The association between dietary total antioxidant capacity and glioma among Iranian adults

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Abstract

Background: Dietary total antioxidant capacity (TAC) has been investigated in relation to different types of cancer. However, data on the link between dietary TAC and glioma are scarce and conflicting. We assessed the relation between dietary TAC and risk of glioma among Iranian adults. Methods: This investigation was a hospital-based case-control study that was done in Tehran between November 2009 and September 2011. Cases were individuals with pathologically confirmed glioma that were diagnosed during the last month (n=128). Controls were individuals, aged between 20 and 75 years, who were hospitalized or were outpatients referred to other wards of the same hospitals (n=256). Usual dietary intakes of participants during the preceding year were examined using a food frequency questionnaire. Data on dietary TAC from foods was gathered from published databases that provided the antioxidant capacity for each food item, measured by ferric reducing antioxidant power (FRAP). Results: Mean age of study participants in case and control groups was 43.4 and 42.7 y, respectively. Compared with participants in the lowest quartile, those in the highest quartile of dietary TAC had a lower odds of glioma (OR: 0.28, 95% CI: 0.15-0.45). This association was strengthened when potential confounders were taken into account (OR: 0.13; 95% CI: 0.05-0.35). Such inverse association was also seen for men (OR: 0.05, 95% CI: 0.01-0.19), but not for women. Furthermore, significant inverse associations were seen between dietary intakes of vitamin C (OR for Q4 vs. Q1: 0.14, 95% CI: 0.05-0.36; P-trend<0.01), vitamin B6 (OR for Q4 vs. Q1: 0.35, 95% CI: 0.13-0.97; P-trend=0.02) and β-carotene (OR for Q3 vs. Q1: 0.43, 95% CI: 0.19-0.98; P-trend=0.57) and glioma, after controlling for potential covariates. Conclusion: We found that dietary TAC as well as dietary intake of vitamin C, vitamin B6 and β-carotene was inversely associated with odds of glioma in Iranian adults.
Introduction

Glioma is the most common type of adult brain tumors that is responsible for 77% of malignant brain tumors [1]. The incidence of primary brain tumors is estimated to be 5.69 per 100,000 person-years in Iran and it is more common in men than women (male/female = 1.48) [2]. Increased age, white race, male sex, and genetic are considered as contributing factors to brain tumor [3].

A diet rich in bioactive redox substances, such as fruit and vegetables was associated with a reduced risk of various common cancers, particularly those of the respiratory and digestive tracts [4–8]. In addition, several studies reported that phytochemicals and nutrients in fruit and vegetables such as vitamins C, E and phenolic compounds can reduce the risk of cancer including glioma by reducing the endogenous formation of N-nitroso compounds [9–13]. Although some studies have considered the effects of individual antioxidants in relation to risk of cancer [14–16], dietary total antioxidant capacity (TAC) has been less studied as a contributing factor to cancer risk [17, 18]. Dietary total antioxidant capacity has been associated with a reduced risk of mortality [19], endometrial cancer [20], breast cancer [21] myocardial infarction [22] and heart failure [23]. Furthermore, intake of some phytoestrogens was inversely associated with glioma in a case-control study in San Francisco Bay Area [24]. However in another study in San Francisco, no significant association was seen between dietary total antioxidant capacity or its combination with vitamin supplements and survival of cancer patients [25]. Also, DeLorenze et al. reported different associations between some antioxidants and survival in various grade of glioma patients [26]. Therefore, TAC is not associated with brain tumors in some previous studies. According to our knowledge, there are few studies regarding the relationship between TAC and the odds of glioma in the world. All these studies came from Western societies; no information is available in this regard from
Middle Eastern populations. Since traditional Iranian dietary pattern includes large size of food with consumption of more refined grain, white rice and bread, hydrogenated oils and a greater percentage of energy from carbohydrates (27), examining the association between TAC and the odds of glioma in this part of the world might add further information to the knowledge in this field. So, in this study, we aimed to evaluate the association between TAC and glioma in the Iranian population.

Participants And Methods

Participants

This hospital-based case-control study was done in Tehran, Iran, between November 2009 and September 2011. Participants, both cases and controls, were selected by using a convenience-sampling method and based on inclusion criteria from the hospitals affiliated to Shahid Beheshti University of Medical Sciences, Tehran. With a power 80%, type I error of 0.05, and desired confidence interval of 0.95, the minimum required sample size was calculated to be 115 cases and 230 control subjects. So, we recruited 128 cases and 256 controls from the hospitals. Case participants were individuals with pathologically confirmed glioma (ICD-O-2 morphology codes 9380–9481) during the last month that had been referred to the department of neurosurgery of the hospitals. In other words, all patients with glioma were newly diagnosed cases with a maximum of one month from the diagnosis of the disease. Cases had to be aged between 20 and 75 years old to be included in the study. Individuals with a history of any type of pathologically confirmed cancer (except glioma), and those with a history of chemotherapy or radiotherapy (due to cancer) were not included in the study. Control participants were healthy individuals aged between 20 and 75 years old who were hospitalized in other wards of the same hospitals or were outpatients referring to the same clinics affiliated to Shahid Beheshti University of Medical Sciences. Cases and controls were matched in terms of age (± 5) and gender. All
cases and controls provided informed written consent. The study was ethically approved by the Research Council of Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran (IUMS).

Dietary assessment
Usual dietary intakes of study participants during the preceding year (during the year before to the diagnosis of glioma in case group and during the year before to the interview in control group) were examined using a validated Willett-format 126-item semi-quantitative food frequency questionnaire (FFQs) [27]. The FFQ consisted of 126 food items with standard portion sizes commonly consumed by Iranian populations. A trained interviewer, who was experienced in completing such questionnaires, administered the FFQ through face-to-face interviews. Interviews with control and case participants were conducted in the presence of individuals who were involved in the preparation and cooking of foods. Participants were requested to report their usual consumption frequency of a given serving of food in the preceding year on a daily, weekly or monthly basis. All reported consumption frequencies were converted to grams per day using household measures [28]. Subsequently, daily intakes of energy and nutrients were determined using the United State Department of Agriculture (USDA) food composition database (30) that was modified for Iranian foods. The interviewer was totally unaware of the research hypotheses, but aware of the participants’ condition (in terms of having the disease). A previous year-long validation study of this FFQ revealed good correlations between dietary intakes assessed by the FFQ and those obtained from the multiple dietary recalls (two recalls in each month of the year) [27]. The energy-adjusted correlation coefficients between the dietary intakes obtained from the FFQ and those from the 24-h dietary recalls were 0.65 for vitamin E, 0.68 for β-carotene and 0.65 for vitamin C. The reliability of the FFQ was assessed by comparing nutrient intakes obtained from the FFQ on two occasions
1-year apart. The correlation coefficients for the reliability of the FFQ for dietary vitamin E, β-carotene and vitamin C intake were 0.78, 0.84 and 0.83, respectively. Overall, these data indicated that the FFQ provides reasonably valid measures of the average long-term dietary intakes [27].

Assessment of TAC

In this study, dietary total antioxidants capacity was computed using ferric reducing antioxidant power (FRAP). Data on TAC (in mmol) from foods was gathered from published databases that provided the antioxidant capacity for each food item, measured by FRAP. If TAC data were not available for food items, the value of the nearest comparable food was assigned (31). Intake of each food item was converted to grams consumed per day and total antioxidant capacity intake (in mmol) was calculated by summing the product of grams consumed over all food items and units of antioxidant content from an antioxidant index database [29].

Assessment of other variables

Required information about age, sex, marital status, place of residence, education, occupation, smoking status, use of supplements, family history of cancer and glioma, history of allergy and head 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 was examined using a pretested questionnaire. Participants’ physical activity during the previous year was assessed using the International Physical Activity Questionnaire (IPAQ) and expressed as metabolic equivalent task (MET)-h/week. Subjects’ weight was measured by a dietitian using a digital scale to the nearest 500 g with the subjects wearing light clothing and no shoes. Height was measured in a standing position with a tape measure to the nearest 0.5 cm with the shoulders in normal position. BMI was calculated as weight (kg) divided by height (m²). We considered farmers as having a high-risk occupation for glioma on the basis of
previous publications (32). Individuals who lived in places near the electromagnetic fields and cell phone and broadcast antennas in the last 10 years were defined as living in high-risk areas [30]. Individuals who consumed fried food at least twice per week were considered as frequent fried food users. This definition was also applied for barbecue use, microwave use as well as consumption of canned foods.

Statistical methods
First, participants were categorized into quartiles of dietary TAC. General characteristics and dietary intakes of study participants across quartiles of dietary TAC were assessed using one-way ANOVA for continuous variables and $\chi^2$ test for categorical variables. In addition, independent samples Student’s $t$ test and $\chi^2$ test were used to compare general characteristics and dietary intakes between cases and controls. To assess the association between dietary TAC and glioma, logistic regression in different models was applied. First, we controlled for age (continuous), sex (male/female) and energy intake (kcal/d). Further adjustments were made for physical activity (continuous), family history of cancer (yes/no), family history of glioma (yes/no), marital status (married/ single/ divorced), education (university graduated/ non university graduated), high risk occupation (farmer/ non-farmer), high risk residential area (yes/no), duration of cell phone use (continuous), 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 (smoker/non-smoker), exposure to chemicals (yes/no), drug use (yes/no), personal hair dye use (yes/no), frequent fried food intake (yes/no), frequent use of barbecue, canned foods and microwave (yes/no) in the second model. Additional controlling was performed for BMI in the last model to see if the association was independent of obesity. In all analyses, the first quartile of dietary TAC was considered as the reference category. To obtain the overall trend of odds ratios across increasing
quartiles of dietary TAC, we considered these quartiles as an ordinal variable in the logistic regression models. Stratified analysis by gender was also done. In addition, we performed the same analyses for some components of dietary TAC in relation to glioma. All the statistical analyses were carried out using SPSS (SPSS Inc., version 18). P values less than 0·05 were considered as significant.

Results

Mean age of study participants in case and control groups was 43.4 and 42.7 y, respectively. General characteristics of study participants across case and control groups as well as across quartiles of the dietary TAC are presented in Table 1. Cases with glioma were more likely to have a family history of brain tumors, live in high-risk areas, be frequently exposed to radiographic X-ray and chemicals and have high-risk occupations, compared with controls. Head trauma was more prevalent among them compared with controls. No significant difference was found between the two groups in terms of age, BMI, sex, family history of cancer, history of allergy, hypertension, supplement use and education. Across categories of dietary TAC, individuals in the highest quartile were more likely to be educated, had greater duration of cell phone use, history of head trauma, drug use, and were less likely to consume fried food frequently and exposure to chemicals compared with those in the lowest quartiles of dietary TAC.

Table 1
General characteristics of study participants across case and control groups as well as across quartiles of the Dietary TAC

| Groups                  | p₆ | Quartiles of dietary TAC | p₇ |
|-------------------------|----|--------------------------|----|
|                         |    | 1                        |    |
|                         |    | 2                        |    |
|                         |    | 3                        |    |
| Age (y)                 |    | 4                        |    |
| Cases (128)             |    | Controls (256)           |    |
| 43.4 ± 14.6             |    | 42.7 ± 13.3              |    |
| Females (%)             |    | 60.0                     |    |
| 41                      |    | 42                       |    |
| 0.75                    |    | 1.1                      |    |
| BMI (kg/m²)             |    | 26.0 ± 4.5               |    |
| 26.2 ± 4.2              |    | 26.1 ± 3.8               |    |
| 0.75                    |    | 0.66                     |    |
| Married (%)             |    | 77.9                     |    |
| 79                      |    | 80                       |    |
| 0.66                    |    | 2.1                      |    |
| University graduated (%)|    | 77.1                     |    |
| 12                      |    | 17                       |    |
| 0.22                    |    | 1.1                      |    |
|                                | 10    | 3     | 0.003 | 4.2  | 6.2  | 6.2  | 4.2  | 0.84 |
|--------------------------------|-------|-------|-------|------|------|------|------|------|
| High-risk jobs \(^2\) (%)     |       |       |       |      |      |      |      |      |
| High-risk residential area \(^3\) (%) | 30    | 21    | 0.05  | 22.1 | 22.9 | 19.8 | 32.6 | 0.17 |
| Duration of cell phone use (y) | 2.85 ± 2.8 | 3.70 ± 2.56 | 0.003 | 3.2 ± 2.6 | 3.1 ± 2.5 | 3.0 ± 2.6 | 4.2 ± 2.9 | 0.004 |
| Exposure to the radiographic x-ray (%) | 16    | 7.4   | 0.01  | 5.3  | 8.3  | 14.6 | 11.6 | 0.15 |
| History of head trauma (%)    | 44    | 29    | 0.004 | 21.1 | 33.3 | 39.6 | 42.1 | 0.01 |
| History of allergy (%)        | 25    | 29    | 0.40  | 29.5 | 28.1 | 26.0 | 28.4 | 0.96 |
| History of hypertension (%)   | 2     | 5     | 0.28  | 2.1  | 5.2  | 3.1  | 6.3  | 0.45 |
| Frequent fried food intake \(^4\) (%) | 91    | 78    | 0.001 | 84.2 | 89.6 | 81.2 | 73.7 | 0.03 |
| Frequent use of barbecue \(^5\) (%) | 16    | 12    | 0.21  | 8.4  | 17.7 | 11.5 | 15.8 | 0.22 |
| Frequent microwave use \(^6\) (%) | 8     | 19    | 0.002 | 20.0 | 8.3  | 13.5 | 18.9 | 0.09 |
| Frequent canned foods intake \(^5\) (%) | 6     | 7     | 0.52  | 5.3  | 5.2  | 3.1  | 9.5  | 0.29 |
| Drug use (%)                  | 8     | 5     | 0.36  | 2.1  | 3.1  | 2.1  | 16.8 | < 0.001 |
| Dental photography (%)        | -     | -     | -     | 58.9 | 45.8 | 55.2 | 58.9 | 0.21 |
| Personal hair dye use (%)     | 22    | 41    | < 0.001 | 43.2 | 26.0 | 37.5 | 32.6 | 0.08 |
| Exposure to chemicals (%)     | 20    | 11    | 0.01  | 3.2  | 16.7 | 15.6 | 17.9 | 0.009 |
| Family history of glioma (%)  | 19    | 5     | < 0.001 | 10.6 | 16.7 | 5.2  | 7.5  | 0.01 |
| Family history of cancer (%)  | 33    | 34    | 0.90  | 37.9 | 33.3 | 32.3 | 29.5 | 0.29 |
| SupPLEMENT USE (%)            | 8     | 16    | 0.36  | 10.5 | 15.6 | 13.5 | 12.6 | 0.77 |
| Physical activity (Met-h/wk)   | 34.7 ± 6.3 | 33.8 ± 5.5 | 0.12 | 33.2 ± 5.4 | 35.1 ± 5.8 | 35.1 ± 5.8 | 33.1 ± 5.7 | 0.01 |

1 All values are means ± SD, unless indicated.
2 Farmers were considered as having a high-risk occupation.
3 Individuals who lived in places near to the electromagnetic fields, cell phone and broadcast antennas in the last 10 years were defined as living in high-risk areas.
4 Individuals with at least two times of fried food intake per week were considered as frequent fried food users.
5 Those with at least two times per week of barbecue use, microwave use as well as consumption of canned foods were considered as frequent users.
6 P values were obtained from independent sample t test or chi-square test, where appropriate.
7 P values were obtained from one-way ANOVA or chi-square test, where appropriate

Dietary intakes of study participants across case and control groups as well as across
quartiles of dietary TAC are provided in Table 2. Cases had higher intake of refined grains, red meats, partially hydrogenated and non-hydrogenated vegetable oils, and lower intake of whole-grains, fruits, vegetables, fats, dairy products, legumes and nuts, calcium, selenium and vitamin E than controls. Individuals in the top quartile of dietary TAC had higher intake of proteins, calcium, vitamin C, whole-grains, fruits and vegetables, legumes and nuts compared with those in the bottom quartile. In contrast, individuals in the highest quartile of dietary TAC had lower intake of sugar-sweetened beverages and non-hydrogenated vegetable oils compared with those in the lowest quartile.
### Table 2
Dietary intakes of study participants across case and control groups as well as across quartiles of the Dietary TAC\(^1\)

| Groups | p\(^2\) | Quartiles of dietary TAC | p\(^3\) |
|--------|--------|--------------------------|--------|
|        | Cases (n = 128) | Controls (n = 256) | 1 | 2 | 3 | 4 | 1 |
| Energy (kcal/d) | 2580 ± 560 | 2561 ± 722 | 0.79 | 2.3 ± 5.0 | 2.4 ± 6.0 | 2.6 ± 7.1 | 2.8 ± 7.5 | < 0.001 |
| Nutrients | | | | | | | | 
| Proteins (g/d) | 98 ± 22 | 97 ± 30 | 0.70 | 8.9 ± 2.0 | 9.3 ± 2.2 | 9.8 ± 2.2 | 1.0 ± 3.8 | < 0.001 |
| Fats (g/d) | 62 ± 19 | 66 ± 22 | 0.05 | 6.4 ± 1.8 | 6.1 ± 2.1 | 6.4 ± 2.1 | 6.8 ± 2.1 | 0.14 |
| SFA (g/d) | 19 ± 7 | 21 ± 9 | 0.08 | 2.0 ± 0.7 | 1.9 ± 0.9 | 2.0 ± 0.8 | 2.1 ± 0.8 | 0.53 |
| Dietary Fiber (g/d) | 23 ± 11 | 23 ± 15 | 0.82 | 24.5 ± 1.9 | 20.4 ± 0.9 | 22.5 ± 1.0 | 24.9 ± 1.4 | 0.07 |
| Ca (mg/day) | 1019 ± 263 | 1139 ± 3580.001 | 9.9 ± 2.4 | 1.0 ± 2.7 | 1.0 ± 2.7 | 1.2 ± 3.8 | < 0.001 |
| Selenium (mcg/d) | 0.06 ± 0.04 | 0.08 ± 0.36 | 0.02 | 0.07 ± 0.005 | 0.06 ± 0.003 | 0.06 ± 0.004 | 0.06 ± 0.003 | 0.48 |
| Vitamin E (mg/d) | 5 ± 2 | 6 ± 3 | 0.03 | 5.6 ± 0.2 | 5.0 ± 0.3 | 5.3 ± 0.2 | 5.5 ± 0.3 | 0.40 |
| Folate (mcg/d) | 349 ± 90 | 382 ± 302 | 0.23 | 3.6 ± 49.5 | 3.3 ± 8.6 | 3.6 ± 8.1 | 4.2 ± 15.6 | 0.11 |
| Vitamin C (mg/d) | 126 ± 59 | 143 ± 113 | 0.11 | 1.2 ± 3.2 | 1.2 ± 6.5 | 1.3 ± 3.9 | 1.7 ± 1.7 | 0.001 |
| Food groups | | | | | | | | |
| Refined grains (g/d) | 501 ± 175 | 421 ± 182 | < 0.001 | 4.2 ± 17.6 | 4.4 ± 17.6 | 4.3 ± 18.5 | 4.8 ± 20.5 | 0.09 |
| Whole grains (g/d) | 150 ± 134 | 177 ± 108 | 0.03 | 1.1 ± 9.4 | 1.5 ± 11.8 | 1.7 ± 13.1 | 1.9 ± 12.3 | < 0.001 |
| White meats (g/d) | 30 ± 13 | 33 ± 22 | 0.23 | 32.6 ± 1.3 | 30.5 ± 1.2 | 29.3 ± 1.1 | 34.5 ± 3.4 | 0.28 |
| Red meats (g/d) | 41 ± 28 | 36 ± 20 | 0.03 | 35.2 ± 2.3 | 37.3 ± 2.3 | 36.6 ± 1.7 | 41.8 ± 2.8 | 0.21 |
| Fruits (g/d) | 325 ± 99 | 361 ± 124 | 0.005 | 3.1 ± 9.9 | 3.1 ± 11.0 | 3.4 ± 9.5 | 4.1 ± 14.6 | < 0.001 |
| Vegetables (g/d) | 258 ± 83 | 274 ± 86 | 0.07 | 2.5 ± 71.2 | 2.5 ± 72.0 | 2.7 ± 8.5 | 2.9 ± 10.5 | < 0.001 |
| Dairy products (g/d) | 309 ± 117 | 355 ± 131 | 0.001 | 3.2 ± 12.1 | 3.4 ± 12.1 | 3.3 ± 14.1 | 3.6 ± 13.7 | 0.15 |
| Legumes and nuts (g/d) | 40 ± 23 | 46 ± 20 | 0.01 | 43.6 ± 2.1 | 38.5 ± 2.0 | 44.9 ± 2.2 | 49.8 ± 2.1 | 0.003 |
| Sugar-sweetened beverages (g/d) | 79 ± 67 | 83 ± 74 | 0.57 | 68.4 ± 5.9 | 64.9 ± 5.3 | 79.7 ± 6.7 | 1.1 ± 9.7 | < 0.001 |
| Partially hydrogenated vegetable oils (g/d) | 15 ± 15 | 9 ± 12 | < 0.001 | 9.3 ± 1.3 | 10.4 ± 1.4 | 13.2 ± 1.4 | 11.0 ± 1.3 | 0.24 |
| Non-hydrogenated vegetable oils (g/d) | 7 ± 6 | 8 ± 5 | 0.03 | 9.3 ± 0.5 | 7.8 ± 0.5 | 6.7 ± 0.5 | 7.6 ± 0.5 | 0.005 |

\(^1\) All values are means ± SE

\(^2\) P values were obtained from independent sample t test or chi-square test, where appropriate.

\(^3\) P values were obtained from one-way ANOVA or chi-square test, where appropriate

Multivariable-adjusted odds ratios and 95% CIs for glioma across categories of dietary TAC are shown in Table 3. Compared with participants in the lowest quartile, those in the
highest quartile of dietary TAC had lower odds for having glioma (OR: 0.28, 95% CI: 0.15–0.45). This association strengthened when potential confounders were taken into account; such that individuals in the top quartile of dietary TAC had 87% lower risk of glioma compared with those in the bottom quartile (OR: 0.13, 95% CI: 0.05–0.35).

Table 3

| Quartiles of dietary TAC | Crude  | Model 1 | Model 2 | Model 3 | \(P_{\text{trend}}\) |
|--------------------------|--------|---------|---------|---------|-----------------|
| 1                        | 1.00   | 1.00    | 1.00    | 1.00    | < 0.001         |
| 2                        | 0.90 (0.51–1.60) | 0.80 (0.45–1.45) | 0.59 (0.28–1.22) | 0.59 (0.28–1.25) | < 0.001         |
| 3                        | 0.42 (0.23–0.78) | 0.35 (0.19–0.67) | 0.23 (0.10–0.51) | 0.23 (0.10–0.52) | < 0.001         |
| 4                        | 0.28 (0.15–0.45) | 0.21 (0.10–0.43) | 0.14 (0.05–0.35) | 0.13 (0.05–0.35) | < 0.001         |

Model 1: Adjusted for age (continuous), gender (male/female) and energy intake (kcal/d).

Model 2: Further adjustments were done for physical activity (continuous), family history of cancer (yes/no), family history of glioma (yes/no), marital status (married/single/divorced), education (university graduated/ non-university education), high risk occupation (farmer/ non-farmer), high risk residential area (yes/no), duration of cell phone use (continuous), 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 (smoker/non-smoker), exposure to chemicals (yes/no), drug use (yes/no), personal hair dye use, frequent fried food intake (yes/no), frequent use of barbecue, canned foods and microwave (yes/no).

Model 3: Additionally adjusted for BMI (continuous).

Gender-stratified multivariable-adjusted odds ratios for glioma across quartiles of dietary TAC are provided in Table 4. Among men, a significant inverse association was found between dietary TAC and glioma; such that after controlling for potential confounders, men in the highest quartile of dietary TAC had 95% lower odds for having glioma compared with those in the lowest quartile (OR: 0.05, 95% CI: 0.01–0.19). No significant association was seen between dietary TAC and glioma among women either before or after controlling for covariates.
Table 4
Multivariable-adjusted odds ratios and 95% CIs for glioma across different categories of dietary TAC, stratified by gender

| Quartiles of dietary TAC |  |  |  |  |
|--------------------------|---|---|---|---|
|                          | 1 | 2 | 3 | 4 |
| **Males**                |   |   |   |   |
| Crude                    | 1.00 | 0.50 (0.22-1.17) | 0.19 (0.08-0.48) | 0.16 (0.06-0.37) |
| Model 1                  | 1.00 | 0.49 (0.21-1.14) | 0.19 (0.07-0.46) | 0.14 (0.06-0.35) |
| Model 2                  | 1.00 | 0.22 (0.06-0.74) | 0.06 (0.02-0.21) | 0.05 (0.01-0.19) |
| Model 3                  | 1.00 | 0.21 (0.06-0.73) | 0.05 (0.01-0.20) | 0.05 (0.01-0.19) |
| **Females**              |   |   |   |   |
| Crude                    | 1.00 | 1.31 (0.57-2.99) | 0.80 (0.33-1.89) | 0.41 (0.12-1.38) |
| Model 1                  | 1.00 | 1.08 (0.46-2.54) | 0.56 (0.22-1.43) | 0.32 (0.09-1.10) |
| Model 2                  | 1.00 | 0.96 (0.26-3.51) | 0.92 (0.23-3.75) | 0.38 (0.06-2.22) |
| Model 3                  | 1.00 | 0.94 (0.26-3.43) | 0.97 (0.23-4.03) | 0.40 (0.07-2.40) |

**Model 1:** Adjusted for age (continuous) and energy intake (kcal/d).
**Model 2:** Further adjustments were done for physical activity (continuous), family history of cancer (yes/no), family history of glioma (yes/no), marital status (married/single/divorced), education (university graduated/ non-university education), high risk occupation (farmer/ non-farmer), high risk residential area (yes/no), duration of cell phone use (continuous), 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 (smoker/non-smoker), exposure to chemicals (yes/no), drug use (yes/no), personal hair dye use, frequent fried food intake (yes/no), frequent use of barbecue, canned foods and microwave (yes/no)
**Model 3:** Additionally adjusted for BMI (continuous)

The association between some components of dietary TAC and glioma are shown in Table 5. A significant inverse association was found between dietary intake of vitamin C and glioma. When potential confounders and BMI were controlled, individuals in the highest quartile of vitamin C intake had 86% lower risk of glioma compared with those in the lowest quartile (OR: 0.14, 95% CI: 0.05–0.36). Such finding was also seen for dietary intake of vitamin B6; such that in fully adjusted model, participants in the top quartile of vitamin B6 intake were 65% less likely to have glioma compared with those in the bottom quartile (OR: 0.35, 95% CI: 0.13–0.97). Furthermore, individuals with moderate intake of β-carotene (third quartile) had 57% less risk of glioma than those with the lowest intake (OR: 0.43, 95% CI: 0.19–0.97). Controlling for potential confounders did not change this association (OR: 0.43, 95% CI: 0.19–0.98).
Table 5
Multivariable-adjusted odds ratios and 95% CIs between some components of dietary TAC and glioma

|                      | Quartiles of components of dietary TAC | \(P_{\text{trend}}^2\) |
|----------------------|----------------------------------------|------------------------|
|                      | 1           | 2                        | 3                        | 4                        |
| Vitamin E            | 1.00        | 0.57 (0.27–1.20)         | 0.60 (0.27–1.36)         | 0.87 (0.37–2.05)         | 0.41 |
| Multivariable-adjusted & 1.00 | 0.57 (0.27–1.20)         | 0.61 (0.27–1.38)         | 0.83 (0.35–1.97)         | 0.39 |
| Multivariable-adjusted + BMI selenium | 1.00 | 2.79 (1.24–6.29)       | 1.73 (0.74–4.03)         | 2.76 (1.16–6.57)         | 0.01 |
| Multivariable-adjusted & 1.00 | 2.80 (1.23–6.34)       | 1.72 (0.74–4.03)         | 2.53 (1.05–6.12)         | 0.01 |
| Vitamin C            | 1.00        | 0.61 (0.29–1.31)         | 0.65 (0.30–1.41)         | 0.14 (0.05–0.35)         | < 0.01 |
| Multivariable-adjusted & 1.00 | 0.61 (0.29–1.30)       | 0.66 (0.30–1.44)         | 0.14 (0.05–0.36)         | < 0.01 |
| Multivariable-adjusted + BMI Vitamin B2 | 1.00 | 1.08 (0.52–2.28)       | 0.48 (0.20–1.13)         | 0.55 (0.18–1.69)         | 0.34 |
| Multivariable-adjusted + BMI Vitamin B6 | 1.00 | 1.12 (0.53–2.35)       | 0.49 (0.20–1.16)         | 0.57 (0.18–1.78)         | 0.39 |
| Multivariable-adjusted β-carotene | 1.00 | 0.94 (0.44–2.02)       | 0.40 (0.17–0.93)         | 0.35 (0.13–0.97)         | 0.04 |
| Multivariable-adjusted + BMI Multivariable-adjusted & 1.00 | 0.93 (0.43–2.00)       | 0.40 (0.17–0.95)         | 0.35 (0.13–0.97)         | 0.02 |
| Multivariable-adjusted + BMI Multivariable-adjusted & 1.00 | 0.97 (0.47–2.04)       | 0.43 (0.19–0.97)         | 0.94 (0.43–2.06)         | 0.61 |
| Multivariable-adjusted + BMI Multivariable-adjusted & 1.00 | 0.93 (0.44–1.96)       | 0.43 (0.19–0.98)         | 0.99 (0.45–2.18)         | 0.57 |

1 Adjusted for age (continuous) and energy intake (kcal/d), sex, physical activity (continues), family history of cancer (yes/no), family history of glioma (yes/no), marital status (married/single/divorced), education (university graduated/ non-university education), high risk occupation (farmer/ non-farmer), high risk residential area (yes/no), duration of cell phone use (continuous), 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 (smoker/non-smoker), exposure to chemicals (yes/no), drug use (yes/no), personal hair dye use, frequent fried food intake (yes/no), frequent use of barbecue, canned foods and microwave (yes/no).

2P trend was obtained by the use of categories of healthy lifestyle score as an ordinal variable in the model.

Discussion
In this study, a significant inverse association was found between dietary TAC (assessed by FRAP) and glioma. Such finding was also seen even after controlling for potential confounders. Furthermore, we found significant inverse associations for some components of the dietary TAC including vitamin C, vitamin B6 and β-carotene either before or after controlling for covariates. To our knowledge, this is the first study to examine the association between dietary TAC and glioma in the Middle East.
Dietary total antioxidant capacity has been investigated in relation to different chronic diseases, particularly cancers. It seems that dietary TAC in assessing diet-disease relations is better than focusing on a single food rich in antioxidants or one special antioxidant due to decreasing the co-linearity problem which might occur when assessing single food and nutrient intake.

Based on our findings, high dietary total antioxidant capacity was associated with decreased odds of glioma. In line with our findings, a large number of studies had shown that dietary TAC had beneficial effects on different types of cancer including breast [21] and endometrial cancer [20]. In a case–control study in the San Francisco, adherence to diet with a high TAC was associated with decreased risk of glioma [24]. In contrast, in a prospective cohort study, DeLorenze et al. reported no significant association between total dietary antioxidant intake and survival for all grade of glioma; except grade IV of the disease [26]. Another study has also failed to reach a significant association between dietary TAC and survival from glioma [25]. It should be noticed that studies showing no significant association mostly assessed survival from glioma. Furthermore, conflicting findings might be explained by different methods used to measure dietary TAC, different study designs, different tools for assessing dietary intakes (FFQ, food record or dietary history) and considering different grades of this type of brain tumor. We found an inverse association with glioma for high intake of vitamin C, vitamin B6 and β-carotene which is consistent with findings from two recent meta-analyses [31, 32]. Pervious studies have shown that dietary antioxidants were effective in decreasing of lipid peroxidation level by scavenging free radicals generated in the brain tissues which caused oxidative DNA damage. Antioxidants also play a role in modulating DNA repair, enhancing the levels of glutathione and activities of superoxide dismutase (SOD) and possibly anti-inflammatory mechanisms [33, 34].
Several antioxidants including vitamin C, carotenoids and polyphenols are the main contributors to total antioxidant capacity of diet. The presence of mentioned antioxidants or foods rich in them during a meal might improve exogenous antioxidants intake and decrease the production of radical species. In addition, these antioxidants have synergistic effects with endogenous antioxidants providing a more efficient protection against oxidative stress and decreasing the risk of cancer. Furthermore, inflammation is a known risk factor for cancer and diet with high total antioxidant capacity has anti-inflammatory properties.

The exact reasons for the observed gender disparity in the associations between dietary TAC and glioma were unclear, but might, at least in part, be in the differential influence of gonadal steroids on cell growth and tumor progression. Another reason for this discrepancy might be the difference in accuracy of reporting dietary intakes among females and males. Thus, actual food choices, self-reported preferences for foods and accuracy of dietary assessment may all vary by gender. It has been shown that gender is the most personal characteristic that related to intake measurement errors for food groups. Higher prevalence of glioma in male Iranians compared with females might explain this observed association. In addition, men have more exposure to cancer risk factors and it might be another reason for gender disparity in the associations between dietary TAC and glioma found in the current study.

Our study has several strengths. This was the first study to examine the association between dietary TAC, as measured by FRAP, and glioma in the Middle East. We also selected the modified version of FRAP detecting both lipophilic and hydrophilic antioxidants to measure dietary TAC. This assay enables us to evaluate the overall effect of antioxidant instead of individual effects of each antioxidant. We controlled for a wide range of confounders to achieve an independent association between dietary TAC and risk
of glioma. In the study, we enrolled new cases of glioma to reduce the possibility of changing habitual dietary intakes in these patients.

The main limitation of this study includes the case-control design of the study. Like other case-control studies, this investigation was susceptible to some biases including selection and recall biases and the findings cannot be extrapolated to the general population. However, case-control studies are efficient in terms of time and cost and appropriate for studying the association of dietary intakes with rare disease such as cancers. The total antioxidant capacity has not been measured for Iranian foods but the samples for antioxidant measurements were supplied from markets in Asia [29]. Although the aim of this study was to assess whether ranking of the dietary total antioxidant capacity based on FRAP assay is associated with glioma risk, we did not have the exact values of vitamin supplements that might contribute to TAC. Unfortunately, in our study, no biomarker data for antioxidants were assessed to strengthen our findings.

Conclusions

Dietary total antioxidant capacity was inversely associated with risk of glioma in Iranian adults. Moreover, such inverse association was also seen for some components of the dietary TAC including vitamin C, vitamin B6 and β-carotene. Further studies, particularly with prospective designs, are needed to confirm our findings.

Declarations

**Ethical Approval and Consent to participate:** All participants provided informed written consent. The study was ethically approved by the Research Council of Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran (IUMS).

**Consent for publication:** Each author acknowledges he/she has participated in the work in a substantive way and is prepared to take public responsibility for the work.
**Availability of supporting data:** Supporting data for this investigation can be available by contacting the supervisor of the research (AE).

**Competing interests:** None of the authors declared potential personal or financial conflicts of interest.

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**Authors' contributions:** MH, MS, GS, PS, OS and AE designed the research, conducted the study, analyzed the data, wrote the manuscript and had the responsibility for the final content. All authors read and approved the final manuscript.

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