Prenatal and Perinatal Factors Associated with Pediatric Autism Spectrum Disorder in East China

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Research Article

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Abstract

Background

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by persistent challenges in social communication and interaction and restricted/repetitive patterns of behavior, interests or activities. An increasing number of studies have revealed that environmental exposure is a potential risk factor for ASD. The relationship between prenatal and perinatal risk factors and ASD has rarely been studied in large samples in China. Therefore, in this study, we compared children with ASD with typical developing (TD) children to assess the ASD-associated prenatal and perinatal risk factors and provide effective information for ASD prevention.

Methods

A case-control study of 709 children with autism spectrum disorder (ASD) and 709 gender-matched children with typical development was conducted to investigate the prenatal and perinatal risk factors of children with ASD compared with children with typical development (TD). Through a self-developed general information questionnaire, the basic information (name, age, gender), prenatal factors (parents' age at the child's birth, parents' education levels, use of assisted reproductive technology, history of miscarriage, gestational diabetes mellitus, gestational hypertension), and perinatal factors (delivery mode, full-term birth, parity, birth weight) of the children in the two groups were examined.

Results

The prenatal and perinatal factors of the groups were submitted to univariate analysis, the parent's age at childbirth, education level, history of miscarriage, use of ART, pregnancy-induced hypertension, and GDM differed significantly between the two groups (P<0.05), and that among perinatal factors, infant parity and maturity also differed significantly between the two groups (P<0.05). These statistically significant factors were included in a binary logistic regression model. The results showed that the prenatal factors of young maternal age at the child's birth (≤24 years vs 25-29 years, OR=2.408,95%CI:1.335~4.345), old paternal age at the childbirth(≥45years vs≤24years, OR=4.744, 95%CI:1.281~17.570), pregnancy induced hypertension (OR=6.178, 95%CI:2.311~16.517) and GDM(OR=0.220,95%CI:0.149~0.324), the perinatal factors of preterm birth(OR=4.434, 95%CI:2.872~6.846) and non-firstborn child(OR=1.387, 95%CI:1.029~1.869) are likely risk factors for ASD.

Conclusion

We show that some prenatal and perinatal factors are associated with a high prevalence of ASD in children.

1 Background

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by persistent challenges in social communication and interaction and restricted/repetitive patterns of behavior, interests or activities (1, 2). In the past decade, the global prevalence of ASD diagnoses has been on the rise. The prevalence of ASD in developed countries is 13.1-29.3 per 1,000 children, accounting for 1.5% of the world's total (3, 4). In Asia, the overall prevalence of ASD is 0.36% (5). Children with ASD represent heavy financial burdens on their families and on society (6, 7), and in most cases, ASD severely affects the quality of life of these children and their families. Most studies on the adult outcomes of children with ASD have shown very limited social integration, poor job prospects and a high incidence of mental health problems (8).

At present, the cause of ASD has not been fully elucidated. Despite high heritability, the genetics of ASD are complicated, and its underlying genetic structure is not well understood. ASD caused by single-gene and chromosomal defects only comprise a small proportion of the total cases (10- 20%) (9, 10). Due to the high heritability reported for ASD, previous studies have focused mainly on finding the potential genetic causes of ASD, while potential environmental triggers or causes are just as important as genetics. Environmental factors were found to explain 55% of the variation among twin pairs with autism. which strongly suggests the role of environmental factors in ASD pathogenesis (11, 12). ASD seems to be the result of the interaction of genetic factors with the prenatal and postnatal environments (13).

An increasing number of studies have revealed that environmental exposure is a potential risk factor for ASD (14, 15). Some studies have also shown that various perinatal factors, e.g., umbilical cord complications(RR=1.50,P=0 .05), fetal distress(RR=1.52, P=0 .01), birth injury or trauma(RR=4.90,P =0 .01), multiple births(RR=1.77,P=0.002), maternal hemorrhage(RR=2.39, P =0.003), low or very low birth weight(<2500g; RR=1.63,P= 0.002, <1500 g; RR:=3.00, P < 0.001), small-for-gestational-age birth(RR=1.35, P = 0.001), congenital malformations (RR=1.80, P < 0.001), low 5-minute Apgar score(RR=1.67, P =0.001), feeding difficulties(RR=3.35, P = 0.01), gestational diabetes mellitus (RR=1.48, 95% CI:1.26–1.75), obesity(OR=1.36; 95% CI: 1.08–1.70), gestational hypertension(OR=1.35, 95% CI:1.11–1.64), neonatal anemia(RR=7.87, P=0.02), hyperbilirubinemia(RR=1.87, P =0.05), etc., may also contribute to ASD in children, and their associations with ASD vary from region to region (16, 17). In addition, demographic changes (e.g., the changing size of birth cohorts across childbearing age groups) and changes in education, employment, and marital status mean that the average age of men and women at childbirth has changed. The effect of the parents' age at childbirth on the risk of ASD in their offspring has also been extensively examined. Advanced childbearing age was found to be associated with an etiology of psychosis and neurodevelopmental diseases, including bipolar disorder, schizophrenia, drug abuse, attention deficit hyperactivity disorder and ASD (18, 19). However, some studies have indicated that the association between advanced parental age at childbirth and an increased risk of ASD in the offspring is not statistically significant (20–24).

The relationship between prenatal and perinatal risk factors and ASD has rarely been studied in large samples in China (25–27). Therefore, in this study, we compared children with ASD with normally developing children to assess the ASD-associated prenatal and perinatal risk factors and provide effective information for ASD prevention.

2 Material And Methods

2.1 Material

2.1.1 Patient Group

A total of 709 patients who received clinical treatment at the Children's Mental Health Research Center of Nanjing Brain Hospital from July 2020 to November 2020, including 562 males and 147 females with an average age of (2.965±0.925) years, were investigated in this study. Frist of all, they were evaluated as positive for ASD according to the Chinese version of the Modified Checklist for Autism in Toddlers (M-CHAT), scores of ABC≥67(The ABC is a well-established parent report checklist used to screen for and diagnose autism).

And then attained the childhood autism diagnostic critical value on the Childhood Autism Rating Scale (CARS)，scores≥30, diagnosed by two psychiatrist, met the diagnostic criteria for ASD in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) , If the two psychiatrist don’t agree on a diagnosis, they’re excluded.

Children with neurological diseases and serious physical, genetic or metabolic diseases, such as Rett syndrome and Fragile X syndrome, were excluded.

2.1.2 Control Group

A total of 709 healthy children, including 562 males and 147 females with an average age of (2.989±0.336) years, who were born at Nanjing Maternity and Child Health Hospital and underwent a follow-up physical examination were included in the control group. These children were assessed for the Bayley Scales of Infant and Toddler Development (Bayley-III) at the age of one year, confirmed to have typical intelligence and development, showed no physical or mental illness based on a physician’s examination and evaluations, and were evaluated as negative for ASD according to the Chinese version of the Modified Checklist for Autism in Toddlers (M-CHAT).

2.2 Methods

2.2.1 Questionnaire and Information Collection

To collect the information of the patient group, we first developed a questionnaire regarding possible risk factors for the onset of ASD based on a survey of the relevant literature (14, 15, 28, 29). The questionnaire included (1) the children’s basic information (name, gender, and age); (2) prenatal factors

[parents’ age at childbirth and education levels; maternal history of gestational hypertension, gestational diabetes mellitus (GDM), miscarriage and use of assisted reproductive technology (ART), etc.]; (3) perinatal factors (delivery mode, infant maturity, parity, birth weight, etc.). The questionnaire was distributed to the parents, and completed questionnaires were collected by the staff of the evaluation office of the Children's Mental Health Research Center of Nanjing Brain Hospital, who also ensured the completeness of the questionnaires.

The information for the control group was collected through online questionnaires or offline interviews conducted by the staff of Nanjing Maternity and Child Health Hospital, who also ensured the completeness of the information.

2.3 Statistical Analysis

Some binary variables (e.g., history of pregnancy-induced hypertension, GDM, miscarriage, use of ART, diagnosed with ASD) were divided into “yes” and “no”. The binary variable parity was divided into firstborn and non-firstborn. The binary variable infant maturity was divided into full-term birth（37-42weeks） and preterm birth（28-37weeks）. The binary variable delivery was divided into vaginal delivery and caesarean delivery.

The graded variables of parents' education levels was divided in three as junior high school or below , high school and college or above. The graded variables of paternal age at childbirth was divided in four as ≤24 years , 25-35 years , 36-44 years and ≥45 years. The graded variables of maternal age at childbirth was divided in three as ≤24 years, 25-29 years and ≥30 years. The graded variable birth weight was divided in three as low birth weight（2500g）, normal birth weight (2500g-4000g) and high birth weight(4000g). The difference in parental age at childbirth as continuous variable.

The data were analyzed using the SPSS 23.0 software. In the univariate analysis, count data were expressed as frequency and percentage, and the intergroup difference was analyzed with the chi-square test, measurement data were expressed as the mean ± standard deviation, and the intergroup difference was analyzed with a t-test. The risk factors that had statistical significance (P<0.05) in the univariate analysis were selected using the enter method and were included in the unconditional multivariate logistic regression model, which was subjected to the two-sided test at a level of α=0.05.

3 Results

3.1 Univariate Analysis of the Two Groups According to Prenatal and Perinatal Factors

The results of the questionnaire survey showed that among the prenatal factors, the parent’s age at childbirth, education level, history of miscarriage, use of ART, pregnancy-induced hypertension, and GDM differed significantly between the two groups (P<0.05), while the absolute value of the difference in parental age at childbirth did not(P>0.05), and that among perinatal factors, infant parity and maturity

also differed significantly between the two groups ($P<0.05$), while birth weight and delivery mode did not ($P>0.05$, Table 1).

Table 1
Single factor analysis of Prenatal and perinatal period in case group and Control Group

Factor	Case Group	Control Group	X^2/T	P
	N/MD %/S	N/MD %/S		
Prenatal				
Paternal education level	124 17.5	18 2.5	110.294	0.000
junior high school or below	125 17.6	80 11.3		
high school	460 64.9	611 86.2		
college or above				
Maternal education level	160 22.6	30 4.2	131.322	0.000
junior high school or below	111 15.7	64 9.0		
high school	438 61.8	615 86.7		
college or above				
Maternal age at childbirth	94 13.3	27 3.8	63.433	0.000
≤24years	347 48.9	294 41.5		
25-29years	268 37.8	388 54.7		
≥30years				
Paternal age at childbirth	40 5.6	18 2.5	18.018	0.000
≤24years	546 77.0	531 74.9		
25-35years	107 15.1	151 21.3		
36-44years	16 2.3	9 1.3		
≥45years				
Difference in parental age at childbirth	2.18 2.508	2.26 2.606	0.623	0.533
Miscarriage	264 37.2	219 30.9	6.358	0.012
yes	445 62.8	490 69.1		
no				
ART	86 12.1	187 26.4	46.613	0.000
yes	625 88.2	522 73.6		
no				

Factor	Case Group	Control Group	X^2/T	P
	N/MD %/S	N/MD %/S		
HDP	24 3.4	8 1.1	8.815	0.004
yes	685 96.6	701 98.9		
no				
GDM	178 25.1	45 6.3	94.125	0.000
Yes	531 74.9	664 96.6		
no				
perinatal				
parity	480 67.7	539 76.0	12.14	0.000
firstborn	229 32.3	170 24.0		
non-firstborn				
birth weight	27 3.8	29 4.0	3.585	0.167
low birth weight	603 85.0	622 87.8		
normal birth weight	79 11.1	58 8.2		
high birth weight				
Term Birth	598 84.3	667 94.1	34.881	0.000
full-term birth	111 15.7	42 5.9		
preterm birth				
delivery	388 54.7	388 54.7	0.000	1.000
vaginal delivery	321 45.3	321 45.3		
caesarean delivery				

3.2 Multivariate Logistic Analysis of Prenatal and Perinatal Risk Factors for ASD

The results of the above univariate analysis showed that 10 variables could be included in the regression model:

Prenatal factors included the maternal history of miscarriage, GDM, gestational hypertension, use of ART, the parents' education levels, the parents' age at childbirth; for these factors, the inclusion and exclusion

criteria were both 0.05.

Perinatal factors included infant parity (firstborn/non-firstborn) and maturity (full-term/preterm); for these, the inclusion and exclusion criteria were both 0.05.

The regression results indicated that among the prenatal factors, maternal history of gestational hypertension significantly increased the risk of ASD in the offspring [odds ratio (OR)=6.178, 95% confidence interval (CI) 2.311-16.517, P<0.001]; maternal GDM significantly increased the risk of ASD in the offspring (OR=0.220, 95% CI 0.149-0.324, P<0.001); maternal history of ART use significantly decreased the risk of ASD in the offspring (OR=0.312, 95% CI 0.222-0.439, P<0.001); high paternal education level (high school and college or above relative to junior high or below) significantly decreased the risk of ASD in the offspring (OR=0.413, 95% CI 0.213- 0.799, P=0.009; OR=0.390, 95% CI 0.201-0.758, P=0.005); and high maternal education level (high school and college or above relative to junior high or below) significantly decreased the risk of ASD in the offspring (OR=0.510, 95% CI 0.279- 0.932, P<0.05; OR=0.216, 95% CI 0.121-0.384, P<0.001). After the mothers were grouped by their age at childbirth, mothers who were ≤24 years at childbirth had a significantly increased risk of ASD in their offspring compared with mothers who were 25-29 years old at the time of the child's birth (OR=2.408, 95% CI 1.335-4.345, P=0.004). After the fathers were grouped by their age at childbirth, fathers who were ≥45 years at childbirth had a significantly increased risk of ASD in their offspring compared with fathers who were ≤24 years old at the time of the childbirth (OR=4.744, 95% CI 1.281-17.570, P=0.020).

Among the perinatal factors, non-firstborn status significantly increased the risk of ASD in the offspring (OR=1.387, 95% CI 1.029-1.869, P<0.05), and preterm birth also significantly increased the risk of ASD in the offspring (OR=4.434, 95% CI 2.872-6.846, P<0.001) (Table 2).

Table 2
Logistic Regression analysis on risk factors of ASD

item	β	S.E.	WaldX^2	P	OR	95%CI
parity	0.327	0.152	4.606	0.032	1.387	1.029~1.869
Term Birth	1.489	0.222	45.172	0.000	4.434	2.872~6.846
Miscarriage	0.251	0.136	3.380	0.066	1.285	0.984~1.679
ART	-1.165	0.174	44.643	0.000	0.312	0.222~0.439
GDM	1.515	0.198	58.761	0.000	0.220	0.149~0.324
HDP	1.821	0.502	13.170	0.000	6.178	2.311~16.517
Paternal education level	-0.885	0.337	8.139	0.017	0.413	0.213~0.799
Junior high school or below	-0.941	0.339	6.885	0.009	0.390	0.201~0.758
high school			7.708	0.005		
college or above						
Maternal education level	-0.673	0.308	33.334	0.000	0.510	0.279~0.932
Junior high school or below	-1.534	0.294	4.788	0.029	0.216	0.121~0.384
high school			27.235	0.000		
college or above						
Paternal ages at childbirth	0.614	0.400	7.718	0.052	1.848	0.884~4.046
≤24years	0.429	0.441	2.358	0.125	1.536	0.648~3.643
25~35years			0.948	0.330		
36~44years						
≥45years	1.557	0.668	5.430	0.020	4.744	1.281~17.570
Maternal ages at childbirth	0.879	0.301	13.689	0.001	2.408	1.335~4.345
25~29years						
	-0.330	0.170	8.519	0.004	0.719	0.515~1.002
≤24years						
			3.798	0.051		
≥30years						
constant	2.561	0.319	64.477	0.000	12.954	

3.3 Multiple Regression analysis of prenatal and perinatal factors on severity of ASD

We also collected the CARS scores of 709 children with ASD, use a t-test, univariate analysis of variance, spearman correlation analysis to discuss whether there is a difference in the CARS scores among the investigated prenatal and perinatal factors. The risk factors that had statistical significance (P<0.05) in the univariate analysis were substituted into the multiple linear regression model, which was subjected to the two-sided test at a level of α = 0.05.

The results showed that, in the univariate analysis, the score of CARS is significantly different in paternal education level(F=1.158, junior high school or below vs college or above, p=0.004), maternal education level(F=0.905, junior high school or below vs college or above, p=0.035) and parity(non-firstborn vs firstborn, t=-2.216, p=0.027), multiple Linear regression analysis showed that the prenatal and perinatal factors investigated by this study did not affect the severity of symptoms in children with ASD. The results of multiple linear regression are shown in the Table3.

Table 3: Multiple Regression analysis of prenatal and perinatal factors on severity of ASD

Item	B	S.E.	P	95%CI
Paternal education level	0.896	0.470	0.057	-0.027-1.819
Junior high school or below high school	0.107	0.392	0.786	-0.663-0.877
Maternal education level	0.085	0.443	0.847	-0.784-0.955
Junior high school or below high school	0.193	0.394	0.625	-0.580-0.965
Parity non-firstborn	0.463	0.270	0.087	-0.068-0.994
constant	35.209	0.170	0.000	

4 Discussion

4.1 Prenatal Risk Factors

4.1.1 Paternal Age at Childbirth

In this study, we found that compared with fathers who were ≤24 years at childbirth, a paternal age of ≥45 years at childbirth significantly increased the risk of ASD in offspring. Our study was consistent in previous studies. Some studies showed that paternal age at childbirth is independently correlated with the incidence of ASD in offspring (30–33), perhaps because de novo mutations (34, 35) and epigenetic changes (36–38) that are affected by paternal age increase the risk of ASD. Other studies found that after adjusting for other perinatal factors and he parents' psychiatric history, the association between the

risk of ASD and the age of mother or father is not statistically significant (39), or that after adjusting for the year of birth and socioeconomic status (SES), maternal age of ≤35years, only advanced paternal age at childbirth is related to the risk of ASD in offspring (32, 40).

In the future, we will increase the sample size so to expand the range of paternal ages at childbirth. Furthermore, the confounding factors related to age at childbirth, such as socioeconomic factors and personality traits, will also be examined to understand their effects on the risk of ASD in offspring.

4.1.2 Maternal Age at Childbirth

Previous studies showed that advanced maternal childbearing age increases the risk of ASD in offspring (16, 41–43). Accumulations of mutations, an increased incidence of complications, increased exposure to drugs or pollution (14), uniparental disomy (44), endocrine disruptors (45), and omega-3 fatty acid supply (46) may be the causes of the increased risk of ASD in the offspring of older pregnant women.

We found that younger mothers (≤24 years old vs 25-29 years old) had an increased risk of ASD in their offspring, which is consistent with the finding of a previous study. This may be because young age is related to education, employment, and other SES indicators. Studies have shown that low SES may be a risk factor for ASD and is causally related to a young age at childbirth. This complex interaction between SES and maternal age may be accompanied by risks of other adverse consequences, including maternal infections and poor health surveillance (47), and is likely to be associated with adverse pregnancy outcomes (48, 49). In addition, without adjusting for SES, the maternal childbearing age at childbirth shows a U-shaped relationship with illness in the offspring (50) or with ASD with intellectual disability in offspring (40). In other SES-adjusted studies, a monotonic association with maternal age is reported (30). Previous studies suggest that a very young or old age at childbirth will increase the risk of ASD in offspring. Compared with those studies, we need to increase our sample size and include samples from more regions while thoroughly recording household socioeconomic factors, such as parental occupation, education level, and income, so that the impact of age and other confounding factors on ASD in offspring can be better understood.

4.1.3 Parental Education Levels

In this study, we found that as the education levels of parents increases, the risk of ASD in the offspring is reduced, likely because low education levels in parents affect their SES. It was reported that the low measured prenatal SES is correlated with an increased risk of ASD in offspring (51). In addition, children with ASD from families with lower SES show increased emotional and behavioral problems (52) and a greater risk of intellectual disability (53, 54). Moreover, the SES-based differentiation of diagnostic services may also cause families in poorer communities to have a delayed diagnosis, which delays intervention and increases the severity of ASD symptoms in children from these communities (54–58). Studies have also shown that language delay is related to the paternal education level (59) and that the use of positive parenting styles is related to the maternal education level (60). The higher the education levels of the parents, the more knowledgeable they are about the disease; as a result, they will find various professional resources to help them understand their child's symptomatic behavior and then adopt a

more rational way to treat the child, while the individuals with low SES often have insufficient resources for these purposes (61).

In the initial data collection stage of this study, we found that the patient group was dominated by those from outside the city who were making special trips to the clinic and that the parents of these patients were mostly migrant workers with low education levels, while the subjects in the normal control group were mostly children seeking outpatient consultations, physical examinations, or assistance with other medical conditions, and these families were evenly distributed throughout the city's household registration. This may bias our results; therefore, in future studies, we will increase the sample size and include more socioeconomic factors (e.g., occupation and family income) for a comprehensive consideration.

4.1.4 High Blood Pressure

In this study, we found that hypertensive disorder of pregnancy (HDP) increases the risk of ASD in the offspring, which is consistent with the results of previous studies. It has been reported that HDP is associated with an increased risk of mental disorders in offspring (62) and increases the risk of ASD (63, 64). In addition, HDP can lead to various emotional and behavioral problems (16, 65, 66) and impaired cognitive development (67, 68).

This may be because that HDP not only complicates 5-10% of pregnancies (69), which affects maternal health and pregnancy outcomes, but it also affects fetal brain development due to an unfavorable fetal environment, such as poor placental vascularization, which makes the infant more susceptible to neurobehavioral disorders. In addition, due to inadequate uterine-placental perfusion and hypoxia, HDP may be related to reduced oxygen and nutrient supply to the fetus (70, 71), which can damage the fetus's brain development and increase the risk of emotional and behavioral disorders later in life (72). The changes in maternal and fetal inflammatory systems and the hypothalamic-pituitary-adrenal axis functions, which have already been shown to be the result of HDP and to be associated with mental disorders in offspring (73–76), can also increase the risk of mental disorders in offspring. At the molecular level, HDP may have a pleiotropic genetic effect on mental and behavioral diseases in offspring, which is likely mediated through epigenetics. The genetic risk factors for mental disorders and hypertension partially overlap. For example, epigenetic DNA methylation and gene expression changes are observed in patients with HDP and in patients with mental disorders (77, 78).

4.1.5 GDM

In our study, we find that GDM increases the risk of ASD in the offspring, which is consistent with some previous reports (79–85). Studies have suggested that GDM's impact on neurodevelopment may be mediated by oxidative stress (86), pro-inflammatory cytokines (87), and epigenetics (88). There were also studies that suggest that GDM causes a variety of adverse obstetric outcomes (e.g., preeclampsia, fetal macrosomia, perinatal mortality, caesarean section, and premature delivery) rather than simply increasing the risk of neurodevelopmental disorders (89–91). In addition, studies have shown that a higher body mass index or pregestational diabetes mellitus instead of GDM increases the risk of ASD in offspring (84,

92), or that only pregestational diabetes mellitus and GDM in obese mothers increases the risk of ASD in offspring (93), suggesting that the exposure to accompanying inflammation, lipotoxicity, metabolic stress, and hyperglycemia may have stronger neurological impact than hyperglycemia alone (94–97). Some studies indicate that GDM at different stages of pregnancy can lead to different neurodevelopmental conditions (83, 98).

4.1.6 ART

In this study, we found that ART is significantly associated with ASD and may be a protective factor against the disease, which is inconsistent with the results of some previous studies (99, 100). But the results are consistent with some previous literatures (101, 102). This may be because women with assisted conception have better pre-pregnancy preparation and reduce behaviors that negatively affect their health through close contact with the healthcare system before and during pregnancy (103). The health status of pregnant women is related to the intellectual disability of their offspring, and therefore, it may be beneficial for pregnant women to have access to advice on promoting good growth conditions for the fetus before and during pregnancy. Some studies indicate that folic acid (FA) intake in early pregnancy and during pregnancy plays an important role in the etiology and severity of ASD; thus, taking FA may be a protective factor (104). Another possibility is that certain elements in the maternal diet (fatty acids, vitamin D, and iron) may play a protective role by combating some of the core ASD symptoms (105, 106). For example, in the late stage of pregnancy, higher iron intake is associated with a reduced risk of ASD since iron contributes to neurotransmitter production, myelination, and immune function. In addition, vitamin D supplementation during pregnancy can reduce the risk of ASD in offspring (107, 108).

However, some studies have shown that ART can increase the risk of ASD in offspring (109, 110). This may be due to several procedures used in ART, such as hormone stimulation, egg retrieval, in vitro fertilization, intracytoplasmic sperm injection, gamete micromanipulation, and exposure to culture media, which may cause environmental stress in gametes and early embryos, which in turn may be associated with an increased risk of birth defects (109). The inconsistency of our findings with those of other studies indicates that further prospective, large-scale, and high-quality research is needed. The limitation leading to this inconsistency is derived from the heterogeneity of the studies, especially in terms of study design (cohort and case-control), ART data recruitment strategies (registration, medical records, parent interviews), and the evaluation of confounding factors.

4.2 Perinatal Risk Factors

4.1.2 Preterm Birth

In this study, we found that preterm birth increased the risk of ASD. This is consistent with previous research reports that abnormal gestational age (premature delivery, late delivery) can increase the risk of ASD (39, 82, 111).

This finding may reflect damage to neurodevelopment that occurred during the prenatal period. Notably, intrauterine growth restriction (IUGR) derived from placental insufficiency is a condition associated with

chronic hypoxia, metabolic disorders, and acidosis (112, 113). The neonatal consequences of intrauterine acidosis include hypoxic-ischemic encephalopathy, intraventricular hemorrhage, and periventricular white matter softening (114). Therefore, IUGR is associated with poor neurodevelopmental results (115), which can lead to behavioral and cognitive difficulties, cognitive deficits (116–118), and ASD manifestations in children. In addition to placental dysfunction, IUGR can be caused by intrauterine infection or genetic abnormalities, both of which are related to neurodevelopmental abnormalities (119, 120).

The increased risk of ASD in children with post-term birth may reflect abnormalities in maternal metabolism, such as obesity, inflammatory changes associated with abnormal maternal metabolism, delivery complications, birth injuries, or postpartum metabolic disorders. For example, circulating inflammatory cytokines and acute phase proteins are systemically increased in obese women (121). Inflammatory mediators have been shown to be able to pass through the placenta and alter neurodevelopment in animal models (122). It has been speculated that in addition to having a direct impact on fetal neurodevelopment, exposure to intrauterine inflammation can trigger lifelong immune dysfunction in the fetal immune system, which may lead to the underlying abnormal neurodevelopment and behavioral abnormalities observed in ASD (123).

4.1.3 Parity

In this study, we found that non-firstborn children had a higher risk of ASD, which is not completely consistent with the findings of previous studies. Previous studies have shown that in families with no children with ASD, a pregnancy interval of less than 24 months is related to an increased chance of a second or third child suffering from ASD, and a pregnancy interval of less than 12 months presents the highest risk; this indicates that with shorter pregnancy intervals, children born later have a continuously increasing risk of having ASD (124). This may be due to (1) the association of shorter pregnancy intervals with adverse pregnancy outcomes (including low birth weight and premature delivery) (125), (2) depletion of maternal nutrients, especially FA (FA is required for DNA synthesis and cell division during pregnancy. Without supplementation, FA levels in serum and red blood cells begin to decline in the second trimester, and the FA level in red blood cells continue to decline for at least 12 months after delivery (126, 127)), and (3) other possible mechanisms, such as maternal iron and polyunsaturated fatty acid levels (128) or stress (129). Conversely, some studies have shown that firstborn children have a higher risk of having ASD, likely because families with a child with ASD may delay further pregnancies, a phenomenon called reproductive stoppage (130–134). Moreover, the ASD phenotype is highly heterogeneous. In some patients, symptoms persist beyond early childhood, while in others, these symptoms only appear in a milder form in late childhood. Therefore, even for a family with a child with ASD, the severity of the child's ASD phenotype may affect the family's decision to have another child (135). The inconsistency of our results with those of other studies suggests that the birth interval of between children should be considered when studying the impact of parity on ASD and that it is important to review the neurodevelopment of children in families with multiple children to perform a classification analysis of the family's ASD exposure. In addition, we need to pay attention to the psychological stress that parents are likely to experience when raising a child with ASD. With the current

changes in fertility policy in China, these investigations can provide references for families planning to have a third child.

This study has certain limitations. First, the sample size was small compared with that of the same type of studies conducted in other countries, and consequently, we were unable to include some possible risk factors or negative results in this study. Additionally, the ages of the children in the patient group and those in the control group were not matched, and because this study was retrospective, the results may be subject to recall bias. However, there was no significant difference in gender between the two groups of children, which eliminates the impact of gender on the results. This study collected the largest reported sample of participants from East China; therefore, the results can be used as a reference for clinical and scientific research.

In short, in this study, we found that the prenatal factors of a maternal age at childbirth of ≤24 years and pregnancy-induced hypertension and the perinatal factors of non-firstborn children and preterm birth may be risk factors for ASD. Improving the living environment during pregnancy, reducing complications during pregnancy, and avoiding exposure of the mother to adverse environments during the prenatal and perinatal periods can be effective entry points for the prevention and treatment of ASD. Moreover, we also found that factors that may be related to the SES of parents may affect the incidence of ASD in offspring. Against the background of China's current three-child policy, it is very important to pay attention to the factors that affect the health of offspring. However, due to the limited sample size and representativeness of this study, its conclusions may not fully represent all prenatal and perinatal risk factors for ASD. It is necessary to conduct more studies in the future to understand the adverse factors of ASD so that more information on the prevention and treatment of pediatric ASD can be provided to families.

Limitations

The present study has limitations. The number of cases in this study is still relatively small compared to similar risk factor studies abroad, leading to some possible risk factors can't be included in this study, or negative results. Conclusions may not be representative of all prenatal and perinatal risk factors for ASD. Future research should further expand the sample size, in-depth study of environmental factors on the impact of disease, to provide more effective and comprehensive prevention and treatment information for children with ASD.

Conclusion

We show that some prenatal and perinatal factors are associated with a high prevalence of ASD in children. Improving the living environment during pregnancy, reducing complications during pregnancy, and avoiding exposure of the mother before and during the perinatal period can be an effective approach to the prevention and treatment of ASD. In this study, we also found that the socioeconomic status of parents may be related to the impact of disease in future generations, in China's current three-child policy open background, pay attention to the factors affecting children health is crucial.

Abbreviations

ASD (Autism Spectrum Disorder); TD (typical development); GDM (gestational diabetes mellitus); M-CHAT (Modified Checklist for Autism in Toddlers); CARS (Child Autism Rating Scale); FA (folic acid); HDP (hypertensive disorder of pregnancy); ART (assisted reproductive technology);

Declarations

All methods were carried out in accordance with relevant guidelines and regulations.

Ethics approval and consent to participate

All parents of children involved in the questionnaire signed an informed consent form. All experimental protocols were approved by the Nanjing Brain Hospital Ethics Committee (Approval certificate number: 2017-KY098-01). Ethical approval for the study was granted by the China Clinical Trial Registration Center (Name of the Ethic Committee: Nanjing Brain Hospital Ethics Committee), ChiCTR-OPC-1701 1995.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used or analysed during the current study available from the corresponding author (Xiaoyan Ke) on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Author Contributions

YL performed the experiments (data curation, formal analysis, investigation)

ND and ZYZ and LH support the part of data collection

YL support the part of data resources

XYK designed the study and oversight the manuscript

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