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Patterns of nutrients intakes in relation to glioma: A case-control study

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SUMMARY

Background & aims: Nutrient pattern analysis is an easy way to compare nutrient intakes across different nations due to the universality of nutrients nature. The current study aimed to investigate the relation between patterns of nutrients intake and glioma in a case-control study in Iranian adults.
Methods: In this hospital-based case-control study, we enrolled 128 pathologically confirmed new cases of glioma and 256 age and sex-matched controls. Dietary intakes of study participants were assessed using the validated Block-format 123-item semi-quantitative FFQ. Data on potential confounders were also collected through the use of pre-tested questionnaire.
Results: Four nutrient patterns were identified through the use of factor analysis. Participants were categorized based on tertiles of nutrient patterns' scores. Adherence to the first nutrient pattern was not significantly associated with the odds of glioma (0.93; 0.40–2.15). Participants with greater adherence to the second nutrient pattern were less likely to have glioma in crude model (0.48; 0.28–0.83). The inverse association remained significant after controlling for age, sex and energy intake (0.42; 0.24–0.78). Further controlling for other potential confounders, including BMI, resulted in the disappearance of the association (0.52; 0.25–1.10). Greater adherence to the third nutrient pattern was directly associated with the odds of glioma (1.92; 1.10–3.35). Even after controlling for sex, age and energy intake, the association was statistically significant (2.83; 1.28–4.21). However, when other confounders were taken into account, the association became non-significant (2.28; 0.89–5.82). The fourth nutrient pattern was not associated with the odds of glioma (0.71; 0.35–1.42).
Conclusion: We failed to find any significant independent association between nutrient patterns and odds of glioma. Further studies needed to confirm these findings.

1. Introduction

Gliomas constitute about 30% of all brain tumors and 80% of all malignant tumors [1]. Global incidence rate of primary malignant brain tumors is 3.7 per 100,000 for men and 2.6 per 100,000 for women [2]. According to the latest studies in Iran, incidence of glioma is 3.9 per 100,000 for men and 2.8 per 100.000 for women [3]. Although the incidence of glioma is low, given the high mortality rate, it is important to identify factors involved in the occurrence [4].

The only known modifiable risk factor for glioma is exposure to high-dose ionizing radiation, which accounts for a small proportion of glioma cases [5]. Dietary determinants of brain tumors have also been investigated. Consumption of fresh fruit and vegetables [6],

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high intake of antioxidants [7], vitamin supplementation [8–10] as well as fresh fish and poultry intake [6] has been linked with a lower risk of glioma in adults. Most studies on the role of diet in glioma have focused on individual nutrients, foods and food groups and less attention has been given to the patterns of dietary intake in particular patterns of nutrients intake. Due to the complex nature of dietary constituents and existent interactions between foods and nutrients [11], it seems that assessment of patterns of nutrient intake might provide a unique picture of the diet contribution to this condition. Studies on nutrient patterns have particular benefits than dietary patterns assessment. In nutrient patterns studies, the impact of all nutrient consumption (micronutrients and macronutrients) examined, and the effect of all nutrients that confound the associations can be omitted. In addition, pattern analysis in nutritional epidemiology would result in a lower number of nutritional variables. Nutrient pattern analysis is an easy way to compare nutrient intakes across different nations due to the universality of nutrients nature. Furthermore, despite huge differences in dietary patterns, different populations might have similar intake of individual nutrients. Nutrient pattern analysis can be an interface between food patterns and food metabolome integrating measurements of both diet and metabolism [12–21].

Given the limited evidence on the glioma-diet relations as well as scarce data on the association of patterns of nutrients intake with chronic conditions, including glioma, the current study aimed to investigate the relation between patterns of nutrients intake and glioma in a case-control study in Iranian adults.

2. Material & methods

2.1. Study population

This hospital-based case-control study was carried out on newly diagnosed patients (maximum one month since the detection) in Tehran, Iran, between November 2009 and September 2011. Cases were selected by using convenience-sampling method from adults referred to Neurosurgery department of Shahid Beheshti University of Medical Sciences whom their disease was pathologically confirmed (ICD-O-2, morphology codes 9380–9481). Controls were selected by using convenience-sampling method from adults in other wards (orthopedic and surgical departments) of the same hospital cases and controls were matched based on age (±5 years) and sex. Individuals with a history of any type of pathologically confirmed cancers (except glioma) and those with a history of chemotherapy or radiotherapy (due to cancer) were not included in this study. Required sample size for the current study was calculated based on prior evidence indicating lower than recommended consumption of fruits and vegetables in about 60% of Iranian adults. We hypothesized that low consumption of fruits and vegetables would double the risk of glioma. Therefore, considering type I error of 5% and the study power of 80%, we needed 115 cases and 230 controls for this study. However, we recruited 128 cases and 256 controls in this study. The participation rate was 100% among cases and 89% among controls. All cases and controls provided their written informed consent. The study was ethically approved by the Medical Ethics Committee of the Tehran University of Medical Sciences, Tehran, Iran.

2.2. Assessment of dietary intakes

Usual dietary intakes of participants during the year before the diagnosis of glioma in the case group and during the year before the interview in the control group were examined using a validated Block-format 123-item semi-quantitative FFQ. The FFQ consisted of 123 food items with standard portion sizes commonly consumed by this population. Trained interviewers administered the FFQ through face to face interviews in the presence of individuals who were involved in the preparation and cooking of foods. All reported consumption frequencies were then converted to grams per day using household measures. Subsequently, daily intakes of energy and nutrients were computed for each person using the US Department of Agriculture food composition database that was modified for Iranian foods. To modify the database, we added some of Iranian foods to the database of the software that was based on USDA food composition table. Also, some values of nutrients for a given food were also changed in the database based on Iranian food composition table. Total energy and nutrient intakes of each participant was calculated through summing up of all calories and nutrient, from each food item. Prior to extraction of patterns of nutrient intakes all nutrient intakes were controlled for total energy intake by the use of residual method.

2.3. Assessment of glioma

Glioma diagnosed is based on pathological test by using International Classification of Diseases for Oncology second edition and morphology codes 9380–9481. After neurological exam and imaging test (MRI or CT scan), final confirmation of glioma was determined by biopsy and pathological test. Only patients with maximally one month of the final confirmation of the disease were included to this study.

2.4. Assessment of other variables

Required information about age, sex, marital status, place of residence, education, occupation, smoking status, use of supplements, family history of cancers and glioma, history of allergy and trauma, history of hypertension, exposure to chemicals in the past 10 years, cooking methods, drug use, personal hair dye use, duration of cell phone use and history of exposure to the radiographic X-ray were examined using a pretested questionnaire. On the basis of previous studies we considered farmers as having a high risk occupation for glioma. Individuals who lived in places near the electromagnetic fields and ceil phone and broadcast antennas in the last 10 years were defined as living in high risk areas. Individuals who consumed fried food at least twice per week were considered as frequent fried food users. This definition was also used for barbecue use, microwave use as well as consumption of canned foods. Physical activity of participants were measured by International Physical Activity Questionnaire (IPAQ) and results expressed by Metabolic Equivalents per week (METs/week). Trained interviewer administers the IPAQ through face to face interviews. Body weight was quantified by digital scale to the nearest 500 g with the subjects wearing the light clothing and no shoes. Height was measured by tape measure to the nearest 0.5 cm with standing status and subject's shoulders in normal position. Body Mass Index (BMI) was calculated by division weight by kilogram to height square by meter. All measurements completed by the trained dietitian.

2.5. Statistical analysis

To avoid attenuation in the association of nutrient patterns and glioma, we focused on nutrient intakes of controls to obtain nutrient patterns. Factor analysis was applied to identify major nutrient patterns based on 35 components in controls. To examine if the distribution of the different nutrients allows the use of principal components, Kaiser–Meyer–Olkin (KMO) test was used. We used Eigen values of ≥ 2 in conjunction with considering scree plot to extract major patterns of nutrients. To obtain independent nutrient patterns, we used varimax rotation. Then, we applied the factor loadings to the nutrient intakes of cases. Participants were categorized into tertiles based on nutrient patterns' scores. General characteristics and dietary intakes were examined across tertiles of nutrient patterns' scores using one-way ANOVA and chi-square test, were appropriate. The association between adherence to the nutrient patterns and the odds of glioma was assessed by using logistic regression in different models. Age (continues), sex (male/female) and energy intake (kcal/d) were adjusted for the first model. Additional controlling for physical activity (continues), family history of cancers (yes/no), family history of glioma, marital status (yes/no), education (university graduated/non-university graduated), high-risk occupation (farmer/non-farmer), high-risk residential area (yes/no), duration of cell phone use (continues), supplement use (yes/no), history of exposure to the radiographic X-ray (yes/no), history of head trauma (yes/no), history of allergy (yes/no), history of hypertension (yes/no), smoking status (smoker/non-smoker), exposure to chemicals (yes/no), drug use (yes/no), personal hair dye (yes/no), frequent fried food intake (yes/no), frequent use of barbecue (yes/no), canned foods and microwave (yes/no) was done in the second model. Finally, the analysis was adjusted for BMI. All confounders were chosen based on previous publications. The statistical analyses were carried out by using SPSS version 18. P values were considered significant at <0.05.

3. Results

General characteristics and dietary intakes of cases and controls are compared in Table 1. Cases were more likely to have high-risk job, high-risk residential area, and history of exposure to the radiographic X-ray, history of head trauma, family history of glioma and history of exposure to chemicals. Cases were also more likely to be frequent fried foods intake, red meat consumer, refined and whole grains consumer. Controls were more likely to be current smoker, hair dye users, supplement users, microwave users and have a long duration of cell phone use, and history of dental photography. Controls had higher intakes of calcium, vitamin E, fruits, dairy products, legumes and nuts.

We identified four nutrient patterns through the use of factor analysis (Table 2). The KMO value was 0.78 indicating good sampling adequacy The first nutrient pattern was high in iron, folate, vitamin B2, vitamin B1, phosphorus, copper and potassium. The second one was greatly loaded with saturated fat, vitamin D, mono unsaturated fat, vitamin E, calcium, molybdenum, vitamin A, poly unsaturated fat and beta-carotene. The third nutrient pattern was characterized by high consumption of manganese, protein, vitamin B3, carbohydrate, zinc, sodium, magnesium and pantothenic acid. The last one was high in selenium, chromium, biotin, dietary fiber, pantothenic acid and vitamin C. Overall; these nutrient patterns explained 65.7% of variance.

General characteristics of study participants across tertiles of nutrient patterns scores are presented in Table 3. Participants with higher adherence to the first nutrient pattern were more likely to be younger, male, frequent users of barbecue and microwave and have a long duration of cell phone use and less likely to have history of allergy and dental photography than those with the lowest adherence. Individuals with the greatest adherence to the second nutrient pattern were more likely to be younger, single, university graduated, frequent microwave users and have a family history of cancer and long duration of cell phone and supplement use and were less likely to have high risk job, history of head trauma, be current smokers and medication users than those with the lowest adherence. Greater adherence to the third nutrient pattern was associated with younger age, male sex and residence in a high risk area. In addition, those in the top tertile of this nutrient pattern score were more likely to have a history of exposure to the radiographic X-ray, history of head trauma and be smokers, frequent users of barbecue and canned foods, medication users, exposure to chemicals and supplement use than those in the bottom tertile. In addition individuals with higher adherence to the third nutrient pattern were less likely to be university graduated, have a history of dental photography and personal hair dye use. Compared with those in the lowest tertile, individuals with greater adherence to

Table 1
General characteristics and dietary intakes of cases and controls.

	Cases n = 128	Controls n = 256	P_{value}
Age (years)	43.4 ± 14.6	42.8 ± 13.3	0.65
Males (%)	58.6	58.2	0.94
Weight (kg)	74.6 ± 13.7	72.1 ± 12.1	0.07
BMI (kg/m^2)	26.3 ± 4.3	26.1 ± 3.8	0.76
Married (%)	78.9	80.1	0.66
University graduated (%)	11.7	16.8	0.19
High-risk jobs[a] (%)	10.2	2.7	0.01
High-risk residential area[b] (%)	30.5	21.5	0.05
Duration of cell phone use (years)	2.8 ± 2.9	3.7 ± 2.6	0.01
History of exposure to the radiographic X-ray (%)	15.6	7.4	0.01
History of head trauma (%)	43.8	28.9	0.01
History of allergy (%)	25.0	29.3	0.37
History of hypertension (%)	2.3	5.1	0.21
History of dental photography (%)	46.1	59.0	0.02
Current smoker	15.6	25.0	0.01
Frequent fried food intakes[c] (%)	90.6	78.1	0.01
Frequent use of barbecue[d] (%)	15.6	12.1	0.34
Frequent microwave use[d] (%)	7.8	19.1	0.01
Frequent canned foods intake[d] (%)	6.3	5.9	0.88
Drug use (%)	7.8	5.1	0.29
Personal hair dye use (%)	21.9	41.0	0.001>
Exposure to chemicals (%)	19.5	10.5	0.01
Family history of glioma (%)	19.5	5.5	0.001>
Family history of cancer (%)	32.8	34.0	0.82
Supplement use (%)	7.80	15.6	0.03
Physical activity (MET-h/d)	34.8 ± 6.3	33.8 ± 6.3	0.13
Energy (kcal/d)	2580 ± 560	2561 ± 722	0.79
Nutrient intakes			
Macronutrient			
Proteins (g/d)	98.2 ± 21.7	97.1 ± 29.7	0.70
Fats (g/d)	61.8 ± 18.6	66.1 ± 21.6	0.05
Saturated fatty acids (g/d)	19.1 ± 7.2	20.7 ± 9.0	0.09
Dietary Fiber (g/d)	23.4 ± 11.2	23.0 ± 14.2	0.82
Mineral			
Calcium (mg/d)	1021 ± 260	1122 ± 321	0.01
Copper (mcg/d)	2.4 ± 0.8	2.3 ± 0.7	0.45
Vitamins			
Vitamin A (IU/d)	1420 ± 702	1348 ± 594	0.32
Vitamin E (mg/d)	5.1 ± 2.5	5.7 ± 3.0	0.03
Vitamin B6 (mg/d)	1.9 ± 0.5	2.0 ± 0.8	0.13
Folate (mcg/d)	349 ± 90	382 ± 302	0.24
Food groups			
Refined grains (g/d)	501.2 ± 174.7	421.0 ± 182.3	0.001>
Whole-grains (g/d)	176.8 ± 134.0	150.0 ± 108.2	0.04
White meats (g/d)	30.1 ± 13.6	32.6 ± 22.5	0.24
Red meats (g/d)	41.4 ± 27.8	36.0 ± 19.8	0.03
Fruits (g/d)	325.3 ± 99.7	360.8 ± 124.2	0.01
Vegetables (g/d)	257.8 ± 82.6	274.2 ± 86.2	0.08
Dairy products (g/d)	309.2 ± 116.7	355.0 ± 131.5	0.01
Legumes and nuts (g/d)	40.6 ± 22.7	46.0 ± 20.0	0.02
Sugar-sweetened beverages (g/d)	79.1 ± 67.3	83.5 ± 74.5	0.57

MET = metabolic equivalent.
Percentages obtain based on column.
[a] Farmers were considered as having a high-risk occupation.
[b] Individuals who lived in places near electromagnetic fields and cell phone and broadcast antennas in the last 10 years were defined as living in high-risk areas.
[c] Individuals who consumed fried food at least twice per week considered as frequent fried food users.
[d] Individuals who used barbecue, microwave and canned foods at least twice per week were considered as frequent users.

Table 2
Component of the nutrient patterns (NP).

	NP1	NP2	NP3	NP4
Iron	0.971	–	–	–
Folate	0.960	–	–	–
Vitamin B2	0.935	–	–	–
Vitamin B1	0.881	–	0.351	–
Phosphorus	0.709	0.325	0.488	–
Copper	0.647	0.399	0.417	0.335
Potassium	0.611	0.414	0.406	–
Vitamin B6	0.499	0.407	0.435	0.444
Sat-fat	–	0.786	–	–
Vitamin D	–	0.762	–	–
Mono-fat	–	0.754	–	–
Vitamin E	–	0.690	–	–
Calcium	–	0.669	0.411	–
Molybdenum	–	0.634	–	–
Vitamin A	–	0.601	0.345	–
Poly fat	–	0.579	0.323	–
Betacaroten	–	0.514	–	–
Fluoride	–	–	0.375	–
Vitamin K	–	0.332	–	–
Iodine	–	–	–	–
Manganese	–	–	0.797	–
Protein	–	0.453	0.747	–
Vitamin B3	0.353	–	0.746	–
Carbohydrate	–	–	0.700	–
Zinc	0.604	–	0.633	–
Sodium	–	–	0.631	–
Magnesium	0.479	–	0.587	0.439
Cholesterol	–	0.366	0.497	–
Vitamin B12	–	–	0.378	–
Selenium	–	–	–	0.882
Chromium	–	–	–	0.846
Biotin	–	–	–	0.821
Dietary fiber	0.633	–	–	0.744
Pantothenic acid	–	0.344	0.525	0.630
Vitamin C	–	–	–	0.506
Percent of variance explained	18.9%	16.8%	16.7%	13.2%

Factor loadings of <0.3 was omitted due to simplicity.

the fourth nutrient pattern had higher BMI and were be married, frequent microwave users and less likely to have history of hypertension than those in the bottom tertile. No other significant differences were seen across tertiles of nutrient patterns' scores.

Dietary intakes of participants across tertiles the nutrient patterns scores are presented in Table 4. Greater adherence to the first nutrient pattern was associated with higher intake of energy, all food groups and nutrients. Individuals with greater adherence to the second nutrient pattern were more likely to have higher intakes of energy, refined grains, red meat, fruits, vegetables, dairy products, legumes and nuts, sugar-sweetened beverages, proteins, carbohydrates, fats, saturated fatty acids, vitamin E and vitamin B6 than those with the lowest adherence. Greater adherence to the third nutrient pattern was associated with greater intakes of all food groups and nutrients except for dairy products, vitamin E and folate. Participants with higher adherence to the fourth nutrient pattern were more likely to have higher intakes of energy, refined grains, white meat, fruits, vegetables, legumes and nuts, proteins, carbohydrates, fats, calcium, vitamin E, vitamin B6 and dietary fiber than those in the bottom tertile.

Multivariable-adjusted odds ratios and 95% confidence intervals for glioma across tertiles of nutrient patterns' scores are shown in Table 5. Adherence to the first nutrient pattern was not significantly associated with the odds of glioma either before (1.10; 0.65–1.86) or after adjustment for covariates (0.93; 0.40–2.15). Participants with greater adherence to the second nutrient pattern were less likely to have glioma in crude model (0.48; 0.28–0.83). The inverse association remained significant after controlling for age, sex and energy intake (0.42; 0.24–0.78). Further controlling for other potential confounders, including BMI, resulted in the disappearance of the association (0.52; 0.25–1.10). Greater adherence to the third nutrient pattern was directly associated with the odds of glioma (1.92; 1.10–3.35). Even after controlling for sex, age and energy intake, the association was statistically significant (2.83; 1.28–4.21). However, when other confounders were taken into account, the association became non-significant (2.28; 0.89–5.82). The fourth nutrient pattern was not associated with the odds of glioma (0.71; 0.35–1.42).

4. Discussion

We failed to find any significant independent association between nutrient patterns and odds of glioma after controlling for potential confounders. It should be noted that adherence to the second nutrient pattern characterized by high intakes of vitamin D, vitamin E, vitamin A, saturated fat, mono unsaturated fat, calcium, molybdenum was inversely associated with odds of glioma after controlling for age, sex and energy intake. When we took other potential confounders into account, the association disappeared. No other associations were observed between nutrient patterns and odds of glioma. To the best of our knowledge, this study is the first examining patterns of nutrient intakes and risk of glioma.

Nutrient pattern analysis is a new approach in nutrition epidemiology that considers all nutrient interactions [11]. Although, nutrient patterns have been examined in relation to several chronic conditions including metabolic syndrome, diabetes, fractures, lung, breast, colorectal, esophageal, head and neck cancers, no information are available liking patterns of nutrient intakes to glioma [15–20,22–24]. Most previous studies in this regard named the nutrient patterns based on the nutrient sources; for example starch-rich NP, vitamin and fiber NP, fat NP, animal product NP. In the current study, we found four nutrient patterns that composed of very complex set of nutrients. Vegetable-rich, vitamin and fiber nutrient patterns were often associated with a lower risk of chronic diseases. Also, animal products and fat nutrient patterns were mostly related to higher risk of cancers. Nonetheless, we found an inverse association between adherence to the fat and fat-soluble vitamins NP and glioma before controlling for confounders.

Earlier studies on the link of nutrients and glioma have been mostly limited to individual nutrient intakes. In this regard, dietary intake of vitamin A, vitamin E, vitamin C, calcium, zinc, copper and essential fatty acids had been assessed. Vitamin A intake was inversely associated with the risk of glioma in the meta-analysis of seven studies (pooled RR = 0.80; 0.62, 0.98) [25]. Dietary intake of vitamin E was not significantly associated with the risk [26]. Greater vitamin C intake reduced the risk of glioma to 14% (pooled RR = 0.86; 0.75, 0.99) [27]. Greater intake of calcium was inversely associated with the odds of glioma in a case-control study (OR = 0.33; 0.12–0.90) [28]. In a case-control study of 637 glioma patients and 876 controls, non-significant association was seen between zinc intake and odds of glioma [29]. It has also been shown that, low dietary intakes of copper were not associated with longer survival of glioma patients [30]. Essential fatty acids have been shown to have therapeutic effects on glioblastoma cells [31]. In the current study, the second nutrient pattern was high in vitamin A, vitamin E, beta-carotene, essential fatty acids and calcium. Considering prior publications, it seems that not only individual nutrients but also combination of different nutrients in the framework of a nutrient pattern, is associated with decreased risk of glioma. However, the protective link of this nutrient pattern does not seem to be much, because of its disappearance after taking potential confounders into account. Our third nutrient pattern was high in proteins, sodium, cholesterol and vitamin B3. These nutrients are found in meats and processed meats. Greater intakes of

Table 3
General characteristics of the study participants cross categories of nutrient patterns' scores.

	Tertiles of NP1 score			P	Tertiles of NP2 score			P	Tertiles of NP3 score			P	Tertiles of NP4 score			P
	T_1 (n 121)	T3 (n 122)	T_3 (n 122)		T_1 (n 121)	T3 (n 122)	T_3 (n 122)		T_1 (n 121)	T3 (n 122)	T_3 (n 122)		T_1 (n 121)	T3 (n 122)	T_3 (n 122)	
Age (years)	46.5 ± 13.7	44.5 ± 13.3	37.7 ± 12.9	<0.001	44.6 ± 13.4	44.6 ± 14.2	39.5 ± 13.2	0.01	44.0 ± 13.0	45.6 ± 14.0	39.0 ± 13.6	<0.001	41.6 ± 14.7	42.9 ± 13.1	44.1 ± 13.4	0.37
Males (%)	50	47	76	<0.001	68	58	54	0.08	35	62	82	<0.001	58	58	64	0.55
BMI(Kg/m^2)	26.1 ± 4.1	25.7 ± 3.7	26.2 ± 4.1	0.57	26.1 ± 4.4	26.0 ± 3.7	25.9 ± 3.8	0.91	26.3 ± 4.6	25.3 ± 3.2	26.4 ± 3.9	0.07	25.1 ± 3.6	26.0 ± 3.8	26.9 ± 4.3	0.01
Married (%)	83.5	79	76	0.42	90	77	71	0.01	79	81	78	0.94	65	87	86	<0.001
University graduated (%)	16	16	15	0.97	3	12	30	<0.001	25	9	12	0.002	16	16	15	0.97
High-risk jobs[a] (%)	6	5	6	0.95	10	3	3	0.03	2	7	8	0.07	7	7	2.5	0.19
High-risk residential area[b] (%)	23	20	31	0.10	26	22	26	0.73	18	24	32	0.04	21.5	29	24	0.41
Duration of cell phone use (years)	3.3 ± 2.3	2.9 ± 2.6	4.1 ± 2.9	0.002	3.2 ± 2.5	3.2 ± 2.5	4.0 ± 3.0	0.02	3.2 ± 2.4	3.0 ± 2.6	4.2 ± 2.9	<0.001	3.4 ± 2.6	3.6 ± 2.5	3.3 ± 2.9	0.58
History of exposure to the radiographic X-ray (%)	8	11	12	0.59	13	9	9	0.46	4	12	15	0.02	11	11	10	0.97
History of head trauma (%)	34	34	32	0.91	42	34	25	0.01	25	38	38	0.05	31	37	33	0.57
History of allergy (%)	36	25	19	0.01	32	25	23	0.24	32	28	20.5	0.11	22	32	26	0.23
History of hypertension (%)	6	6	2	0.19	4	7	2.5	0.29	5	5	3	0.77	8	3	2	0.03
History of dental photography (%)	69	45	50	0.001	60	46	57	0.06	64	54	46	0.02	50	60	54	0.27
Current smoker (%)	21	20	26	0.41	31	21	15	0.01	7	18	41	<0.001	25	26	16	0.09
Frequent fried food intakes[c] (%)	80	83	82	0.86	80	87	78	0.17	83.5	81	80	0.81	81	80	84	0.78
Frequent use of barbecue[d] (%)	9	11	20.5	0.02	13	13	14	0.98	6	13	21	0.002	14	16	11	0.51
Frequent microwave use[d] (%)	17	8	21	0.015	12	13	22	0.05	21	11	16	0.09	8	16	23	0.01
Frequent canned foods intake[d] (%)	5	2.5	9	0.08	2.5	4.9	9	0.08	2.5	4	10	0.03	4	5	7	0.51
Drug use (%)	8	4	6	0.39	14	3	8	<0.001	2	3	13	<0.001	5	7	6	0.72
Personal hair dye use (%)	46	35	17	<0.001	26	36	36	0.18	48	34	17	<0.001	30	41	28	0.06
Exposure to chemicals (%)	11	11	20	0.06	19	9	13	0.07	7	14	20	0.02	12	16	14	0.66
Family history of glioma (%)	8	11.5	11.5	0.64	12	9	11	0.80	6	14	11.5	0.10	12	8	11	0.56
Family history of cancer (%)	32	29	42	0.08	30	29	44	0.02	36	26	40	0.06	27	36	39	0.12
Supplement use (%)	83	88.5	89	0.42	93	86	81	0.02	80	88.5	92	0.02	88	90	83	0.22
Physical activity (MET-h/week)	34.2 ± 5.9	33.7 ± 4.8	34.4 ± 6.6	0.62	34.8 ± 5.9	34.0 ± 5.6	33.6 ± 5.9	0.29	33.3 ± 5.0	34.6 ± 6.2	34.5 ± 6.0	0.16	34.0 ± 6.3	34.3 ± 5.2	34.1 ± 6.0	0.94

MET = metabolic equivalent.
Percentages obtain based on column.
[a] Farmers were considered as having a high-risk occupation.
[b] Individuals who lived in places near electromagnetic fields and cell phone and broadcast antennas in the last 10 years were defined as living in high-risk areas.
[c] Individuals who consumed fried food at least twice per week considered as frequent fried food users.
[d] Individuals who used barbecue, microwave and canned foods at least twice per week were considered as frequent users.

Table 4
Dietary intakes of study participants across categories of nutrient patterns' scores.

	Tertiles of NP1 score			P	Tertiles of NP2 score			P	Tertiles of NP3 score			P	Tertiles of NP4 score			P
	T_1 (n 121)	T_2 (n 122)	T_3 (n 122)		T_1 (n 121)	T_2 (n 122)	T_3 (n 122)		T_1 (n 121)	T_2 (n 122)	T_3 (n 122)		T_1 (n 121)	T_2 (n 122)	T_3 (n 122)	
Energy (Kcal/d)	2159 ± 575	2433 ± 359	3114 ± 659	<0.001	2377 ± 527	2470 ± 611	2861 ± 771	<0.001	2132 ± 433	2452 ± 407	3123 ± 715	<0.001	2465 ± 688	2507 ± 496	2737 ± 787	0.01
Food groups																
Refined grains (g/d)	370 ± 144	419 ± 157	554 ± 181	<0.001	497 ± 202	426 ± 142	421 ± 178	0.001	374 ± 158	431 ± 159	538 ± 179	<0.001	396 ± 166	435 ± 167	512 ± 184	<0.001
Whole-grains (g/d)	147 ± 116	147 ± 103	185 ± 134	0.01	172 ± 126	146 ± 113	160 ± 118	0.24	83 ± 63	162 ± 106	234 ± 128	<0.001	168 ± 122	171 ± 118	139 ± 116	0.06
White meats (g/d)	30 ± 12	29 ± 10	37 ± 31	0.01	30 ± 13	31 ± 12	35 ± 30	0.17	29 ± 11	29 ± 11	37 ± 30	0.001	28 ± 12	31 ± 12	36 ± 30	0.01
Red meats (g/d)	33 ± 18	34 ± 15	46 ± 29	<0.001	32 ± 17	37 ± 20	45 ± 27	<0.001	32 ± 15	34 ± 16	48 ± 29	<0.001	36 ± 24	38 ± 17	40 ± 26	0.39
Fruits (g/d)	306 ± 98	353 ± 111	381 ± 123	<0.001	306 ± 100	326 ± 100	408 ± 119	<0.001	345 ± 110	321 ± 104	374 ± 125	0.001	292 ± 96	351 ± 95	398 ± 128	<0.001
Vegetables (g/d)	244 ± 67	271 ± 77	285 ± 97	<0.001	237 ± 66	254 ± 72	309 ± 91	<0.001	253 ± 72	263 ± 77	285 ± 95	0.007	237 ± 68	272 ± 73	291 ± 97	<0.001
Dairy products (g/d)	286 ± 113	355 ± 113	378 ± 130	<0.001	260 ± 96	326 ± 105	433 ± 107	<0.001	347 ± 120	328 ± 121	344 ± 133	0.46	322 ± 128	343 ± 106	355 ± 137	0.09
Legumes and nuts (g/d)	35 ± 17	45 ± 20	53 ± 22	<0.001	39 ± 19	40 ± 18	53 ± 23	<0.001	41 ± 18	41 ± 21	50 ± 23	<0.001	41 ± 21	44 ± 20	47 ± 22	0.05
Sugar-Sweetened beverages (g/d)	67 ± 59	80 ± 69	98 ± 81	0.01	64 ± 52	71 ± 56	45 ± 27	<0.001	71 ± 66	66 ± 59	106 ± 81	<0.001	80 ± 81	77 ± 62	87 ± 69	0.56
Nutrients																
Proteins (g/d)	80 ± 15	93 ± 12	119 ± 32	<0.001	90 ± 18	94 ± 21	108 ± 36	<0.001	81 ± 14	93 ± 15	118 ± 33	<0.001	92 ± 22	9.6 ± 19	105 ± 36	0.001
Carbohydrate (g/d)	353 ± 126	394 ± 66	501 ± 111	<0.001	404 ± 97	402 ± 126	443 ± 134	0.01	333 ± 82	398 ± 64	517 ± 127	<0.001	395 ± 129	408 ± 88	446 ± 136	0.002
Fats (g/d)	54 ± 12	62 ± 15	78 ± 24	<0.001	50 ± 11	618 ± 13	82 ± 22	<0.001	60 ± 17	61 ± 19	72 ± 24	<0.001	64 ± 22	62 ± 16	68 ± 23	0.04
Saturated fatty acids (g/d)	16 ± 5	19 ± 6	25 ± 11	<0.001	14 ± 4	189 ± 4	27 ± 10	<0.001	19 ± 8	19 ± 8	22 ± 9	0.01	21 ± 11	19 ± 6	20 ± 8	0.24
Calcium (mg/d)	866 ± 189	1099 ± 173	1297 ± 342	<0.001	924 ± 215	1029 ± 217	1310 ± 320	<0.001	1009 ± 265	1038 ± 248	1216 ± 346	<0.001	1048 ± 295	1071 ± 220	1146 ± 369	0.03
Vitamin E (mg/d)	5 ± 2	5 ± 2	6 ± 3	<0.001	4 ± 2	5.2 ± 2.1	8 ± 3	<0.001	6 ± 3	5 ± 2.5	6 ± 3	0.09	5 ± 3	5 ± 2	6 ± 3	<0.001
Vitamin B6 (mg/d)	1.6 ± 0.3	1.8 ± 0.3	2.4 ± 1	<0.001	1.7 ± 0.5	1.8 ± 0.5	2.3 ± 0.9	<0.001	1.8 ± 0.5	1.8 ± 0.4	2.2 ± 0.9	<0.001	1.7 ± 0.6	1.8 ± 0.4	2.3 ± 0.9	<0.001
Folate (mcg/d)	292 ± 47	346 ± 50	474 ± 411	<0.001	375 ± 404	344 ± 118	394 ± 117	0.29	356 ± 415	342 ± 60	415 ± 116	0.06	358 ± 406	340 ± 62	414 ± 142	0.06
Dietary Fiber (g/d)	18 ± 6	22 ± 9	29 ± 19	<0.001	23 ± 16	22 ± 13	24 ± 10	0.44	25 ± 19	21 ± 9	24 ± 9	0.03	17 ± 13	20 ± 3	33 ± 14	<0.001

All values were adjusted for age, sex and energy, except for dietary energy intake, which was only adjusted for age and sex. Comparisons were made using ANOVA.

Table 5
Multivariable-adjusted odds ratios for glioma across tertiles of nutrient patterns' scores.

	Crude	Model 1	Model 2	Model 3
Tertiles of NP1 score				
T_1 (n 121)	1.00	1.00	1.00	1.00
T_2 (n 122)	0.85 (0.49–1.46)	0.87 (0.50–1.51)	0.56 (0.28–1.12)	0.57 (0.28–1.14)
T_3 (n 122)	1.10 (0.65–1.86)	1.19 (0.61–2.30)	0.91 (0.39–2.08)	0.93 (0.40–2.15)
P_{trend}	0.72	0.67	0.69	0.74
Tertiles of NP2 score				
T_1 (n 121)	1.00	1.00	1.00	1.00
T_2 (n 122)	0.80 (0.48–1.34)	0.78 (0.46–1.31)	0.89 (0.46–1.73)	0.89 (0.46–1.73)
T_3 (n 122)	0.48 (0.28–0.83)	0.42 (0.24–0.78)	0.51 (0.24–1.07)	0.52 (0.25–1.10)
P_{trend}	0.01	0.01	0.08	0.10
Tertiles of NP3 score				
T_1 (n 121)	1.00	1.00	1.00	1.00
T_2 (n 122)	1.99 (1.14–3.46)	2.31 (1.28–4.21)	1.71 (0.84–3.50)	1.86 (0.90–3.84)
T_3 (n 122)	1.92 (1.10–3.35)	2.83 (1.35–5.93)	2.18 (0.86–5.55)	2.28 (0.89–5.82)
P_{trend}	0.02	0.01	0.10	0.08
Tertiles of NP4 score				
T_1 (n 121)	1.00	1.00	1.00	1.00
T_2 (n 122)	0.63 (0.37–1.08)	0.63 (0.36–1.07)	0.66 (0.34–1.27)	0.65 (0.34–1.25)
T_3 (n 122)	0.86 (0.51–1.44)	0.84 (0.49–1.43)	0.75 (0.38–1.49)	0.71 (0.35–1.42)
P_{trend}	0.56	0.50	0.40	0.32

Model 1: adjusted for age, sex and energy intake.
Model 2: further adjustments were made for physical activity, family history of cancers, family history of glioma, marital status, education, high-risk occupation, high-risk residential area, duration of cell phone use, supplement use, history of exposure to the radiographic X-ray, history of head trauma, history of allergy, history of hypertension, smoking status, exposure to chemicals, drug use, personal hair dye, frequent fried food intake, frequent use of barbecue, canned foods and microwave.
Model 3: Further adjusted for BMI.

meats and processed meats has been directly associated with the risk of glioma [32]. However, controlling for potential confounders made this relationship non-significant.

Second nutrient pattern is mostly represented by lipid components (fatty acids, cholesterol and fat-soluble vitamins) and its inverse association with glioma appears to replicate previous findings based on individual components of this nutrient pattern [10]. Lack of association in multivariable analysis might partly be attributed to vitamin A (which has been shown to be associated with glioma) and vitamin E (which is not associated). Hence, a factor including many components not associated and some components associated with glioma might need to be investigated by methods other than mathematical construction. Dietary intakes of vitamins E and calcium were significantly different and those of vitamin A and copper were approximately the same in cases and controls (Table 1). Therefore, the association between adherence to NP2 and glioma might be explained by intakes of effective components.

Several mechanisms have been suggested for the roles of nutrients in glioma. Vitamin A prohibits proliferation and migration of glioblastoma cells [33]. Ascorbic stearate (A derivative of vitamin C) has anti-proliferative and apoptotic effects [34]. Tocopherol is an effective inhibitor of cell cycle [35]. Calcium protects against glioma by DNA modification and induction of apoptosis [10]. Zinc is a trace element that influences replication enzymes of DNA and RNA. Copper is a cofactor for angiogenesis and accumulates in brain tumors [36]. Copper deficiency inhibits the development of glioma cells [37]. N-nitroso compounds, highly exist in processed meats, are potent carcinogens [8].

This study has several strengths. We controlled for a wide range of potential confounders. However, the potential effects from residual confounders cannot be excluded. We enrolled new cases of glioma in the study. So the possibility of changing usual dietary intakes has been reduced. This study has also some limitations. As several nutrients (copper, vitamin B6, pantothenic acid, potassium) showed large factor loadings in most NPs, it seems that the four NPs cannot be made completely orthogonal. This might explain lack of association we reached between NPs and glioma. Our findings are subject to selection and recall bias that are common in the case-control studies. As with all epidemiological studies, misclassification of study participants due to the use of FFQ is unavoidable. In addition, cases in the present study were selected from hospitals. Generalizability of study findings might be weakening in this methodological choice.

In conclusion, no significant independent association was found between nutrient patterns and odds of glioma. Further studies are required to confirm these findings.

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Conflicts of interest

Hanieh Malmir, Mehdi Shayanfar, Minoo Mohammad-Shirazi, Hadi Tabibi, Giuve Sharifi, Ahmad Esmaillzadeh declare that they have no conflict of interest.

Authorship

Hanieh Malmir, Mehdi Shayanfar, Minoo Mohammad-Shirazi, Hadi Tabibi, Giuve Sharifi and Ahmad Esmaillzadeh contributed to the conception, design, data collection, statistical analyses, data interpretation, manuscript drafting, approval of the final version of the manuscript and agreed for all aspects of the work.

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List of abbreviations

FFQ	Food frequency questionnaire
NP	Nutrient pattern
ICD-O-2	International Classification of Diseases for Oncology 2nd
MRI	Magnetic resonance imaging
CT scan	Computerized tomography scan
IPAQ	International physical activity questionnaire
MET	Metabolic equivalent of task
BMI	Body mass index
ANOVA	Analysis of variance
RR	Relative risk
OR	Odds ratio
DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid

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