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The Role of Risk and Protective Factors in Autism Spectrum Disorders

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ABSTRACT

Background: Identifying the risk factors and protective measures for Autism Spectrum Disorders (ASD) can significantly contribute to their prevention. This study aimed to ascertain the risk factors and protective measures associated with ASD.

Methods: This retrospective case-control study was conducted in Sari, Iran, from 2020 to 2021. A total of 196 children, aged 2-17 years, were recruited by convenience sampling from the Baghban (Touba) Clinic, Zareh Psychiatric Hospital Clinic, and Bu-Ali Child and Adolescent Psychiatric Clinic. The case group consisted of 98 children with ASD, diagnosed based on the DSM-V criteria, while the control group included 98 children without ASD. Subsequently, potential risk factors in both groups were examined. The odds ratio was calculated at a 95% confidence level, with a significance level of $P<0.05$.

Results: After adjusting the odds ratio (95% CI), ASD was found to be significantly associated with relatives' consanguinity [0.625 (0.409, 0.953)], breastfeeding [0.743 (0.582, 0.950)], and the child's history of head trauma [15.911 (1.78, 142.238)]. A closer degree of relatives' consanguinity increased the risk of autism in children by 1.6 times. Children who were breastfed for a longer period (up to 2 years) were 1.34 times less likely to develop autism. Moreover, children with a history of head trauma were approximately 16 times more likely to develop autism compared to children without such a history.

Conclusion: Breastfeeding has been identified as a protective factor, while the existence of closer relatives' consanguinity and a history of head trauma have been identified as risk factors for ASD. Further studies on these factors are recommended.

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Introduction

Autism Spectrum Disorders (ASD) are a type of developmental neuropsychiatric disorder. They impair the growth of the central nervous system during development, leading to brain dysfunction, which affects communication, learning, and emotions. In other words, this disorder encompasses a set of behaviors characterized by significant impairment in various areas of development. These areas include social interactions, communication, the scope of activity, and repetitive and stereotyped patterns, including speech [1].

According to the World Health Organization, in 2021, one in every 160 children has ASD [2]. Based on a report from the Centers for Disease Control and Prevention (CDC), about 1 in 54 children has been identified with Autism Spectrum Disorder [3]. A study conducted in Iran in 2019 reported that the prevalence of autism was 0.1 percent, with a male-to-female ratio of 2 to 1 [4].

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A recent study suggested the role of both genetic and environmental factors in the development of autism [5].

Additionally, a positive association has been reported between Autism Spectrum Disorders (ASD) and risk factors associated with the period before or after birth, as well as during or related to pregnancy. For instance, a positive association has been found between this disorder and maternal psychiatric disorders, epilepsy, obesity, hypertension, diabetes, polycystic ovary syndrome, infection, asthma, fertility induction, hyperemesis, lower maternal age, complications of childbirth, low birth weight, infant infection, seizures, asphyxia at birth, and complications of the newborn [6].

Another study reported that factors such as vaccination and maternal smoking history did not correlate with a higher risk of ASD. In contrast, older parents are associated with the disorder. Prenatal complications associated with trauma, ischemia, and hypoxia have been strongly associated with ASD. Meanwhile, pregnancy-related risk factors such as maternal obesity, maternal diabetes, and a history of cesarean section had a weaker (but significant) relationship with this disorder [7]. Similar findings suggest that Autism Spectrum Disorders (ASD) can be diagnosed before the age of two [8, 9], and another study has proposed the possibility of diagnosing autism in infancy [10]. However, most studies have examined these patients at the age of three, and evidence suggests that these children do not receive formal treatment until they are five years old or older [11]. This delay in diagnosis significantly postpones the optimal time for intervention, posing a major challenge for the family and the community.

In contrast, early detection of ASD in toddlers and infants can lead to a rapid referral of children to medical centers. In other words, early detection of ASD increases the likelihood that the child will receive interventions tailored to their clinical and educational needs, thereby improving the quality of life for these patients, their families, and the community [12].

Due to the contradictory results in studies, the numerous challenges this disorder poses for the individual, family, and society, and its increasing prevalence, the need for diagnosis, screening, and early intervention is more critical than ever. In this retrospective study, an attempt was made to investigate the risk factors likely to contribute to the occurrence of this disorder. Identifying vulnerability factors could play a crucial role in the early diagnosis of this disorder, providing the basis for timely treatment and rehabilitation of patients. Therefore, this project aimed to identify the risk factors and protective measures associated with ASD in 2020-2021.

Methods

Design

This retrospective case-control study was conducted in Sari in 2020-2021.

Participants

Children were referred to the Baghban (Touba) Clinic, the Clinic of Zareh Psychiatric Hospital, and the Bu-Ali Child and Adolescent Psychiatric Clinic for the study, which occurred between December 2020 and December 2021. The subjects were selected from the study setting using convenience sampling and divided into case and control groups based on the outcome (with or without ASD). Ninety-eight children with ASD were assigned to the case group, and 98 children without ASD were allocated to the control group.

ASD patients were diagnosed by a child psychiatrist using the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version-Persian Version (KSADs-PL) [13]. The inclusion criteria were an age between 2-17 years and the willingness of the legal guardian or parent of the child to participate in the study. The exclusion criteria were the unwillingness of the legal guardian or parent of the child to continue participating in the study and incomplete medical records. The control exclusion and inclusion criteria were the same as those for cases. The non-ASD controls were selected from outpatients referred for medical problems to the same three clinics during the same study period.

In this study, group or frequency matching was utilized, and two groups, case and control, were matched in terms of the child's age, gender, and nationality. Consequently, the variables maintained a similar ratio (for gender) or mean (for age) across both groups. The case group was divided into sub-categories based on its characteristics (the child's age and gender), and subsequently, the appropriate control group was identified. For instance, in the gender variable, categories for girls and boys were established. The mean age of the child was also taken into account. The control group was then matched accordingly. Two psychiatric residents who had received the necessary training in this field collected data. Each control subject was also clinically evaluated by a child psychiatrist using KSADs-PL to rule out ASD and other psychiatric disorders.

Sample Size

The sample size for this study was determined based on the variable of low birth weight in the study by Maya et al. [21]. The findings of that study, along with the formula recommended for case-control studies, led to the estimation of an optimal sample size of 89 patients per group. This estimation considered a 95% confidence interval (CI), a risk ratio 2.14, and a type II error of 20% (β=0.20). However, to account for a potential 10% sample attrition, the final selection consisted of 98 patients per group.

$$n = \frac{2 * \left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 [\bar{P} + (1 - \bar{P})]}{(P_1 - P_2)^2} =$$

$$\frac{2 * (1.96 + 1.28)^2((13.15)^2 + (1 - 13.15)^2)}{(15.8 - 10.5)^2} = 89.18$$

Variables and Measurement

Our team prepared a retrospective survey that covered demographic, prenatal, and postnatal factors in accordance with previous studies [5, 6, 7, 14]. The survey included the following factors: child's gender, parents'

age, and education level, parental relationship, history of folic acid consumption during pregnancy, history of complete bed rest or maternal bleeding during pregnancy, history of active or passive smoking, other tobacco use, substance abuse, alcohol consumption, drug use, X-ray exposure, trauma to the mother's abdomen, febrile illness or hyperthermia during pregnancy, assisted fertility, mode of delivery, history of abortion in the mother before and after the birth of a child with autism, breastfeeding, gestational age at birth, head circumference, weight and height of the child at birth, congenital anomalies, history of jaundice, epilepsy, microcephaly/macrocephaly, grain/milk allergy, side effects of the measles vaccine, history of neonatal intensive care unit (NICU) hospitalization, and history of head trauma.

Checklist to assess possible risk and protective factors: Initially, we searched for studies in databases about the risk and protective factors of autism spectrum disorders. Subsequently, a set of questions was compiled and used to design a checklist. This checklist comprised four parts: 1) The aims and title of the study; 2) A guarantee of confidentiality; 3) Demographic data (including the participants' names, ages, genders, and nationalities); 4) A list of yes-or-no questions about potential risk and protective factors.

A researcher-made checklist was utilized to assess the possible risks and protective factors. Ten child and adolescent psychiatrists confirmed the validity of this checklist.

Kiddie-Schedule for Affective Disorders and Schizophrenia - Present and Life-time Version - Persian Version (KSADs- PL.: The diagnosis of ASD was made using KSADs- PL.

Ethical Consideration

This study received approval from the ethics committee of Mazandaran University of Medical Sciences (ID: IR.MAZUMS.REC.1398.1247). The Helsinki Declaration's provisions were adhered to throughout this study. For instance, informed oral consent was obtained from the guardians or parents of the subjects, a process approved by the ethics committee of Mazandaran University of Medical Sciences. The subjects' voluntary participation in the study was ensured, with no bribes or pressure applied to gather data. Subjects were not deprived of routine care and treatment and retained the right to withdraw from the study at any time. The confidentiality of data and the identity of the subjects were among the most significant ethical considerations in this study. Furthermore, the researchers adhered to the Committee on Publication Ethics principles throughout all stages of the study.

Data Collection

The study's objective was clearly explained to all participants. All participants provided informed consent, and their participation in the study was voluntary. The presence or absence of potential risk and protective factors in the subjects was then examined using a checklist. Finally, the relationship between risk and protective factors and the study outcome was examined in both groups.

Data Analysis

Data were analyzed using SPSS software. Quantitative descriptive statistics, such as mean and standard deviation, were used for normal data, and frequency and percentage were used for qualitative data. Initially, a univariate analysis was performed for all variables. For this purpose, independent t-test, Chi-square, and Fisher's exact test were used. At this stage, a significance level of $P<0.05$ was considered. Then, to select the best predictor variables, variables with a significance level of less than 0.2 [15] were selected and entered into a binary logistic regression model. At this stage, eight variables (relatives' consanguinity, history of passive smoking by the mother during pregnancy, history of abortion in the mother before and after the birth of a child with autism, history of breastfeeding, history of jaundice, epilepsy, and history of child's head trauma) entered the model. The forward Wald logistic regression test identified the role and contribution of risk and protective factors. The odds ratio (OR) was calculated with a 95% confidence interval (CI).

Results

In this study, we initially invited 590 subjects, including patients with ASD (n=150) and individuals without ASD (n=440). However, after excluding 394 individuals who either refused to participate, failed to complete the questionnaires, were improperly matched, or had missing data, we included 196 participants in our analysis. This group comprised 98 cases and 98 controls (Figure 1).

Demographic and Clinical Characteristics of Subjects

The findings revealed that 76.5% of the children were boys. The children's mean age was 8.77±4.01 years, ranging from 3 to 17 years. The mothers' mean age at birth was 35.5±5.9 years, ranging from 20 to 52 years, and the fathers' mean age was 40.03±6.5 years, ranging from 26 to 69 years.

Most mothers (49%) and fathers (42.9%) held diplomas. A significant proportion of parents (68.9%) reported no familial relationship. Furthermore, most fathers (91.8%) and mothers (80.1%) had no known history of mental illness. Additionally, 99.5% of the siblings had no history of mental disorders or death from unknown causes.

94.7% of pregnancies occurred naturally, and 81.6% of mothers mentioned using folic acid during pregnancy. 83.2% of mothers stated that they had no history of complete bed rest or bleeding during pregnancy. Most mothers also mentioned no active (99.5%) or passive (89.8%) smoking during pregnancy. All mothers reported no history of smoking, substance abuse, or alcohol abuse during pregnancy. Additionally, 97.4% of mothers had no history of X-ray exposure during pregnancy. Most mothers had no history of abortion before (91.3%) and after (93.9%) the birth of a child with autism. Also, the majority of mothers (96.9%) reported that they had no history of abdominal trauma during pregnancy. The results showed that 65.8% of deliveries were cesarean sections. Most mothers reported no history of drug use (86.2%), fever (99.5%), or hyperthermia (99.5%)

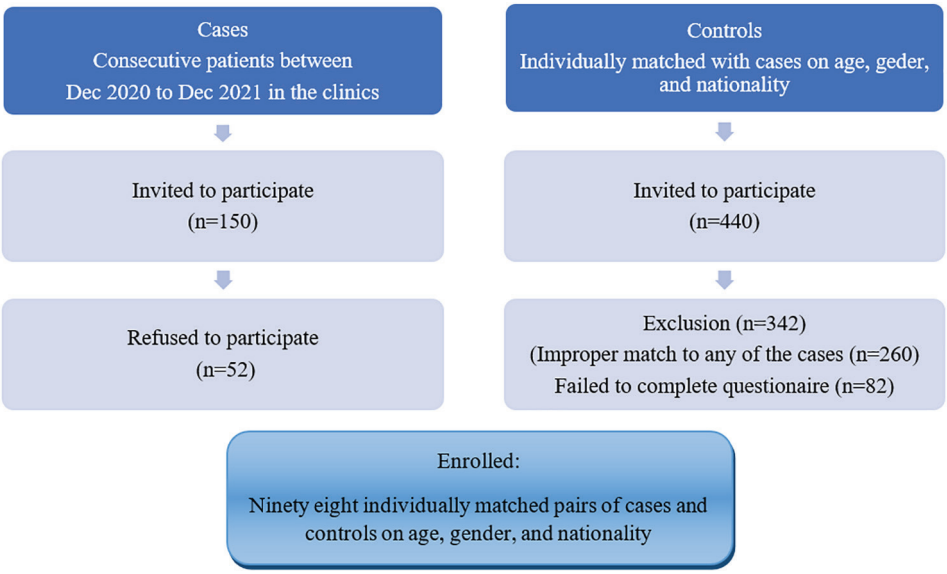

Figure 1: The study process

during pregnancy. The history of breastfeeding in 72.4% of children was between 18 and 24 months. The mean gestational age at birth was 37.63±2.04 weeks (27 to 41 weeks). The average head circumference of newborns was 34.68±3.76 cm (range: 30 to 55 cm), the mean birth weight of infants was 3207.15±532.83 grams (range: 900 to 4700 grams), and the mean height of children at birth was 50.13±1.95 cm (range: 40 to 58 cm).

Most children did not suffer from congenital anomalies (95.9%), jaundice (42.3%), epilepsy (93.9%), microcephaly (99.5%), macrocephaly (99%), grain allergy (96.4%), or allergy to breast milk (99.5%). Additionally, most children (99.5%) did not experience side effects from the measles vaccine, hospitalization in the NICU (95.4%), or a history of head trauma (91.8%).

Results of Univariate Analysis

An independent t-test showed that the case group (8.79±4.19) and the control group (8.76±3.84) were not significantly different in terms of child age (P=0.958). Additionally, 76.5% of children in each group were boys (P=1.000), indicating that the two groups were matched in age and gender. Table 1 compares the differences between the individual characteristics of the children and childhood events in the two groups.

The independent t-test indicated no significant difference between the two groups regarding age at birth, child head circumference, weight, and height at birth (P>0.05). Additionally, there was no significant difference between the two groups in terms of congenital malformations, microcephaly, macrocephaly, history of hospitalization in the NICU, breastfeeding, breast milk allergy, grain allergy, complications from the measles vaccine, and cesarean section delivery (P>0.05). However, jaundice at birth (P=0.042), epilepsy (P=0.005), and a history of head trauma (P<0.0001) were significantly higher in children with autism (Table 1).

Table 2 shows the differences between health-related conditions in the family and maternal exposures during pregnancy in the case and control groups.

An independent t-test indicated no significant difference between the two groups regarding maternal age (P=0.241) and paternal age (P=0.688) at delivery. Additionally, Fisher's exact test showed no significant difference between the two groups in terms of the history of mental disorders in the parents, sudden death or mental disorders in siblings, history of abortion before or after the birth of a child with autism, assisted fertility, history of bleeding, X-ray exposure, history of smoking (active or passive), folic acid use, trauma to the abdomen, fever, and maternal hyperthermia during pregnancy (P>0.05). However, the chi-square test showed a significant difference between the two groups regarding the parental relationship (P=0.001). None of the mothers reported a history of other smoking, substance abuse, or alcohol abuse during pregnancy.

Results of Logistic Regression Analysis

The Hosmer and Lemeshow test showed a good model fit in the fifth step, and the results are valid and can be cited (P=0.244, df=5, χ^2=6.704).

At the end of the fifth step of the forward Wald logistic regression test, the five variables "relatives' consanguinity," "history of abortion in the mother after the birth of a child with autism," "history of breastfeeding," "history of epilepsy in the child," and "history of trauma to the child's head" remained. The confidence intervals of the variables "relatives' consanguinity," "history of breastfeeding," and "history of trauma to the child's head" do not include the number one, and the significance level of these variables is less than 0.05. Therefore, according to the fitted model, these variables are the influential factors (Table 3).

Findings indicated that children of parents who were not related or had a more distant (fourth-degree relatives) relationship were 1.6 times less likely to develop ASD than those who were closely related (third-degree relatives). Additionally, children who were breastfed for a longer duration were 1.34 times less likely to develop autism. Furthermore, children with a history of head trauma were about 16 times more likely to have autism than children without a history of head trauma.

Table 1: The difference in the individual characteristics of the newborn and childhood events in the case and control groups

Variables	Case (n=98) n (%)	Control (n=98) n (%)	Test	Statistics value P value
Characteristics of the newborn				
Gestational age, mean (SD), w	37.44 (2.23)	37.81 (1.84)	Independent t-test	t=1.237 P=0.218
Head circumference, mean (SD), cm	34.07 (1.75)	34.88 (4.22)	Independent t-test	t=0.720 P=0.475
Weight at birth, mean (SD), gr	3204.4 (599.5)	3209.7 (464.9)	Independent t-test	t=0.067 P=0.974
Height at birth, mean (SD), cm	50.25 (2.56)	50.03 (1.24)	Independent t-test	t=0.567 P=0.573
Events occurring in childhood				
Jaundice			Chi-square	X^2=8.186
No	41 (41.8)	42 (42.9)		*P=0.042
Yes (Jaundice at birth)	6 (6.1)	18 (18.4)		
Yes (Healing without medical treatment)	23 (23.5)	15 (15.3)		
Yes (Healing with phototherapy)	28 (28.6)	23 (23.5)		
Congenital malformation	4 (4.1)	4 (4.1)	Fisher's exact test	P=1.000
Microcephaly	0 (0.0)	1 (1.0)	Fisher's exact test	P=1.000
Macrocephaly	1 (1.0)	1 (1.0)	Fisher's exact test	P=1.000
Epilepsy	11 (11.2)	1 (1.0)	Fisher's exact test	*P=0.005
Head trauma			Fisher's exact test	Value=14.238
No	83 (84.7)	97 (99.0)		*P<0.0001
Yes (without loss of consciousness)	14 (14.3)	1 (1.0)		
Yes (with loss of consciousness)	1 (1.0)	0 (0.0)		
Admission to the NICU	6 (6.1)	3 (3.1)	Fisher's exact test	P=0.497
Breastfeeding			Fisher's exact test	Value=7.631
No	12 (12.2)	4 (4.1)		P=0.102
Less than 6 months	11 (11.2)	5 (5.1)		
6-12 months	3 (3.1)	4 (4.1)		
12-18 months	6 (6.1)	9 (9.2)		
18-24 months	66 (67.3)	76 (77.6)		
Allergy to mother's milk	1 (1.0)	0 (0.0)	Fisher's exact test	P=1.000
Allergy to mother grain	5 (5.1)	2 (2.0)	Fisher's exact test	P=0.445
Rubella vaccination side effect	1 (1.0)	0 (0.0)	Fisher's exact test	P=1.000
C-section delivery	66 (67.3)	63 (64.3)	Fisher's exact test	P=0.763

*P<0.05; SD: Standard deviation, NICU: Neonatal Intensive Care Unit

Table 2: Comparison of health-related conditions in the family and maternal exposures during pregnancy in case and control groups

Variables	Case (n=98) n (%)	Control (n=98) n (%)	Test	P value
Health-related conditions in the family as risk factors for ASD				
Maternal age at delivery, mean (SD), y	27.17 (5.72)	26.29 (4.79)	Independent t-test	t=-1.176 P=0.241
Paternal age at delivery, mean (SD), y	31.47 (6.59)	31.13 (5.18)	Independent t-test	t=-0.402 P=0.688
Consanguinity			Chi-square	X^2=14.097
Unrelated	74 (75.5)	61 (62.2)		*P=0.001
Third relatives	18 (18.4)	12 (12.2)		
Fourth relatives	6 (6.1)	25 (25.5)		
Father's mental disorders	10 (10.2)	6 (6.1)	Fisher's exact test	P=0.435
Mother's mental disorders	20 (20.4)	19 (19.4)	Fisher's exact test	P=1.000
Sibling's mental disorders	0 (0.0)	1 (1.0)	Fisher's exact test	P=1.000
Abortion before the birth of ASD child	86 (87.8)	93 (94.9)	Fisher's exact test	P=0.126
Abortion after the birth of ASD child	12 (12.2)	5 (5.1)	Fisher's exact test	P=0.134
Maternal exposures during pregnancy				
Assisted fertility (IVF)	2 (2.0)	3 (3.1)	Fisher's exact test	P=1.000
Bleeding in pregnancy	17 (17.3)	16 (16.3)	Fisher's exact test	P=1.000
X-Ray	3 (3.1)	2 (2.0)	Fisher's exact test	P=1.000
Active smoker	1 (1.0)	0 (0.0)	Fisher's exact test	P=1.000
Passive smoker	6 (6.1)	14 (14.3)	Fisher's exact test	P=0.097
Folic acid	79 (80.6)	81 (82.7)	Fisher's exact test	P=0.854
Trauma to mother's abdomen in pregnancy	5 (5.1)	1 (1.0)	Fisher's exact test	P=0.212
Fever in pregnancy	0 (0.0)	1 (1.0)	Fisher's exact test	P=1.000
Hyperthermia in pregnancy	1 (1.0)	0 (0.0)	Fisher's exact test	P=1.000

*P<0.05; SD: Standard deviation, ASD: autism spectrum disorders, IVF: in vitro fertilization

Table 3: Risk factors associated with autism spectrum disorder in the fifth step of the logistic regression model

Variables	B	Standard error (SE)	Wald	df	P-value	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
Relatives' Consanguinity	-0.471	0.216	4.755	1	0.029	0.625	0.409	0.953
Abortion after the birth of ASD child	-1.663	0.893	3.465	1	0.063	0.190	0.033	1.092
Breastfeeding	-0.297	0.125	5.635	1	0.018	0.743	0.582	0.950
Child's Epilepsy	1.990	1.102	3.263	1	0.071	7.314	0.844	63.364
Child's head trauma	2.767	1.118	6.129	1	0.013	15.911	1.780	142.238
Constant	1.052	0.445	5.580	1	0.018	2.864	-	-

Discussion

This study aimed to determine the risk and protective factors associated with ASD. Children in the two groups were matched in age, gender, and nationality. Other studies also matched the two groups regarding age and gender [5, 16, 17]. Malek et al. matched the two groups in age [18].

In this study, there was no significant difference between the two groups in terms of age at birth, head circumference, and weight and height at birth. These findings are consistent with those of Mohammadian-Khoshnoud et al. in terms of age at birth [16]. Malek et al. also reported no significant difference between the case and control groups regarding birth before 32 weeks and after 42 weeks [18]. However, Mamidala et al. reported that ASD was more common in preterm infants [19]. Regarding child weight, Maia et al. found no association between birth weight and autism [14]. Mohammadian-Khoshnoud et al. also reported that ASD was not significantly associated with birth weight but was significantly associated with lower head circumference and shorter neonatal height at birth [16]. Conversely, one study found an association between low birth weight and ASD [6].

In the present study, there was no significant difference between the two groups regarding congenital malformations, microcephaly, macrocephaly, history of hospitalization in the NICU, breastfeeding, breast milk sensitivity, grain allergy, measles vaccine complications, and cesarean section delivery. In contrast, Maia et al. reported that congenital anomalies were significantly associated with autism [14]. Malek et al. also reported that microcephaly was more common in children with autism than in the control group [18]. Additionally, Malek et al. found a significant relationship between a child's allergy to milk/grain and the experience of measles vaccine side effects with autism [18]. However, the latest report from the World Health Organization in 2021 shows no significant association between the measles vaccine and ASD [2]. Malek et al. also found that a lack of breastfeeding until the age of two was a predictor of autism [18].

In the present study, congenital jaundice, epilepsy, and a history of head trauma were more common in children with autism. Similarly, Maia et al. reported a significant association between childhood jaundice and seizure periods with autism [14]. Mamidala et al. also found a significant relationship between congenital jaundice and autism [19]. Other studies have reported a significant relationship between epilepsy and autism [4, 6, 18]. Maia et al. also reported a significant relationship between neonatal hospitalization in the NICU and a history of head trauma in children with autism [14]. Regarding the mode of delivery, some studies reported no significant relationship between cesarean-section delivery and autism [16, 18]. However, another study found this relationship to be significant [7].

In this study, there was no significant difference between the case and control groups in terms of parents' age, history of mental disorders in the parents, sudden death or mental disorders in siblings, history of abortion before or after the birth of a child with autism, assisted fertility, history of bleeding, X-ray exposure, history of active or passive smoking, folic acid use, maternal abdominal trauma, fever, and maternal hyperthermia during pregnancy. These findings are consistent with studies conducted in Iran regarding parental age [16, 18]. However, some studies in other countries have shown that mothers of children with autism were older [14, 17, 19-21].

Malek et al. reported no association between parental mental disorder and a child with autism. However, they found that the presence of learning disabilities in first-degree family members, including siblings of a child with autism, was higher than in the control group [18]. Gao et al. also reported that parental depression may be a risk factor for autism in children [5]. Other studies have linked maternal mental disorders to a child with autism [4, 6]. Additionally, one study showed a relationship between assisted reproductive techniques and ASD [6]. Regarding maternal exposure to X-rays during pregnancy, Gao et al. reported that maternal exposure to X-rays at the univariate analysis stage was considered a possible risk factor for autism in the child. Still, this relationship was not confirmed in regression analysis [5].

In the present study, none of the mothers had a history of substance or alcohol abuse during pregnancy. In contrast, Gao et al. reported that maternal smoking and alcohol consumption during pregnancy were considered possible risk factors for a child with autism in the univariate analysis stage. Still, this relationship was not confirmed in regression analysis [5]. Modabbernia et al. also showed that a mother's history of smoking was not associated with ASD [7]. Gao et al. reported that not consuming folic acid during pregnancy was considered a possible risk factor for a child with autism during the univariate analysis phase. Still, this relationship was not confirmed in regression analysis [5]. Modabbernia et al. pointed out an association between folic acid deficiency and childhood autism [7].

Regarding maternal factors such as abortion before and after the birth of a child with autism, history of trauma to the

mother's abdomen during pregnancy, history of complete bed rest or maternal bleeding, and substance abuse, similar findings were not reported in other studies. However, there was a significant difference between the two groups regarding relatives' consanguinity in this study. More than 18% of parents of children with autism had third-degree relatives' consanguinity, compared to about 12% in the control group. Similar results have been reported in the study by Mohammadian-Khoshnoud et al. [16].

In this study, the forward Wald logistic regression test showed that children of parents who did not have a relationship or had a more distant relationship (fourth-degree relatives) were 1.6 times less likely to develop ASD compared to those with a closer relationship (third-degree relatives). In other words, consanguinity between parents can be considered a possible risk factor for a child with ASD. Similarly, Mohammadian-Khoshnoud et al. reported that third-degree consanguinity in parents was significantly associated with children with autism [16].

Regarding the history of breastfeeding, the findings showed that children who were breastfed for a longer time were 1.34 times less likely to develop autism. Prolonged breastfeeding may play a role in protecting the child from developing ASD. Similarly, Malek et al. reported that a lack of breastfeeding until the age of two was a predictor of autism [18]. However, it is important to note that it is impossible to establish a cause-and-effect relationship in case-control studies, and only the ratio of risks can be deduced within the confidence interval. Therefore, children with ASD may have had difficulties with breastfeeding, which may have led mothers to use alternative feeding methods.

Additionally, the findings of this study showed that children with a history of head trauma were about 16 times more likely to develop ASD than children without a history of head trauma. In other words, a history of head trauma can be a possible risk factor for ASD. Similarly, Maia et al. reported a significant relationship between neonatal hospitalization in the NICU and a history of head trauma in children with autism [14]. Modabbernia et al. also reported that birth complications, such as trauma, were strongly associated with ASD [7]. It should be noted that the agitation and difficulty of controlling children with ASD may increase the likelihood of such events. Therefore, further studies with a prospective cohort approach are recommended.

One limitation of this study was that the data collected were based on parents' memories, so recall bias, one of the main limitations of all case-control studies, could threaten the predictive power of this study. To control and reduce this limitation, the researchers used both data recorded in medical documents and interviews with parents, and the compatibility between these two data sources largely mitigated this limitation. The low sample size and the failure to record some variables in pediatric medical records were other limitations of this study.

Conclusion

The findings of this study revealed a significant difference between children with ASD and others in terms of relatives' consanguinity, history of jaundice, epilepsy, and head trauma.

Finally, the fitted model of this study demonstrated that relatives' consanguinity and a history of head trauma are possible risk factors for ASD. Additionally, breastfeeding a child up to the age of two may play a role in protecting a child from developing ASD. Therefore, informing and educating parents and families about these risk factors and potential protective factors for children with ASD can significantly contribute to reducing the incidence of this disorder. Furthermore, increasing awareness about these factors can facilitate the early diagnosis of the disease and prompt interventions for affected individuals. Further studies, especially those employing a prospective cohort approach with larger sample sizes, are recommended to identify additional risk factors and protective factors for ASD.

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