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Autism Spectrum Disorder and Dietary Intake of Vitamin E

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ABSTRACT

Background: Autism Spectrum Disorder (ASD) is a complicated condition that affects brain development, possibly caused by genetics and environmental factors. Individuals with ASD manifest a lack of balance between pathways that cause oxidative stress and levels of anti-oxidant agents. However, the association between ASD and dietary intake of antioxidants, such as vitamin E, is not yet clear.

Objectives: This study aimed to compare the dietary vitamin E intake in children with ASD and typically developing (TD) children.

Methods: Totally, 110 individuals with ASD from 5 to 15 years were selected as the case group and 110 TD children of the same age group were selected as the control group. The (GARS 2) was used to confirm the participants' ASD diagnoses. The food frequency questionnaire (FFQ) was used for collecting the required information on the child's diet. The Nutritionist IV software was used to evaluate the intake of different types of vitamin E.

Result: A significantly lower intake of dietary vitamin E was observed in individuals with ASD relative to the control group (15.66 ± 12.72 vs. 28.60 ± 10.85 mg/day, $p > 0.001$). After adjusting for confounders such as age, gender, mother's age, Body Mass Index (BMI), and diet, decreased vitamin E intake was associated with an increased risk of developing ASD (OR = 0.90, 95% CI: 0.85–0.94, $p < 0.001$).

Conclusion: An increased intake of vitamin E may be associated with a decreased risk of ASD. Further research is required to confirm this finding.

1 | Introduction

Autism spectrum disorder (ASD) is a complex disorder that affects brain development, causing problems with social interaction, restricted and repetitive behaviors, and interests. There is ongoing debate as to whether the rate at which ASD occurs in the population is on the rise, or if the higher reported rates in recent decades are attributable to heightened awareness, evolving diagnostic criteria, and more sensitive diagnostic systems [1]. Despite an increase in autism diagnoses reported by the State Welfare Organization, Iran lacks a definitive estimate of its autistic population. A national study suggests a prevalence of around 1 in 160 children by age 5, but many receive a late diagnosis, often after age 3 [2]. Public awareness about autism remains low, leading to stigma and isolation for families. Parents grapple with inaccurate diagnoses, limited support resources, and concerns about their child's future [3]. Research highlights the need for culturally sensitive approaches and targeted interventions to improve diagnosis, support, and overall understanding of ASD [2–4].

ASD impacts social interaction in several ways, including difficulty with nonverbal cues, conversation, and social awareness. A number of genetic and environmental factors influence the likelihood of developing the condition [1, 5]. Researchers investigating the causes of ASD focused recently on oxidative stress and inflammation status because oxidative and inflammatory biomarkers are reported to be elevated in autistic individuals and may be associated with symptom severity, suggesting they play a role in the disease [6]. Furthermore, oxidative stress and inflammation seem to be interconnected, potentially revealing a complex underlying mechanism in ASD. Ultimately, studying these areas could lead to the development of better diagnostic tools, methods to track disease progression, and even new treatment options [6–8].

Several lines of evidence suggest that oxidative stress and inflammation may play a role in the underlying mechanisms of ASD [9–11]. However, it remains unclear whether these factors trigger the onset of ASD or regulate its pathogenesis and symptomatology. Several studies indicated that individuals with ASD manifest a lack of balance between pathways that cause inflammation and those that reduce it, characterized by elevated levels of inflammatory mediators and reduced levels of anti-inflammatory agents [12]. Moreover, recent studies have reported that oxidative stress may contribute to brain inflammation and ASD-like behaviors [10]. Numerous studies have demonstrated reduced levels of ROS-scavenging enzymes, including superoxide dismutase (SOD), catalase, glutathione (GSH), and glutathione peroxidase (GPx) in individuals with ASD compared to neurotypical individuals [10, 13]. Moreover, evidence suggests the presence of neuroinflammatory conditions in ASD, which are often linked to and exacerbated by elevated ROS levels [14]. Given the current body of evidence, strategies that target oxidative stress and inflammation could potentially serve as effective approaches to tackle ASD.

Embedded within cellular membranes, vitamin E effectively thwarts lipid peroxidation, a process initiated by reactive peroxyl radicals. Tocopherols, the active forms of vitamin E, act as radical scavengers, neutralizing these harmful molecules and protecting membrane integrity [15]. Vitamin E, particularly alpha-tocopherol, directly scavenges free radicals and protects cell membranes from oxidative damage. Vitamin E deficiency can lead to increased levels of reactive oxygen species (ROS) which have been implicated in ASD [16, 17].

Vitamin E may affect ASD through several mechanisms, including its antioxidant properties [18], its ability to regulate gene expression [19], and its influence on immune activity [20]. Based on some investigations, there is early evidence that children with ASD have lower blood levels of vitamin E [16, 17]. However, the link between ASD and the amount of dietary intake of vitamin E is not clear. So, this investigation aimed to provide new insights into the association of dietary intake of vitamin E and the risk of ASD, paving the way for more targeted therapeutic strategies. We hypothesized that lower dietary vitamin E intake is associated with an increased risk of developing ASD.

2 | Methods

In this case–control study, 110 individuals with ASD aged between 5 and 15 years were selected as the case group from the autistic charity center, Tehran, Iran. Inclusion criteria for the case group include diagnosis of autism by a psychiatrist, 5–12 years old, no history of any other neurological disorders, non-use of any type of medicine affecting food intake, and not having other diseases that can affect food intake such as metabolic diseases. Simultaneously, 110 typically developing (TD) children of the same age group from schools near the autism center, which we ensured did not have ASD using the Structured Clinical Interview for DSM Disorders, Non-patient Edition (SCID-NP) through psychiatrist's assessments, were selected as the control group in Tehran, Iran. Although there is a potential bias by selecting the control group from schools near the autism center and controls should be ideally recruited from the general population, choosing people from a nearby school makes the people of the case and control groups to be similar socially and economically. Inclusion criteria for the control group include no history of any neurological disorders, no using any type of medication that affects food intake, and not suffering from diseases that can affect food intake such as metabolic diseases, individuals with intellectual disabilities or other neurological disorders were excluded from both groups. Written consent was acquired at the baseline, and an oral description of the goals and methods of the investigation, along with the information's confidentiality, was given. After that, participants filled out an informed consent form. People whose data could not be collected were excluded from the study.

The weight of the children participating in the study was measured with light clothes, without shoes, with a 100-g precision, and height was measured without shoes by a wall-mounted meter with 0.5 cm precision. Body mass index (BMI) was calculated by dividing weight (in kg) by the square of height (in m). Personal information including age, gender, and mother's age was collected using a general questionnaire. Gilliam Autism Rating Scale (GARS 2) was used for both groups to confirm the participants' ASD diagnoses [21]; formal diagnoses were made

by psychiatrists according to DSM-5 criteria, ensuring accurate diagnoses of ASD. There are three subscales in GARS 2 including stereotyped behaviors, communication, and social interactions, with 14 items in each subscale and every question has a score ranging from 0 to 3 [22].

2.1 | Dietary Intake

To gather necessary information about the child's diet, the Food Frequency Questionnaire (FFQ) [23], previously validated in Iran, was used. Using these questionnaires, information related to the intake of calories, whole and refined grains, fruits and vegetables, simple sugars, fat, salty snacks, dairy products, and meats during a year was evaluated. Household measures were taken into account for portion sizes and then were converted to grams. The food composition table (FCT) of the United States Department of Agriculture (USDA, Release 11, 1994 adapted for Iranian foods) was applied to assess the amount of energy and nutrients. The Iranian FCT was considered for local foods that did not exist in the FCT. Additionally, the Nutritionist IV version 4.1 software (First Databank Division, The Hearst Corporation, San Bruno, CA, USA) was used to evaluate the intake of nutrients in children, and the intake of total vitamin E and alpha-tocopherol, as the most biologically active form of vitamin E, was examined.

2.2 | Statistical Analysis

The Kolmogorov–Smirnov test was used to determine if the data was normally distributed. The Chi-squared and independent samples *t*-tests, respectively, were used to compare the two groups' qualitative and quantitative variables. The Mann–Whitney *U* test was used for data that were not normally distributed. After adjusting for confounding variables, the relationship between vitamin E intake in the diet and ASD was investigated using logistic regression modeling with reporting the odds ratio (OR), which shows the likelihood of an event occurring in the exposed group relative to the non-exposed group, and a confidence interval (CI), which offers a degree of accuracy and confidence in the data by providing a range of values within which the true parameter is likely to lie. All statistical analyses were carried out with SPSS version 21 and a significance level of $p < 0.05$.

2.3 | Ethics Approval

This study has been approved by Local ethics review boards at Shahid Beheshti University of Medical Sciences, Tehran, Iran (Ir. SBMU.retech.1397.1137).

3 | Results

Table 1 presents the general information for two groups: children with ASD and TD children. Based on the findings, the average ages of the children in the TD and ASD groups were 12.49 ± 2.17 and 12.94 ± 1.02 years, respectively ($p > 0.05$). The age of mothers in the ASD group was higher than that of the TD children group (35.5 ± 7.54 vs. 25.7 ± 4.57 year, $p = 0.006$). The average weight (50.39 ± 14.14 kg vs. 62.05 ± 16.98 kg), height (153.20 ± 14.1 cm vs. 165.75 ± 13.92 cm) and BMI (21.16 ± 4.20 vs. 22.22 ± 4.56 kg/m^2) of TD children were significantly lower than those of children with autism (All $p < 0.05$) (Figure 1).

Table 2 compares the average nutrient intake in the two groups. Daily calorie intake was higher in TD children than in those with ASD (3071.58 ± 1050.43 vs. 2402.27 ± 850.35 kcal/day, $p < 0.001$). The mean protein intake was statistically indistinguishable between the two groups. Additionally, the TD group demonstrated a higher intake of carbohydrates (401.32 ± 139.96 vs. 284.98 ± 103.44 g/day, $p < 0.001$) and total fat (126.61 ± 52.43 vs. 99.34 ± 48.99 g/day, $p < 0.001$) compared to the ASD group. The amounts of the intake of saturated fatty acids (37.06 ± 28.13 vs. 28.28 ± 16.09 g/day, $p = 0.006$) and unsaturated fatty acids (91.84 ± 39.38 vs. 71.07 ± 36.26 g/day, $p < 0.001$) were significantly higher in the control group than in the case group. However, no significant difference was found between the groups regarding the ratio of saturated fatty acids to unsaturated fatty acids. Also, the intake of vitamin E was significantly higher in the control group than in the case group (28.60 ± 10.85 vs. 15.66 ± 12.72 mg/day, $p < 0.001$).

TABLE 1 | Participants' demographics in the study.

	Controls ($n = 108$)	Cases ($n = 100$)	p
Age (year)	12.49 ± 2.17	12.94 ± 1.02	0.29[a]
Males (n)	70 (65%)	63 (63%)	0.13[b]
Mothers' age (year)	25.7 ± 4.57	35.5 ± 7.54	0.006[a]
Height (cm)	153.20 ± 14.12	165.75 ± 13.92	3.34×10^{-4}[a]
Weight (kg)	50.39 ± 14.14	62.05 ± 16.98	2.12×10^{-4}[a]
BMI (kg/m^2)	21.16 ± 4.20	22.22 ± 4.56	2.28×10^{-4}[a]
Height percentile	71.0	98.8	2.18×10^{-4}[a]
BMI percentile	93.4	96.5	3.21×10^{-4}[a]

[a]Independent samples *t*-test.
[b]Chi-squared test.

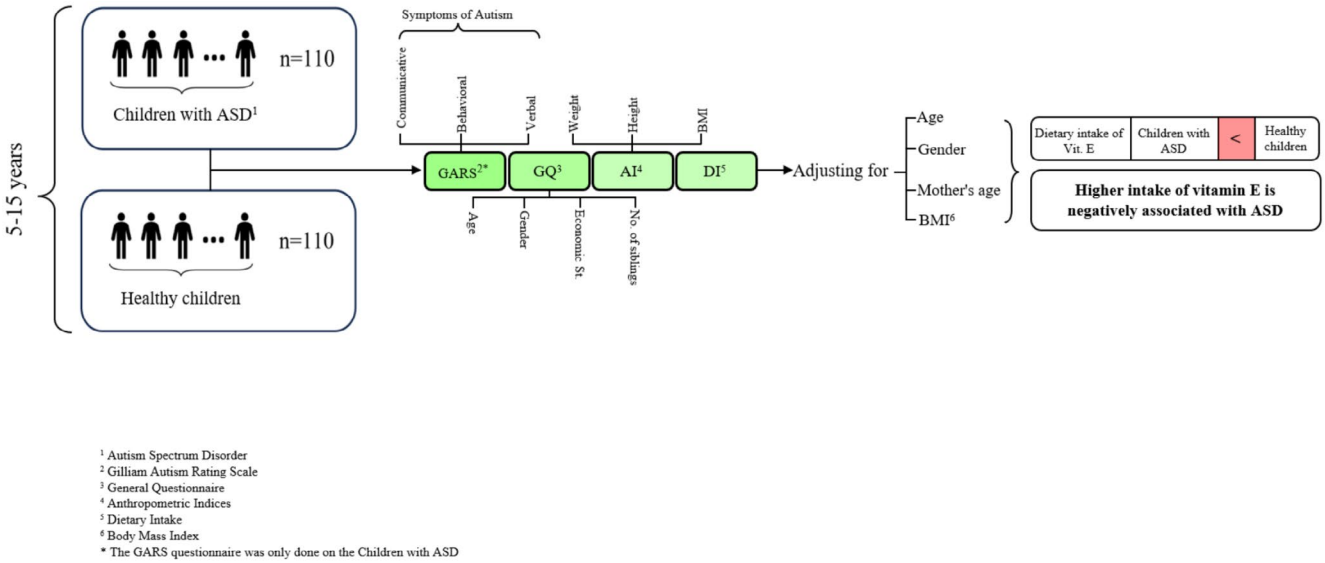

FIGURE 1 | The association between autism and vitamin E.

TABLE 2 | Dietary intake of the participants.

	Controls ($n=108$)	Cases ($n=100$)	p
Calorie (kcal/day)	3071.58 ± 1050.43	2402.27 ± 850.35	9.08×10^{-7}
Protein (g/day)	101.16 ± 44.31 (~13% of total kcal)	100.71 ± 39.49 (~17% of total kcal)	0.93
Carbohydrate (g/day)	401.32 ± 139.96 (~51% of total kcal)	284.98 ± 103.44 (~47% of total kcal)	1.29×10^{-10}
Total fat (g/day)	126.61 ± 52.43 (~36% of total kcal)	99.34 ± 48.99 (~36% of total kcal)	1.48×10^{-3}
Simple sugar	135.24 ± 52.45	125.03 ± 48.45	0.147
Saturated fatty acids	37.06 ± 28.13	28.28 ± 16.09	0.006
Unsaturated fatty acids	91.84 ± 39.38	71.07 ± 36.26	1.77×10^{-3}
Saturated fatty acids/unsaturated fatty acids ratio	0.42 ± 0.38	0.44 ± 0.23	0.685
Total vitamin E (mg/1000 kcal/day)	8.79 ± 3.77	7.14 ± 7.52	1.78×10^{-3}
Alpha-tocopherol (mg/1000 kcal/day)	6.51 ± 2.48	4.36 ± 4.75	8.60×10^{-5}

TABLE 3 | Logistic regression of the association between autism and dietary intake of vitamin E.

	OR (95% CI)	p[a]
Model 1	0.91 (0.88–0.94)	4.37×10^{-4}
Model 2	0.90 (0.85–0.94)	2.5×10^{-5}

[a]Model 1: Crude, Model 2: adjusted for confounding factors including age, gender, mother's age, BMI, and dietary intake of calories, protein, carbohydrates, total fat, simple sugars, saturated fatty acids, and unsaturated fatty acids.

As presented in Table 3, decreased vitamin E intake was associated with an increased risk of developing ASD (OR = 0.91, 95% CI: 0.88–0.94, $p<0.001$). The result remained significant after adjustment for age, gender, maternal age, BMI, and dietary intake of calories, protein, carbohydrate, total fat, simple sugars, saturated fatty acids, and unsaturated fatty acids (OR = 0.90, 95% CI: 0.85–0.94, $p<0.001$).

4 | Discussion

The purpose of this study was to compare the vitamin E intake of children with ASD to that of neurotypical individuals. The findings revealed a significantly lower intake of vitamin E among ASD individuals, suggesting decreased vitamin E intake was associated with an increased risk of developing ASD. In line with our findings, a study investigating the relationship between levels of plasma vitamin E and ASD reported that vitamin E levels were insufficient in the ASD group compared to the control group [15]. Similarly, Al-Gadani et al. showed a significantly

reduced serum level of vitamin E in ASD children [16]. In addition, Adam et al. reported lower levels of vitamin E in children with ASD [17]. Research has revealed that individuals with ASD demonstrated impairments in antioxidant defense mechanisms and a reduction in vitamin E levels is associated with a diminished capacity of glutathione (GLU) to function as an antioxidant defense in children with ASD [24, 25]. Specifically, changes in the way that key antioxidant enzymes involved in neutralizing reactive oxygen species (ROS) were observed in both human and animal studies of ASD participants. These changes were not confined to the brain but also extended to the peripheral blood [10, 26–29].

On the other hand, some dietary factors may influence both the risk of ASD and vitamin E absorption. For example, the amount of dietary fats affects the percentage of vitamin E intestinal absorption in the intestine [30, 31]. Furthermore, some recent studies reported that the specific types of dietary fatty acids such as omega-3 fatty acids may improve the symptoms of ASD [32]. Poly unsaturated fatty acids (PUFAs) need vitamin E to be protected against oxidative stress [33]. Due to the high abundance of oxidizable lipids in the brain, which require protection from oxidative damage, the intake of vitamin E, a prominent lipophilic antioxidant present in the brain, may potentially have a role in to the prevention of ASD [16]. Considering that the significant role of oxidative damage in the development of autism, numerous research studies have been conducted to explore the potential of various antioxidants as treatment options. Research has investigated the potential benefits of antioxidants such as coenzyme Q10, melatonin, trans-resveratrol (RSV), N-acetylcysteine (NAC), and others in treating symptoms of ASD [34–36]. It has been discovered that antioxidants may help people with ASD who struggle with irritability, hyperactivity, and communication issues [37, 38]. Among these, vitamins, particularly vitamin E, have garnered significant attention in recent times. Several studies have concentrated on investigating the antioxidant properties of these vitamins, specifically in situations marked by elevated oxidative stress levels, such as chronic psychological stress [39]. Under long-term, moderate stress circumstances, a significant increase in pro-inflammatory factors was also observed, concurrent with a notable decrease in endogenous antioxidants like SOD and glutathione peroxidase (GPx).

Research has revealed that individuals diagnosed with autism exhibit elevated levels of autoimmune signals, including antinuclear antibodies, along with pro-inflammatory cytokines like IL-6 and TNF-α across various bodily tissues [40]. These findings could potentially contribute to the cognitive challenges experienced by such individuals. Moreover, heightened oxidative stress and impaired mitochondrial function have been observed to contribute to neural harm [41]. Individuals with autism often display changes in gamma-aminobutyric acid (GABA) neurotransmitter activity, as well as alterations in serotonin and dopamine levels [42]. Vitamin E helps regulate the activity of enzymes involved in converting glutamate to GABA in various brain regions, thereby promoting balance in the GABA inhibitory system [43].

Based on the obtained results, we hypothesized that increased intake of vitamin E has a possible association with a reduction in the risk of autism. However, this study had some limitations. First, the comorbidities that can mimic or exacerbate ASD symptoms (e.g., intellectual disability) were not assessed. Second, the study's participants were exclusively Iranian children, limiting the generalizability of the results to other age and ethnic groups. Third, the control group was not assessed for undiagnosed ASD or a neurodevelopmental delay such as ADHD. Fourth, the study did not account for the potential impact of medications on the risk of ASD. Prenatal exposure to antiseizure medications such as topiramate and valproate was reported to be associated with increased risks of autism [44]. Fifth, while the study explored vitamin E consumption patterns, it did not assess the concentration of vitamin E in blood serum. Sixth, there are some limitations related to the use of FFQ for food intake assessment, such as underreporting and overreporting of the foods consumed. Finally, data on nutritional habits, which may influence the amount of vitamin E obtained from foods, is not available. Additional investigations are needed to support the association of ASD and vitamin E and to assess the impact of dietary vitamin E and vitamin E supplementation on autism symptoms.

4.1 | Potential Implications for Dietary Recommendations and Interventions

The findings of our study, alongside prior research on the aforementioned association, suggest some dietary recommendations and interventions. Given the correlation between autism and reduced vitamin E intake, raising vitamin E intake may be a useful prophylactic strategy. One way to achieve this could be to promote the consumption of foods high in vitamin E, like leafy green vegetables, nuts, seeds, and vegetable oils among at-risk children [45]. In addition, because the study highlights the potential role of vitamin E in the antioxidant defense system, it reinforces the importance of ensuring a well-balanced diet for individuals with ASD. This might involve consulting with nutritionists to develop personalized dietary plans that address potential nutritional deficiencies and promote overall antioxidant intake [46]. It is important to note that these are potential implications, and more research is needed before making definitive dietary recommendations for ASD.

4.2 | Limitations

One limitation of the study is the difference in maternal age between the ASD and typically developing (TD) groups, which may act as a confounding factor. Although we aimed to minimize socioeconomic differences by selecting controls from the same geographic area, the maternal age difference may have implications for ASD risk. Future studies should aim to control for maternal age more rigorously or adjust for it in statistical analyses. Additionally, the control group might not represent the general population due to the proximity of recruitment locations. Larger, more diverse samples from varied geographical regions could address this limitation in subsequent research.

5 | Conclusion

As far as we can determine, this study provides the initial evidence of a potential association between vitamin E and the risk

of ASD. These outcomes offer more evidence in favor of the existing body of experimental data, indicating that vitamin E intake was significantly lower in participants with ASD diets in contrast to the TD group. Furthermore, the negative correlation of vitamin E intake and ASD suggests that a higher vitamin E intake may be linked to a lower incidence of ASD. Further long-term studies are needed to strengthen the evidence.

Author Contributions

Khadijeh Abbasi Mobarakeh, Zahra Mahmoodi, Zahra Mousavi, Masoomeh Ataei, Somayyeh Bararnia Adabi, Samira Bahu Sele Nabi, Mahdi Moradi, Zahra Saeedirad, and Saeid Doaei designed the study and were involved in the data collection, analysis, and drafting of the manuscript. Saeideh Mohammadi, Seyed Ali Namakian Yazdi, Barbod Alhuie, Narjes Ashoori, Maryam Gholamalizadeh, and Saeid Doaei were involved in the design of the study, analysis of the data, and critical review of the manuscript. All authors read and approved the final manuscript.

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Ethics Statement

A written consent form was obtained from the parents at the baseline of the study from Shahid-Beheshti University of Medical Sciences in Tehran, Iran (Code Ir.sbmu.nnftri.rec. 1397.4656). In the methods section, we have included a statement confirming that all procedures were carried out in compliance with the relevant guidelines and regulations.

Consent

Forms of informed consent were signed by all participants. Informed consent was obtained from participants and their parents in the study. Institutional consent forms were utilized as part of the protocol for this study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Because no informed consent was provided by participating agencies for open data sharing, and the university has prohibited researchers from providing data to journals, not all data are freely accessible. It is possible for researchers to send their requests via email to the corresponding author if needed. You can obtain the datasets used and analyzed during this study by contacting the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.