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Adherence to the Mediterranean dietary pattern in relation to glioma: a case-control study

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ABSTRACT

Background: Although Mediterranean diet (MD) was associated with a lower risk of mortality and cancer, no data are available investigating the association between adherence to the MD and risk of glioma.

Methods: In this case-control study, we enrolled a total of 128 newly diagnosed patients with glioma, confirmed by pathological assessment, and 256 hospital-based controls from 2009 to 2011 in Tehran, Iran. A valid and reliable Block-format food frequency questionnaire (FFQ) was used to assess dietary intakes. Adherence to the MD was examined using the scoring method suggested by Trichopoulou et al. Logistic regression was used to examine the associations of interest.

Results: After controlling for age, sex, and energy intake, participants in the highest tertile of MD score had not significantly lower odds of glioma than those in the lowest tertile (OR: 0.58, 95% CI: 0.32-1.03, P_{trend} =0.06). However, after taking other potential confounders into account, individuals with the greatest adherence to the MD score were 74% less likely to have glioma than those with the lowest adherence (OR: 0.26, 95% CI: 0.12-0.55, $P_{trend} < 0.001$). Additional adjustments for dietary intakes and BMI did not significantly alter this association (OR: 0.36, 95% CI: 0.16-0.78, P_{trend} =0.009; OR: 0.36, 95% CI: 0.16-0.78, P_{trend} =0.01, respectively).

Conclusion: We found that adherence to the MD was associated with a lower likelihood of having glioma. Prospective cohort studies are needed to further examine these findings.

KEYWORDS: Mediterranean; Diet; MD; Glioma; Cancer; Brain tumor

INTRODUCTION

Glioma, the most prevalent brain tumor, refers to a carcinomatous growth or tumor composed of cells retrieved from neuroglial tissue [1]. Gliomas account for about 77% of all brain malignant tumors [2]. The globally estimated incidence rate of brain tumors is 3.7 and 2.6 per 100,000 for men and women, respectively [3]. A recent national study in Iran has reported a mortality rate of 2.92 and 2.46 per 100,000 in men and women, respectively [4]. Abnormal proliferation and malignant transformation of glial cells might be affected by several environmental factors [5, 6].

Epidemiological evidence supports the role of diet in the pathogenesis of glioma [7, 8]. Most studies that assessed the diet-glioma associations have focused on individual nutrients, foods or specific food groups [9-13]. However, foods or nutrients are not consumed in isolation and there might be synergistic and antagonistic interactions between food components [14]. Therefore, investigating the relation of dietary patterns with glioma is valuable [15]. The Mediterranean diet (MD), with several beneficial effects on human health [16, 17], was presented for the first time by Keys in the 1950s. This dietary pattern is characterized by high intakes of monounsaturated fatty acids (MUFAs) from olive oil, vegetables, fruit, nuts, fish, cereals and legumes and low to moderate intakes of dairy products (mainly cheese and yogurt) along with low consumption of meat products [18, 19]. Investigations on the link between this dietary pattern and health outcomes have shown an inverse association between adherence to MD eating pattern and risk of non-communicable diseases including cardiovascular disease [20, 21], hypertension, obesity, and impaired lipid metabolism [22]. In addition, adherence to MD has also been associated with 10-25% reduced risk of several cancers [23].

Most studies on the relationship between diet and cancers have been conducted in Western populations [24, 25] and few studies have been carried out in the Middle-East [26, 27], a region

with different dietary behaviors from Western countries [28]. High consumption of refined grains and saturated fats and lower intakes of monounsaturated fatty acids in this area might explain the high prevalence of several cancers [28]. To our knowledge, no investigation has reported the association between adherence to MD eating pattern and risk of glioma. Given the inverse association between some components of MD and glioma in previous studies [7, 9, 12], it seems that the whole Mediterranean dietary pattern might be associated with glioma. Therefore, we aimed to examine the association between the adherence to the Mediterranean dietary pattern and risk of glioma in the framework of a case–control study in Iran.

MATERIALS AND METHODS

Study population: The methods of our study has been described in detail elsewhere [29]. Briefly, this is a hospital-based case-control study that was conducted between November 2009 to September 2011 in Tehran, Iran. In this project, we recruited 384 subjects (range: 20-75 years); of them, 128 were cases with pathologically confirmed glioma (in the first month following diagnosis) who had attended Neurosurgery department of the hospitals affiliated to Shahid Beheshti University of Medical Sciences and 256 subjects were controls, who were chosen from apparently healthy individuals referred to other wards (orthopedic or surgery wards). Individuals with clinical symptoms or signs of any other cancers in their medical history (except glioma) or those with a history of chemotherapy or radiotherapy were not included in this study. Written informed consent was obtained from all cases and controls. The study protocol was approved by the ethics committee of the Food Security Research Center at the Isfahan University of Medical Sciences, Isfahan, Iran.

Dietary intake assessment: Gathering information on dietary intakes of cases, for 1 year before diagnosis, and controls, for 1 year before the interview date, was conducted using a Block-

format-validated 123-item semi-quantitative food-frequency questionnaire (FFQ) [30]. Individuals' average intakes of different dietary items (per day, week or month) were extracted from this interviewer-administered FFQ. Daily energy and nutrients intakes were calculated by Nutritionist IV software based on the USDA Food Composition Table [31]. In a previous study [30], using this FFQ, a proper correlation coefficient was found between dietary intakes by this questionnaire and those by 24-hour dietary recalls (two recalls in each month of a year). Estimated correlation coefficients (comparing the FFQ and 24-hour dietary recalls) for b-carotene, vitamin E and vitamin C were 0.84, 0.78 and 0.83, respectively [30].

Adherence to Mediterranean diet: According to the methodology introduced by Trichopoulou et al [20], calculation of Mediterranean dietary score was done by considering nine components [fish, vegetables, fruits, nuts, legumes, whole grains, the ratio of MUFA to saturated fatty acids (SFAs), meats (red meat, poultry and proceed meats), and dairy]. The score of 1 was dedicated to participants who were at the top median intakes of vegetables, fruits, fish, nuts, legumes, whole grains and ratio of MUFA to saturated fatty acids (SFAs) and bottom median intakes of meats and dairy. The score of 0 was given for those who were at the top median intakes of meats, dairy and bottom median intakes of whole grains, fruits, vegetables, fish, nuts, legumes and ratio of MUFA to SFAs. We estimated the overall MD score by summing up each component's score.

Assessment of glioma: The diagnosis of glioma was done based on the pathological test by using International Classification of Diseases for Oncology second edition (ICD-O-2) and morphology codes 9380-9481 [32]. Glioma patients were allowed to enter the project if they passed a maximally one month of the disease confirmation.

Assessment of other variables: All participants were interviewed by a trained dietitian using a pre-tested questionnaire on demographics, medical history (cancer and glioma, head trauma,

allergy and hypertension), relevant lifestyle habits including dealing with chemicals in the past 10 years, methods of cooking, drug use, personal hair dye use, cell phone use and history of exposure to the radiographic X-ray. Subjects were asked to indicate their physical activity during the last year using the International Physical Activity Questionnaire (IPAQ). Then, physical activity was extracted as Metabolic Equivalents per week (METs/week). Assessment of anthropometric measurements was performed using standardized procedures. Body mass index was computed using relevant equation. Considering previous studies, we considered farming as a high-risk job [33]. In addition, residential places near electromagnetic fields, cell phone and broadcast antennas over the last 10 years was defined as high-risk areas [34]. The use of microwave, canned foods, fried foods and barbecued-foods was also defined as high-risk foods, when they were consumed at least twice a week.

Statistical analysis: In the present study, subjects were categorized according to tertiles of the MD score. Comparison of general characteristics of study participants across tertiles of MD score was examined using one-way analysis of variance (ANOVA) for continuous variables and Chi-square test for categorical variables. Assessment of dietary intake of participants across tertiles of MD score was conducted using analysis of covariance (ANCOVA). These models were adjusted for age, gender, and total energy intake. Binary logistic regression, in four different levels of adjustments, was applied to evaluate the association between MD score and glioma. The adjustments were done for age (continuous), sex (male/female) and energy intake (kcal/d) in the first model. Further adjustments were made for physical activity (continues), cell phone using time (continuous), family history of cancer and glioma (yes/no), taking supplements (yes/no), medication use (yes/no), marital status (married/single/divorced), educational level (university graduated/ non-university education), high-risk job (farmer/non-farmer), high-risk

living area (yes/no), history of exposure to the radiographic X-ray (yes/no), history of head trauma (yes/no), allergy (yes/no), and hypertension (yes/no), smoking status (smoker/non-smoker), exposure to chemicals (yes/no), personal hair dye use (yes/no), frequent consumption of fried foods (yes/no), barbecued foods (yes/no), canned foods (yes/no) and microwave heat-treated foods (yes/no). We also additionally adjusted for several food groups including refined grains (continuous), tea and coffee (continuous), and egg intake (continuous) in an additional model. These items were considered based on earlier findings [35, 36]. In the final model, we controlled for BMI (continuous) to reach the obesity-independent association. In all statistical analyses, the lowest tertile of the MD score was considered as the reference category. The overall trend of odds ratios across tertiles of MD score was computed by considering these tertiles as an ordinal variable. All statistical procedures were conducted using SPSS software (version 19.0; SPSS Inc, Chicago IL). P-values less than 0.05 were defined as statistically significant.

RESULTS

The characteristics and dietary intakes of cases and controls are presented in **Table 1**. Compared with those without glioma, cases were more likely to have high-risk jobs, family history of glioma, history of head trauma, history of exposure to chemicals and radiographic X-rays, and reside in high-risk areas. In addition, glioma patients were more likely to be frequent fried foods consumer. In contrast, history of dental photography, smoking, personal hair color use, taking supplements, using microwave heat-treated foods and cell phone use were more prevalent among controls than cases. In addition, controls had higher intakes of total fat, MUFA, calcium, fruits, nuts, whole grains, dairy products, tea and coffee than cases.

The general characteristics of study participants across tertiles of the Mediterranean dietary score are summarized in **Table 2**. Compared with the participants in the lowest tertile, subjects in the highest tertile of Mediterranean dietary score were more likely to be married, medication users, have frequent intakes of fried foods, and history of head trauma. They were also less likely to have history of exposure to the X-ray radiographic imaging. There were no significant differences in other general characteristics across tertiles of Mediterranean dietary score.

The prevalence of glioma across tertiles of the Mediterranean diet score is displayed in **Figure 1**. Compared to those in the bottom tertile of MD diet score, those with the greatest adherence to this dietary pattern were less likely to have glioma (28% vs. 39%, respectively).

Dietary intakes of participants across tertiles of Mediterranean dietary score are shown in **Table 3**. Greater adherence to the MD score was significantly associated with higher consumption of fruits, vegetables, fish, nuts, legumes, whole grains, energy, MUFA, vitamin B6, folate, magnesium and lower consumption of dairy. There was no significant difference in dietary intakes of meat products, tea and coffee, protein, total fat, carbohydrate, cholesterol, SFA, dietary fiber, vitamin B1, and calcium across tertiles of MD score.

Four different levels of adjustments with a wide range of potential confounders were used to assess the odds of glioma across tertiles of MD score (**Table 4**). After controlling for age, sex, and energy intake, participants in the highest tertile of MD score had not significantly lower odds of glioma than those in the lowest tertile (OR: 0.58, 95% CI: 0.32-1.03, P-trend =0.06). However, after further adjustments for potential confounders, individuals with the highest adherence to the MD score were 74% less likely to have glioma compared with those with the lowest adherence (OR: 0.26, 95% CI: 0.12-0.55, P-trend < 0.001). Taking dietary intakes into account did not significantly alter the association (OR: 0.36, 95% CI: 0.16-0.78, P-trend =0.009).

The findings remained unchanged after further controlling for BMI in the last model (OR: 0.36, 95% CI: 0.16-0.78, P-trend =0.01).

DISCUSSION

This hospital-based case-control study assessed the association between adherence to the MD and odds of glioma. After adjustment for environmental potential confounders, we observed an inverse relationship between adherence to the MD and odds of glioma. These findings persisted in multivariate models controlling for several confounders, including dietary intakes and BMI. To the best of our knowledge, this is the first study that investigates the relationship between MD and glioma.

According to the latest findings, glioma is one of the lethal malignancies worldwide, by which nearly 90 percent of patients with glioma die within three years after diagnosis [37]. Among environmental factors that affect the risk, diet is a potential modifiable cause [7]. In terms of diet, earlier studies have focused on the relationship between nutrients and foods [38, 39] and less attention has been paid to dietary patterns. Among dietary patterns, the beneficial effects of MD have long been reported for several health-related outcomes including cancers [40]. Mediterranean dietary pattern emphasizes on higher intakes of fish, fruits, vegetables, nuts, legumes, whole grains, and olive oil (rich in MUFAs) and lower intakes of foods from animal origin (different types of meat and dairy) [19]. Such combinations of foods and food groups in this dietary pattern results in a higher intake of antioxidants, various types of polyphenols as well as high consumption of dietary fiber, and unsaturated fats [41]. The majority of earlier studies investigating the association between MD and cancers have shown a protective role for this dietary pattern against risk of cancers [42-44]. In addition, a recent updated dose-response meta-analysis indicated that for each 2 point increment in the total score of MD, there was a 10%

decrease in the risk of mortality from all causes [45]. In the current study, we found that after controlling for potential confounders, individuals with the highest adherence to the MD were 74% less likely to have glioma. In accordance with our findings, a previous case-control study reported that higher adherence to the Dietary Approaches to Stop Hypertension, which encourages the consumption of healthy food items including higher consumption of nuts and legumes, vegetables, fruits, and whole grains, was associated with a 72% decreased odds of glioma [46]. In addition, combined findings of 17 observational studies about the consumption of fruit and vegetables revealed a lower risk of glioma among those with the highest intake [11]. Another meta-analysis that examined the association between fish intake and risk of brain tumors demonstrated a protective role for fish intake against brain cancer [47]. This was also the case for other components of MD. A recent dose-response meta-analysis on whole-grain intake and risk of total cancers indicated that whole grain consumption was associated with a lower risk of total cancers [48]. Taken together, it seems that food components of the MD may explain the protective association of this dietary pattern with glioma.

Various physiological mechanisms might provide explanations for the link between MD and glioma. Olive oil is one of the main components of MD. Squalene is a bioactive compound in olive oil with tumor-suppressing properties which might help reducing oxidative damage to DNA in the cells [49]. In addition, the phenolic content of olive oil, through its chemopreventive effects and regulating cancer cell signaling and cell cycle progression and antioxidant properties might play a role [50]. Another possible mechanism is the high intake of vegetables, fruit, and whole grains in this dietary pattern, which can lead to higher intakes of dietary fiber in this eating style. Dietary fiber might reduce the risk of cancer through increasing the bulk of stool and thus reducing transit time. In addition, fermentation of fiber into short-chain fatty acids in the

intestine may improve cells differentiation and apoptosis [51]. It is well established that oxidative stress, by producing reactive oxygen species, is involved in the pathogenesis of glioma [7]. The high amount of plant foods in this diet results in a diet rich in flavonoids, carotenoids, vitamin C and E, their important antioxidant properties can neutralize free radicals and inhibit DNA impairment [52, 53]. Finally, high intakes of MUFA to SFA in this pattern may improve hormonal metabolism and insulin resistance, through which it can inhibit the development of cancers [54, 55].

This study has several strengths. This is the first study that examined the association between adherence to the MD and glioma. In addition, due to adjustment for several confounders, the association we reached is independent of other factors. Enrollment of newly diagnosed patients is another strength. This study is from the Middle-East, where data on diet-disease relationships are scarce. Some limitations, however, should also be considered. The nature of case-control design with its inherent possibility of selection and recall bias would not allow us to confer causality. Assessment of dietary intakes by FFQ can result in misclassification of study participants. Although the effect of a large number of confounding variables was adjusted for in our analysis, the residual confounding effect cannot be ignored. In addition, findings of the present study cannot be easily generalized to general population. However, subjects in the present study were selected from the main hospitals, where all glioma patients in the country were referred to. Therefore, participants had diverse dietary intakes and were of different socio-economic status. In addition, the generalizability of the findings to other populations must be done with caution, due to the different dietary habits of population in the Middle-East.

In conclusion, in this case-control study, we found evidence indicating an inverse association between adherence to the Mediterranean dietary pattern and odds of glioma in Iranian adults. Further studies, particularly with a prospective design, are necessary to confirm our findings.

Author contributions

SMM, and AE conceived the study design and participated in data collection. MSh, MMS, and AE contributed to the statistical analyses and data interpretation. SMM, SR, GS helped in drafting this manuscript. AE supervised the study. The final version of the manuscript has been read and approved by all authors.

Conflicts of interest

No personal or financial conflicts of interest declared by all authors.

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

	Groups		
	Controls (*n=256*)	Cases (*n=128*)	*P**
Age (years)	42.8±13	43.4±14	0.65
BMI (kg/m^2)	26.1±3.8	26.2±4.3	0.76
Physical activity (METs)	33.8±5.5	34.8±6.3	0.12
Duration of cell phone use (years)	3.7±2.5	2.8±2.9	0.003
Males (%)	58.2	58.6	0.94
Married (%)	80.1	78.9	0.66
University graduated (%)	16.8	11.7	0.19
Family history of glioma (%)	5.5	19.5	<0.001
Family history of cancer (%)	34	32.8	0.82
High-risk jobs[a] (%)	2.7	10.2	0.003
High-risk residential area[b] (%)	21.5	30.5	0.05
History of exposure to the radiographic X-ray (%)	7.4	15.6	0.01
Smoker (%)	25	15.6	0.04
Frequent fried food intake[c] (%)	78.1	90.6	0.002
Frequent use of barbecue[d] (%)	12.1	15.6	0.34
Frequent microwave use (%)	19.1	7.8	0.004
Frequent canned foods intake (%)	5.9	6.3	0.88
Medication use (%)	5.1	7.8	0.29
Personal hair dye use (%)	41	21.9	<0.001
Exposure to chemicals (%)	10.5	19.5	0.01
History of dental photography (%)	59	46.1	0.02
History of head trauma (%)	28.9	43.8	0.004
History of allergy (%)	29.3	25	0.37
History of hypertension (%)	5.1	2.3	0.21
Supplement use (%)	15.6	7.8	0.03
Energy (kcal/day)	2561±722	2580±560	0.79
Nutrient intakes			
Protein (g/day)	97±30	98±22	0.70
Fat (g/day)	66±22	62±19	0.05
Carbohydrate (g/d)	412±128	425±101	0.31
Cholesterol (mg/day)	235±121	251±141	0.24
SFA (g/day)	21±9	19±7	0.09
MUFA (g/day)	22±8	20±7	0.02
Dietary fiber (g/day)	23±14	23±11	0.82
Vitamin B1 (mg/d)	2.4±1.2	2.5±0.60	0.46
Vitamin B6 (mg/day)	1.9±0.7	1.8±0.5	0.13
Folate (µg/day)	382±301	349±90	0.23
Calcium (mg/day)	1138±358	1019±263	0.001

Magnesium (mg/d)	520±154	524±133	0.79
Food groups			
Fruits	361±124	325±99	0.005
Vegetables	274±86	258±82	0.07
Meat products	56±34	59±28	0.38
Fish	12.6±12	13.6±14	0.50
Legumes	36±17	34±21	0.42
Nuts	4.9±4	3.8±3	0.004
Whole grains	150±108	176±134	0.04
Dairy products	355±131	309±116	0.001
Tea and coffee	736±387	618±299	0.003

Data are presented as mean ± standard deviation (SD) or percentages

[a] Farmers were considered as having a high-risk occupation.

[b] Subjects who lived in places nearby electromagnetic fields and cell phone and broadcast antennas in the last 10 years were considered as living in high-risk areas

[c] Persons who consumed fried food at least twice per week were considered as frequent fried food users

[d] Persons who used barbecue, microwave and canned foods at least twice per week were considered as frequent users

[*] Obtained from independent-samples t-test or Chi-square test, where appropriate.

Table 2. General characteristics of participants across tertiles of Mediterranean dietary score.

	Tertiles of MD dietary scores			
	T1 *n=113*	T2 *n=158*	T3 *n=113*	*P*[*]
Age (years)	42.4±14	43.5±13	42.8±12	0.36
BMI (kg/m^2)	26.1±4	26.1±4	26.2±3	0.97
Physical activity (METs)	33.7±5.5	34.4±6	34.2±5.7	0.60
Duration of cell phone use (years)	3.6±2.5	3.2±2.4	3.5±3.1	0.40
Males (%)	55.8	61.4	56.6	0.59
Married (%)	71.7	78.5	89.4	0.008
University graduated (%)	16.8	15.8	12.4	0.82
Family history of glioma (%)	8	10.8	11.5	0.64
Family history of cancer (%)	32.7	35.4	31.9	0.80
High-risk jobs[a] (%)	4.4	5.1	6.2	0.83
High-risk residential area[b] (%)	23.9	21.5	29.2	0.34
History of exposure to the radiographic X-ray (%)	9.7	13.9	5.3	0.07
Smoker (%)	23	25.3	15.9	0.17
Frequent fried food intake[c] (%)	85.8	79.7	82.3	0.43
Frequent use of barbecue[d] (%)	10.6	11.4	18.6	0.14
Frequent microwave use (%)	14.2	12	21.2	0.10
Frequent canned foods intake (%)	5.3	1.9	12.4	0.001
Medication use (%)	0.9	5.7	11.5	0.003
Personal hair dye use (%)	33.6	32.3	38.9	0.50
Exposure to chemicals (%)	11.5	12	17.7	0.30
History of dental photography (%)	56.6	55.7	51.3	0.68
History of head trauma (%)	28.3	31.6	42.5	0.06
History of allergy (%)	25.7	24.7	34.5	0.17
History of hypertension (%)	3.5	5.7	2.7	0.43
Supplement use (%)	17.7	11.4	10.6	0.21

Data are presented as mean ± standard deviation (SD) or percent

[a] Farmers were considered as having a high-risk occupation.

[b] Subjects who lived in places nearby electromagnetic fields and cell phone and broadcast antennas in the last 10 years were considered as living in high-risk areas

[c] Persons who consumed fried food at least twice per week were considered as frequent fried food users

[d] Persons who used barbecue, microwave and canned foods at least twice per week were considered as frequent users

[*] Obtained from ANOVA or Chi-square test, where appropriate

Table 3. Selected food groups and nutrients intakes of participants across tertiles of Mediterranean dietary score.

	Tertiles of MD dietary scores			
	T1 *n=113*	T2 *n=158*	T3 *n=113*	*P* [a]
Food groups(g/day)				
Fruits	303±9	346±7	397±9	<0.001
Vegetables	227±6	259±5	323±6	<0.001
Meat products	60.7±2.6	55.5±2.2	57.4±2.6	0.32
Fish	10.9±1.1	12.3±0.95	15.9±1.1	0.007
Legumes	26.6±1.6	34.6±1.3	44.6±1.6	<0.001
Nuts	3.2±0.3	4.2±0.2	6.4±0.3	<0.001
Whole grains	134±10	160±8	181±10	0.008
Dairy products	366±11	336±9	317±11	0.01
Tea and coffee	645±34	716±28	719±34	0.20
Nutrients				
Energy (Kcal/day)	2377±57	2534±48	2804±57	<0.001
Protein (g/day)	96.3±1.4	96.3±1.1	100±1.4	0.08
Fat (g/day)	62.5±1.3	64.5±1.1	66.9±1.3	0.08
Carbohydrate (g/d)	420±3.6	417±3	410±3.6	0.20
Cholesterol (mg/day)	242±10	231±8	251±10	0.36
SFA (g/day)	20.8±0.6	20.3±0.5	19.1±0.6	0.16
MUFA (g/day)	20±0.5	21±0.4	23±0.5	0.001
Dietary fiber (g/day)	21.7±1.2	22.4±1	22.5±1.3	0.08
Vitamin B1 (mg/d)	2.3±0.09	2.3±0.07	2.6±0.09	0.08
Vitamin B6 (mg/day)	1.8±0.05	1.8±0.04	2.1±0.05	<0.001
Folate (µg/day)	331±23	353±19	436±24	0.006
Calcium (mg/day)	1106±25	1080±21	1115±26	0.54
Magnesium (mg/d)	504±10	512±8	550±10	0.003

Data are presented as mean ± SE

[a] All values were adjusted for age, sex and energy, except for dietary energy intake, which was only adjusted for age and sex using ANCOVA.

Table 4. Odds ratios (95% CI) of glioma by tertiles of the Mediterranean dietary score.

	Tertiles of MD dietary scores			
	T1	T2	T3	P_{trend}*
Crude	1.00	0.77 (0.46, 1.27)	0.62 (0.35, 1.08)	0.09
Model 1	1.00	0.74 (0.44, 1.24)	0.58 (0.32, 1.03)	0.06
Model 2	1.00	0.52 (0.28, 0.98)	0.26 (0.12, 0.55)	<0.001
Model 3	1.00	0.60 (0.32, 1.14)	0.36 (0.16, 0.78)	0.009
Model 4	1.00	0.60 (0.32, 1.15)	0.36 (0.16, 0.78)	0.01

*Binary logistic regression was used to obtain OR and 95% CI. The overall trend of OR across increasing tertiles was examined by considering the median score in each category as a continuous variable.

Model 1: adjusted for age, sex, and energy intake

Model 2: further adjustments were made for physical activity, family history of cancer, family history of glioma, marital status, education, high-risk job, high-risk living area, cell phone usage time, 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, medication use, personal hair dye use, frequent fried food intake, frequent use of barbecue, canned foods and microwave

Model 3: additionally, adjusted for refined grains, tea and coffee, egg

Model 4: further adjustments were made for BMI

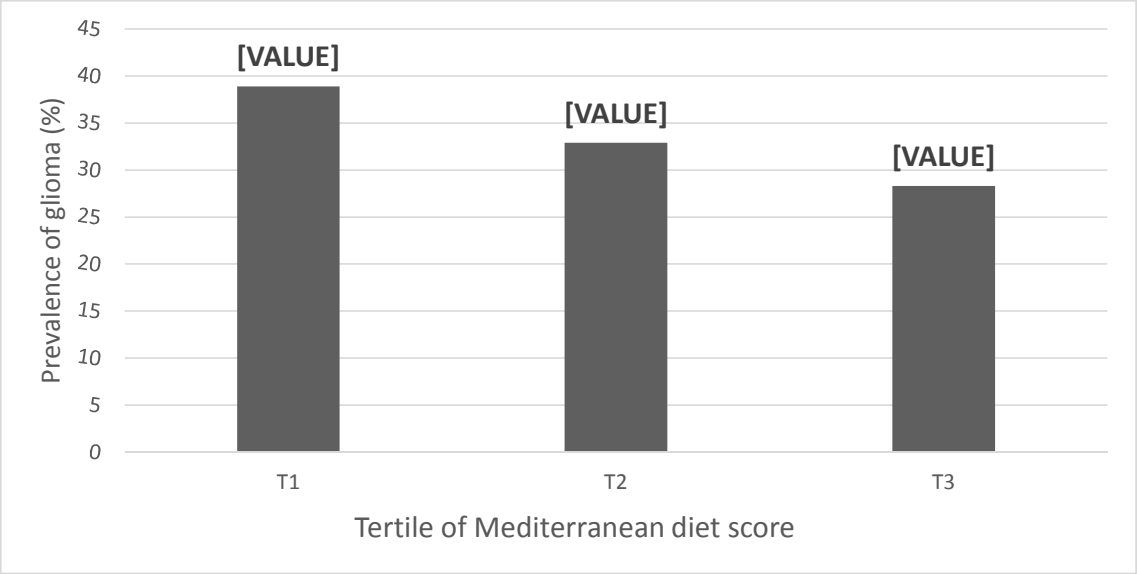

Figure 1. The prevalence of glioma across tertiles of Mediterranean diet score.