Prenatal, perinatal, and postnatal factors associated with autism spectrum disorder cases in Xuzhou, China

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Background: The aim of the present study was to explore the prenatal, perinatal, and postnatal risk factors in children with autism spectrum disorder (ASD) from Xuzhou, China by comparing them with healthy children.

Methods: Children with ASD who received rehabilitation training at special education schools and rehabilitation institutions in Xuzhou were selected as the ASD group, and healthy children during the same period were selected as the healthy non-ASD group. A questionnaire based on the possible causes and susceptibility factors of ASD in children was issued and given to all children in this study.

Results: The findings of the present study revealed a higher prevalence of prenatal, perinatal, and postnatal factors in children with ASD compared with healthy children. There were significantly more males than females in the ASD group, and the proportion of boys to girls was 5.81:1 (P<0.05). Logistic regression analysis suggested that the risk factors of male children developing ASD were feeding difficulties, poor living environment during pregnancy, maternal exposure to cigarette smoking during pregnancy, and perinatal hypoxia. Factors associated with ASD risk among were identified, such as living environment during pregnancy, delivery method, feeding difficulties, and epilepsy (P<0.05). Feeding difficulties and living in the countryside during pregnancy might be risk factors for ASD in girls according to the logistic regression analysis.

Conclusions: This survey confirmed the high prevalence of prenatal, perinatal, and postnatal factors in children with ASD. Some of these factors may be effective entry points for the prevention and treatment of ASD.

Keywords: Autism spectrum disorders (ASDs); prenatal; perinatal; postnatal; occupational therapy

Introduction

Autism spectrum disorders (ASDs) are a group of complex neurodevelopmental disorders that are lifelong; their pathogenesis remains unclear. The latest statistics from the Centers for Disease Control and Prevention (CDC) on the prevalence of ASD in the United States is 1/59, an increase of 15% compared with the data released in 2014. The specific diagnostic criteria for childhood autism include social skills and communication deficit associated with restrictive and repetitive behaviors, interests, or activities

based on the 5th edition of the Diagnostic Statistical Manual of Mental Disorders (DSM-5) (1). The prevalence of ASD has risen significantly in the past 20 years from 4.8 per 10,000 in 1979 to 116.1 per 10,000 in 2006 in the UK (2), and from 113 per 10,000 in 2012 to1 per 59 children in 2018 in the USA (1). Rehabilitation costs for ASD patients were higher than those for neurotypical children in the USA in 2014 (3). The increasing in the population and the rising cost of rehabilitation for those with ASD have become a serious social problem. The pathogenesis and mechanism of ASD are unknown. It was initially believed that the etiology of ASD was heterologous, including environment, infection, immunity, perinatal period, epilepsy and comorbidities, neuroanatomy and imaging, genetics, and social psychology. These factors are likely to have an important impact on the pathogenesis of ASD. However, it is believed that the mechanism underlying ASD etiology is most likely to be polygenic and potentially epistatic, and those environmental factors may interact with genetic factors to increase risk (4).

Most researchers consider genetic factors to play an important role in the etiology of ASD (4,5). Studies on twins have identified high heritability, showing that the prevalence of identical twins in a child with ASD was 88%. Also most siblings of a child with ASD are at higher risk of autism and other developmental disorders. Over 3000 genes and thousands of gene variants have been identified to date, including rare mutations and common polymorphisms, which might be associated with ASD. Increasing evidence shows that ASD heritability has complex heterogeneity, and the genetic variability responsible for ASD can be successfully identified in approximately 20–30% of cases (6). Other while, boys are at a higher risk of autism according to CDC, reporting that ASD is about 4.5 times more common among boys, which is considered to be due to a gene abnormality in the sex chromosome (7). However, more and more literature show that genetic factors possibly account for only 35–40% of the causes of autism. The remaining 60–65% are likely due to other factors such as environmental pollution. Recently published studies investigated that the interaction between gene and environment can lead to autism (8).

The fact that the occurrence of autism in monozygotic twins is not completely consistent suggests that environment is also an important cause of autism, including prenatal, perinatal and environmental factors (1,9). The first report about complications during pregnancy and their association with the risk of autism was published in 1956 (10). Three papers, including a large meta-analysis, were published before 2007 and some recently published

articles have focused on the significance of individual factors in the development of ASD (5,11). More and more studies have found that several perinatal and postpartum factors could be the cause of ASD (11,12), such as umbilical cord complications, fetal distress, birth injury or trauma, multiple births, maternal hemorrhage, premature delivery, low or very low birth weight, size small for gestational age, congenital malformations, low 5-min Apgar score, feeding difficulties, neonatal anemia, and hyper-bilirubinemia. These studies also showed that ASD factors of prenatal, perinatal, and environmental varied among regions.

There are few studies in China that consider the relationship between prenatal, perinatal, and postnatal risk factors with ASD (13,14). Therefore, the aim of the present study was to identify the prenatal, perinatal, postnatal, and environmental factors associated with ASD by comparing children with ASD with neurotypical children.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tp-21-54).

Methods

Participants

The participants were divided into 2 groups: the ASD group and the healthy group. This study was approved by ethics committee of the Affiliated Hospital of Xuzhou Medical University (NO. XYFY2020-KL151-01). Written informed consent was obtained from parents of guardians of study participants <16 years of age. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

ASD group

All cases with ASD were selected from special educational schools and autism rehabilitation facilities in Xuzhou, north of Jiangsu Province, located in the middle eastern part of China, from March 2016 to March 2018. These schools and facilities are affiliated with China Disabled Persons' Federation (CDPF) in Xuzhou, and their employees have received CDPF's technical guidance on autism rehabilitation.

Children with ASD in the present study met following criteria: (I) DSM-5 criteria for ASD; (II) Child Autistic Rating Scale score ≥30; (III) Autism Birth Cohort (ABC) score ≥67 (15); and (IV) The informed consent of the guardian was obtained The exclusion criteria were

known neurogenetic conditions (e.g., tuberous sclerosis, neurofibromatosis, fragile X syndrome, Down syndrome, phenylketonuria), congenital malformations, brain injuries, encephalitis, or other encephalopathies, or visual and hearing impairments.

Healthy group

Children in the healthy group had normal intelligence, normal development, and no physical and mental illnesses, as confirmed by the class teacher or school doctor. These children matched the ASD cases by age and sex and were selected from the same administrative district kindergarten and primary school from June 2017 to March 2018. The parents of children in the healthy groups agreed to complete the survey.

Questionnaire and procedures

The research team designed a questionnaire on the etiology and susceptibility of children with ASD according to previously published studies (15). The questionnaire comprised 10 items and 155 subitems covering the basic information of the children, including illnesses, family genetic factors, health status of the parents during the mother's pregnancy, childbearing history feeding and growth history before 2 years of age, past medical history of child, vaccinations, parental occupation and education, and drug and food allergies.

From a procedural point of view, research group staff first explained the purpose and significance of the study to the parents or guardians and teachers who knew the child for at least 6 months and understood the disease status of the children under investigation. The parents and teachers were then provided consent. The research staff explained in detail the questionnaire to the parents and answered their questions to minimize confusion and misunderstanding. The quality of the questionnaire data was then evaluated. Returned questionnaires with more than 10% of unanswered questions or unclear responses were considered invalid. The researchers completed the questionnaires with missing or unclear responses by follow-up with parents via telephone, email, WeChat, and Tencent QQ (an instant messenger issued by Tencent Company).

Statistical analysis

After checking the original data, the cases that did not meet

the inclusion criteria were excluded. The data of the ASD group and the healthy group were recorded using EpiData software (http://www.epidata.dk/).

According to the questions setting in the questionnaire, it was divided into 2 kinds of variables: two classification variables and grade variables. For 2 classification variables, the value "0" indicated "none or nonexistence", and the value "1" indicated "expressed or existed". The maternal age during pregnancy, maternal duration of illness during pregnancy, parents' smoking and drinking history, general situation of infant birth, postpartum feeding methods, main rearing methods, children's past disease and treatment history, parents' occupation and education level were divided into 0, 1, 2, 3 grades, and 4 grades.

Statistical data were analyzed using SPSS version 19.0 (IBM, Armonk, NY, USA). In the present study, the measurement data were represented by mean ± standard deviation ($\bar{x}$ ± s), and compared with t-test. Enumeration data were expressed as number of cases or percentages and analyzed by χ^2-test. The categorical data in the ASD group and healthy group were tested by χ^2-test. If the test results show that there is a significant gender difference between the two groups, that is, there is an imbalance in the proportion of internal structure between the two groups, then stratified 2 tests based on gender classification is conducted. All variables with difference by t or χ^2-test were considered in the regression equation and logistic regression analysis was carried out. P<0.05 indicated statistically significant differences.

A bivariate logistic regression was also conducted to generate crude odds ratios (ORs) with 95% confidence intervals (CIs). A multivariable logistic regression was conducted for significant variables (P<0.05) and borderline significant variables, and adjusted ORs with 95% CIs were generated. A stepwise logistic regression was then used to generate a final model. Adjusted ORs and their 95% CIs were reported.

Results

Gender and demographic characteristics of ASD children

In the healthy group, 201 cases [119 males (59.2%) and 82 females (40.8%)] met the control group's admission criteria. The male-to-female ratio in this group was 1.4:1. In the ASD group, 190 questionnaires were issued, of which 177 cases [151 males (85.3%) and 26 females (14.7%)] met the ASD criteria. The male-to-female ratio in the ASD group

Table 1 Comparison of general information of children in the healthy group and autism spectrum disorder (ASD) group

Projects	Healthy group (n)	ASD group (n)
No. questionnaires	210	190
Reclaimed number of questionnaires	202	180
Complied with the standard set of questionnaires	201	177
Males	119	151
Females	82	26
Male-to-female ratio	1.4:1	5.8:1
No. twins	1	12
No. cases with epilepsy	1	12
No. cases with febrile convulsion	14	21
No. cases with febrile convulsion and epilepsy	0	4
No. cases with a family history of mental illness	0	3
No. cases with a family history of ASD history	0	1
No. cases involved in ASD gene screening	1	17

Table 2 Comparison of age and sex characteristics between the healthy group and autism spectrum disorder (ASD) group

Subgroup	Cases	Age (years)	Sex [cases (%)]	
			Male	Female
Healthy group	201	5.044±1.481	119 (59.2)	82 (40.8)
ASD group	177	5.350±2.539	151 (85.3)	26 (14.7)
Test statistic value		1.407*	28.027#	
P value		0.161	0.000	

*t-value, #χ^2-value.

was 5.8:1 (*Table 1*).

In the ASD group, the average age at diagnosis was 34.588±14.757 months; the minimum month of diagnosis was 12 months and the maximum age was 10.5 years.

The age of children in both groups was expressed by mean ± standard deviation. The average age for the 2 groups was 5.044±1.481 years in the healthy group and 5.350±2.539 in the ASD group. There was no significant difference in terms of age between groups (t=1.407, P=0.161). This suggest that there was a significant difference in sex between the healthy group and ASD group (P<0.01) (*Table 2*).

As shown in *Table 2*, there were sex-related differences between the ASD and healthy groups, which suggested that different risk factors are likely to lead to ASD in children of different sexes. Therefore, the risk factors of ASD in male and female children were analyzed.

One-way analysis of variance (ANOVA) of factors among male ASD children

As shown in *Table 3*, there were significant differences between the ASD group and healthy group for males in 14variables:maternal exposure to cigarette smoke, alcohol consumption of both parents living environment during pregnancy, hypertension in pregnancy, perinatal hypoxia, birth length, delivery method, amniotic fluid pollution, principal caregivers, time for breastfeeding feeding difficulties, relationship between parents and children, gastrointestinal disease, and respiratory infection (P<0.05).

One-way ANOVA of factors among female ASD children

As shown in *Table 4*, there were significant differences

Table 3 Prenatal, postpartum, and perinatal factors in males

Factors	Healthy group		ASD group		χ^2-test	P value
	n	%	n	%		
Prenatal factors						
Exposure to cigarette smoking					12.901	0.005
Always	22	18.5	58	38.4		
>3 months	12	10.1	12	7.9		
≤3 months	8	6.7	6	4.0		
No smoking	77	64.7	75	49.7		
Exposure to alcohol					8.386	0.039
Always	12	10.1	35	23.2		
>3 months	15	12.6	13	8.6		
≤3 months	9	7.6	11	7.3		
No alcohol	83	69.7	92	60.9		
Place of residence during pregnancy						
Countryside	17	14.3	54	35.8	15.837	0.000
City	99	83.2	90	59.6	17.637	0.000
Hypertension in pregnancy	1	0.8	10	6.6	5.693	0.026
Perinatal factors						
Perinatal hypoxia	2	1.7	17	11.3	9.332	0.002
Birth length (cm)					8.870	0.031
≤50	5	4.2	21	13.9		
50–55	107	89.9	126	83.4		
>55	4	3.6	3	2.0		
Unknown	3	2.5	1	0.7		
Delivery method					11.474	0.009
Prematurity	6	5.0	15	9.9		
Difficult labor	2	1.7	5	3.3		
Exceeded full-term	3	2.5	17	11.3		
Full-term delivery	108	90.7	114	75.5		
Amniotic fluid pollution	2	1.7	11	7.3	4.561	0.043
Postnatal factors						
Principal caregivers					4.105	0.043
Parents	108	90.8	124	82.1		
Grandparents	11	9.2	27	17.9		
Time for breastfeeding feeding					8.195	0.017
≤6 months	20	16.8	11	7.3		

Table 3 (*continued*)

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Table 3 (*continued*)

Factors	Healthy group		ASD group		χ^2-test	P value
	n	%	n	%		
6–12 months	25	21.0	25	16.6		
≥12 months	41	34.5	70	46.4		
Feeding difficulties	13	10.9	79	52.3	50.763	0.000
Relationship between parents and children	115	96.6	134	88.7	5.786	0.016
Gastrointestinal diseases	39	32.8	13	8.6	24.990	0.000
Respiratory infection	63	52.9	44	29.1	15.760	0.000

ASD, autism spectrum disorder.

Table 4 Prenatal, postpartum, and perinatal factors in females

Factors	Healthy group		ASD group		χ^2-test	P value
	n	%	n	%		
Prenatal factors						
Place of residence during pregnancy						
Countryside	7	8.5	9	34.6	10.638	0.003
City	74	90.2	15	57.7	14.428	0.000
Perinatal factors						
Delivery factor					9.580	0.022
Prematurity	3	3.7	3	11.5		
Difficult labor	1	1.2	1	3.8		
Exceeded full-term	1	1.2	3	11.5		
Full-term delivery	77	94.0	19	73.1		
Postnatal factors						
Feeding difficulties	10	12.2	19	73.1	37.253	0.000
Epilepsy	0	0	4	15.4	13.101	0.003
Respiratory infection	42	51.2	6	23.1	6.332	0.013
Otolaryngological diseases	17	20.7	1	3.8	4.053	0.067

ASD, autism spectrum disorder.

between the ASD group and healthy group for females in 6 variables as follows: place of residence during pregnancy, delivery method, feeding difficulties, epilepsy, respiratory infection, and otolaryngologic diseases (P<0.05).

Multivariate Logistic regression analysis of male autistic children

Taking children's autism as dependent variable, 14 items with statistical significance in one-way ANOVA of male

Table 5 Analysis of risk factors of male autism

Variable	β	P	OR	95% CI
Exposure to cigarette smoking	1.823	0.006	6.191	1.678–22.838
Living in the countryside during pregnancy	2.848	0.011	17.251	1.899–156.745
Perinatal hypoxia	3.660	0.005	38.859	2.944–512.930
Feeding difficulties	2.508	0.001	12.284	2.768–54.507

Table 6 Analysis of risk factors of male autism

Variable	β	P	OR	95% CI
Feeding difficulties	3.315	0.001	27.522	3.662–206.857
Living in the countryside during pregnancy	3.196	0.009	24.438	2.243–266.281

group were put into logistic regression equation, and all variable regression method was used The results showed that feeding difficulties (OR: 12.284, 95% CI: 2.768–54.507), living in the countryside during pregnancy (OR: 17.251, 95% CI: 1.899–156.745), exposure to cigarette smoking (OR: 6.191, 95% CI: 1.678–22.838), and perinatal hypoxia (OR: 38.859, 95% CI: 2.944–512.930) were risk factors for ASD for male children (*Table 5*).

Multivariate logistic regression analysis of female ASD children

Similar to the analysis of the risk factors of male autistic children, 6 factors of statistical significance of the variance analysis of the single factor of the female group were put into the logistic regression equation, and the total variable regression method was adopted. The results showed that feeding difficulties (OR: 27.522, 95% CI: 3.622–206.857) and living in the countryside during pregnancy (OR: 24.438, 95% CI: 2.243–266.281) were risk factors for ASD for female children (*Table 6*).

Discussion

In the present study, we investigated 155 possible factors associated with the occurrence of ASD in children from Xuzhou, China using questionnaires. We found that the number of boys with ASD was significantly higher than that of girls, and the difference was significant, indicating that sex has possible high-risk factors in the pathogenesis of ASD. In the single-factor analysis of the incidence of ASD in boys, 11 factors were related to the occurrence of

ASD. Of these, 4 factors (feeding difficulties, living in the countryside during pregnancy, exposure to cigarette smoking and perinatal hypoxia) were determined by multiple factor regression analysis to be high-risk factors for ASD among girls.

In the single-factor analysis of the incidence of ASD in girls, 6 factors were related to the occurrence of ASD as follows: place of residence during pregnancy, delivery factor, feeding difficulties, epilepsy, respiratory infection, and otolaryngologic diseases. Multiple-factor regression analysis showed that 2 factors (feeding difficulties and living in the countryside) during pregnancy were risk factors for ASD among girls in the 6 related factors.

Therefore, from the results of this survey, at least some factors, such as feeding difficulties, living in the countryside during pregnancy, exposure to cigarette smoking and perinatal hypoxia, were ASD high-risk factors for children.

Many researchers have found that there is a sex difference in ASD children, with the sex ratio in prevalence estimates for boys versus girls generally being around 4:1 in (2,3,16). It is generally believed that boys are significantly more likely to develop ASD than girls. Wing's work found a 15:1 ratio for the male-to-female incidence in Asperger's syndrome or higher functioning autism disorder and a 2:1 ratio in people with autism disorder and learning difficulties (16). In the present study, 177 children with ASD from Mainland China were analyzed, with a sex ratio of 5.8:1, which is slightly higher than the proportion of 4–5:1 reported in Western countries (17), and slightly lower than ASD in Chinese males and females, with a ratio of 6.5–9:1 (13).

The reason for the sex discrepancy is unclear. Fombonne found that male children had more severe socio-

communicative symptoms than females (18). Wing first introduced the hypothesis of male gene innate vulnerability to support men's characteristics of autism, while females showed only partial autism (16). Schendel *et al.* also found that the birth defect rate of male ASD patients was higher than that of female ASD patients through a survey of 617 ASD children (19). Studies of twins showed that the heritability of ASD ranged between 77% and 99% (20). It has been suggested that females require more mutations at the genetic level to develop ASD. From a clinical point of view, the diagnostic rate of ASD in women may be lower, because women are better at overcoming their own difficulties to cover up their ASD symptoms, which may affect the diagnostic rate (21). Van Wijngaarden-Cremers *et al.* showed that there were no significant sex differences in high-functioning ASD adults and pointed out that males and females might present with different ASD phenotypes (22), and this might affect diagnostic rates, as ASD in females is less well understood, and therefore, less easily detected.

Increasingly more researchers consider the difference in the prevalence of ASD between men and women to be of significance (21,23,24). Further in-depths studies of sex-related pathogenicity load and susceptibility to ASD, and the stratification between males and females, that explore the pathogenesis and status of genetic, endocrine, epigenetic, and environmental levels associated with sex factors in the pathogenesis of ASD, will strengthen understanding of this condition.

Maternal smoking has been found to be associated with the development of ADHD or inattention, behavioral disorders and antisocial behavior, and emotional problems among children (25). Smoke is a complex mixture of gases and particulate matter, whether directly smoked or inhaled as secondhand smoke. The main components of smoke include nicotine, volatile organic compounds, and metals, such as cadmium, chromium, arsenic, lead, and many gas pollutants. Studies have found that once nicotine enters the bloodstream, it is distributed to all major organs of the body, such as the lungs, brain, and liver, and can freely enter the fetal body through the maternal placental barrier for circulation (26). Further studies have found that nicotine can interact directly with acetylcholine receptors in the fetal brain and affect the release of other neurotransmitters, including dopamine, noradrenaline, adrenaline, acetylcholine, serotonin (5-hydroxytryptamine), γ-aminobutyric acid (GABA), glutamate, and β-endorphin. In addition to nicotine, cigarette smoke contains heavy metals, such as lead and arsenic, that can damage the developing nervous system, influence the brain development, affect intellectual development, and cause behavioral damage after birth. Therefore, lead, mercury, arsenic, and cadmium are considered contributing factors to childhood autism (27,28). Therefore, the exposure of pregnant women to cigarette smoke can increase the risk of ASD in their children.

In the present study, we found that living in rural areas during pregnancy was a risk factor for ASD. Raina *et al.* found that the incidence of autism in rural areas is higher than that in urban areas (29). Pesticide exposure is common in rural China. According to traditional Chinese customs, pregnant women engage in field work and they are exposed to pesticides during pregnancy. Increasing literature suggests that exposure to pesticides during pregnancy and early childhood is an environmental risk factor for ASDs (30). Through blood sampling during pregnancy, it was found that maternal exposure to high levels of organochlorine compound pesticides during pregnancy could affect the occurrence of ASD (31). Studies have found that organochlorine pesticides are persistent pollutants (32), which can act on the central nervous system through GABA receptor-mediated chloride channels (33). Similarly, it has been observed that maternal exposure to chlorpyrifos, an organophosphorus insecticide, increases the risk of autism in children (34). Animal experiments have also shown that pregnant rats exposed to low doses of glyphosate herbicides can create animal models similar to ASD (35). In addition to organochlorine pesticides, organophosphate insecticides can also affect the maturation and synaptic and axonal transmission of nerve cells by inhibiting the production of acetylcholinesterase in the brain, limiting the transmission of nerve signals in the peripheral and central nervous systems. Therefore, pesticide contamination can affect the development of the central nervous system through the placenta and blood–brain barrier, which is considered to be associated with ASD (36). There are also high levels of air pollutants in rural areas close to factories and waste incineration facilities. Studies have found that late pregnancy exposure to PM2.5 and PM10 is a risk factor for ASD in offspring (37). Therefore, more attention should be paid to the living environment during pregnancy. Particular environmental factors, such as pesticides, noise, and dust, may increase the risk of ASD (37). Perinatal ischemic-hypoxic (ICH) is defined as the occurrence of any one or more of the following acute (placental abruption, fetal malpresentation, dystocia, cord complications, 5-min Apgar

score <7, respiratory distress syndrome, and asphyxia) and chronic (preeclampsia) conditions. Perinatal hypoxia has always been the focus of ASD etiology research. In a previous published study, more than 60 perinatal and neonatal factors were analyzed, and it found that a low 5-min Apgar score was a positive factor for ASD risk (9). Children with lower 5-min Apgar scores had a 3-fold increased risk of ASD.

Our results showed that the proportion of perinatal hypoxia in ASD patients was higher than that in the control group, especially in boys. Logistic regression analysis showed that the OR value was as high as 38.85, that is, the possibility of ASD in children was 38.85 times higher than that in pregnant women without a history of perinatal hypoxia. Further studies have suggested that perinatal hypoxia is a risk factor for ASD (11). Duan *et al.* found that perinatal hypoxia may lead to excessive activation of the dopamine system after brain nerve damage, thereby increasing the risk of ASD (13). Increased maternal age is also considered a risk factor for autism. Studies have found that older mothers have a poor uterine environment and are prone to more obstetric complications, such as premature infants, low infant body weight, and brain hypoxia, which are associated with ASD (38). The present study also suggests that perinatal hypoxia is a risk factor for autism. Therefore, strengthening perinatal health care and reducing brain injury during birth are effective measures to prevent ASD in children.

The dietary behavior of children with ASD is one of the hotspots of current research (39). The main dietary behaviors of ASD children are eating difficulties, such as pickiness, refusal to eat, and destructive eating behavior. It is accompanied by rigid and repetitive dietary patterns that eventually lead to nutritional imbalances (17). Feeding difficulties associated with ASD formation include postnatal preference and anorexia (40). The present study also found that boys with feeding difficulties were 12 times more likely to develop ASD than boys with a normal diet. This may be associated with the difficulty of concentrating, narrow interests, and the abnormal perception of children with ASD, which can exhibit dietary problems, including partial eating, poor appetite, and digestive disorders. Feeding difficulties are considered a potential risk factor for ASD and a potential cause of symptoms. Compared with normal children, children with ASD have persistent gastrointestinal problems (41), including a higher rate of constipation (42). Another study showed that intestinal microorganisms can participate in the pathogenesis of ASD through the intestinal-brain axis (43). The evidence suggests a link between intestinal dysfunction and ASD symptoms.

Increasing evidence suggests a link between intestinal dysfunction and ASD symptoms. The most common micronutrient deficiencies in ASD are vitamin D, calcium, potassium, pantothenic acid, and choline. Timely supplementation of calcium and vitamin D is important for the skeletal health of ASD children. In addition, feeding difficulties may cause or aggravate the deficiency of important nutrients in the body, which in turn increases the likelihood of ASD. Previous clinical studies have shown that after a 3-month vitamin D supplement for ASD children, language function, stereotypic behavior, and social decline improved (44).

Considering the dietary behavior and dietary structure of ASD, dietary therapy is of particular importance (45). Some scholars believe that adjusting the diet can be used to improve children's ASD behaviors. A gluten-free casein diet is believed to improve children's behavioral symptoms, gastrointestinal symptoms, sleep quality, and aggressive behavior. However, the treatment is still at an early stage of research, so it is not certain whether a gluten-free and casein-free diet is really beneficial for children with ASD (46). There have been other recent reports that the ketogenic diet is considered to significantly improve the behavioral symptoms of ASD; however, this warrants further study (47).

Conclusions

Improving living environment during pregnancy, reducing pregnancy complications, avoiding maternal exposure to smoke pollution during pregnancy, and correcting and improving children's diet and diet quality, can be effective entry points for ASD prevention and treatment. Due to the limited sample size and representativeness of this study, the conclusions may not fully represent all the risk factors of ASD. Future studies should further expand the sample size and update the content of the survey.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.

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