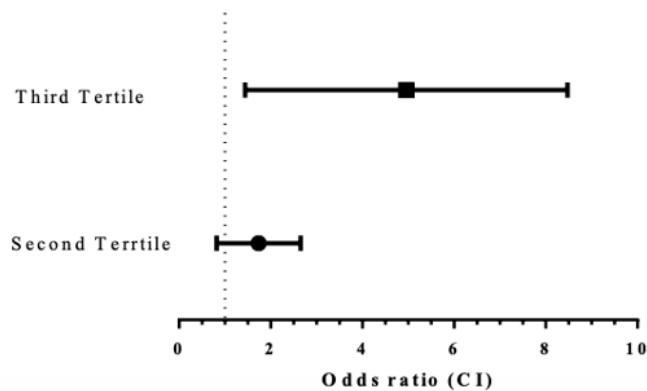


Figure 1



Multivariable adjusted odds ratios and 95% confidence intervals for migraine by tertiles of PRAL (mEq/day) (a), NEAP (mEq/d) (b), protein/potassium ratio (c) adjusted for age (year, continuous), sex, BMI (kg/m<sup>2</sup>, continuous), total daily energy intake (Kcal/d, continuous) as well as daily intake of carbohydrates (g/d), total fat (g/d), Na (mg/d), and dietary food groups (i.e. total refined grains, whole grains, total sugar, vegetables, fruits, red meat, poultry and egg, processed meat, fish, dairy, and nuts).