Journal of Autism and Developmental Disorders (2023) 53:2954–2963
https://doi.org/10.1007/s10803-022-05603-1

ORIGINAL PAPER

Risk factors for ASD

Risk Factors for Autism Spectrum Disorder in Shanghai, China: A Population-based Case-control Study

Yuanyuan Lin[1] · Guanghai Wang[2,3] · You Yang[1] · Xingming Jin[1] · Hong Huang[4] · Yiwen Zhang[1] · Zhijuan Jin[1]

Accepted: 4 May 2022 / Published online: 20 May 2022

Abstract
Autism spectrum disorder (ASD) is a pervasive neurodevelopmental disorder that brings heavy burdens to families and the society. This case-control study explored risk factors for ASD based on 74,252 children aged 3–12 years who were recruited from general education kindergartens, primary schools, and special education schools in Shanghai, China. One hundred ninety-two children were identified with ASD according to the Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition. Male sex, the presence of anoxia or asphyxia at birth, artificial feeding, adverse maternal psychological status, complications during pregnancy and higher paternal education were associated with ASD even after controlling for age, residential district, family history of mental disorders, parental personality, and amount of daily TV viewing.

Keywords Autism spectrum disorder · Case-control · Pre- and peri-natal risk factors

Autism spectrum disorder (ASD) is a pervasive neurodevelopmental disorder characterized by severe social communication defects and stereotyped, repetitive behaviors(American Psychological Association, 2013). ASD seriously affects individual's physical and mental health as well as their quality of life, and also brings heavy burdens to families and the society(Rogge & Janssen, 2019).

✉ Yiwen Zhang
zhangyiwen@hotmail.com

✉ Zhijuan Jin
syjzj714@hotmail.com

1 Department of Developmental and Behavioral Pediatrics, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

2 Pediatric Translational Medicine Institute, Department of Developmental and Behavioral Pediatrics, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

3 Ministry of Education-Shanghai Key Laboratory of Children's Environmental Health, Shanghai, China

4 Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

The prevalence of ASD is reported to be increasing, which has provoked global concern. From 2014 to 2016, the prevalence of ASD in America increased from 16.8 per 1000 children aged 8 years to 18.5 per 1000 children(Maenner et al., 2020). Over the same time period, the prevalence in China increased from 0.12–0.70%(Zhou et al., 2020).The increase in ASD prevalence is commonly attributed to changing diagnostic criteria for ASD. The latest manual for clinical diagnostic criteria is the fifth edition of the Diagnostic and Statistical Manual (DSM-5) which was published in 2013. The use of these revised diagnostic criteria might have had an impact on the prevalence of ASD(Fombonne et al., 2021) as they have been shown to improve diagnostic sensitivity and specificity(Wiggins et al., 2019).

Symptoms of ASD can be observed within the first years of life(Pierce et al., 2019; Miller et al., 2017). However, the average age of diagnosis is about 4 years old in United States(Maenner et al., 2021) and ASD patients are most often diagnosed at older ages in low- and middle- income countries(Rudra et al., 2017). This delay in diagnosis usually results in children missing the optimal time for intervention. Therefore, identifying modifiable risk factors as early as possible is critical.

In Europe and the United States, early screening for ASD has been conducted.(Stenberg et al., 2021; Magnus et al., 2006; Schendel et al., 2012). The Study to Explore Early Development (SEED) in United States was population-based, multi-center, multi-stage, and multi-disciplinary. Specifically, parent-screening assessments were used to identify children likely to have ASD in communities or schools. Children who screened positive were moved on to a second stage of clinical observation, evaluation, diagnosis, and early intervention. However, in many low- and middle-income countries, there are significant obstacles to overcome in order to carry out well-established and scientific research, such as limited recognition of ASD, lack of resources and the need for expensive diagnostic tools(Fombonne et al., 2021; Marlow et al., 2019). In China, most previous studies on risk factors for ASD have been based in clinical settings rather than communities, which are considered to be low-resource environments. It becomes more significant that most population-based studies of ASD prevalence relied solely on the results of screening tools, such as the Modified Checklist for Autism in Toddlers (CHAT) and were rarely confirmed by a second round of evaluation based on DSM-5 criteria to confirm the diagnosis(Wang et al., 2019; Shi et al., 2017). Further, they mainly focused on children in mainstream schools, ignoring those in special schools(Sun et al., 2019). Unlike other countries, most children with ASD in China receive compulsory education in special schools, especially those with moderate and severe impairments.

It has been reported that heritability of ASD is about 50 – 80%, suggesting environmental factors also contribute to developing ASD(Sandin et al., 2014; Bai et al., 2019). To date, many environmental factors have been mentioned related to ASD. For example, prenatal complications or history of medication during pregnancy has been investigated and these factors have also demonstrated in animal models(Bilbo et al., 2018). Some studies found no association between ASD risk and prenatal antidepressant use after adjusting for maternal psychological status, suggesting that maternal psychological status during pregnancy may be more important(Brown et al., 2017). Research also suggests that children with ASD are more likely to experience family adversities, such as neglect from their parents and caregivers, which might negatively impact their brain development(Kuenzel et al., 2021). Although causal associations have not yet been established, poor parenting quality is considered to be a contributing factor in ASD. Few studies have addressed this topic, especially in China, where parenting culture is definitely different from that in Western countries(Yarger & Redcay, 2020). It is important to note that children with ASD have been found to spend more time on screen than typically developing children(Dong et al., 2021). Parents of children with ASD are more likely use screen time to calm their child, especially in families with poor parenting. And several studies have suggested that excessive screen exposure has a negative effect on language and behavioral development, which may in turn worsen autistic symptoms(Slobodin et al., 2019).

We conducted a population-based, case-controlled epidemiological study of children aged 3 to 12 in Shanghai to explore potential risk factors for ASD. A multi-stage stratified cluster sampling was used to assess children, including those in mainstream kindergartens, primary schools, and special need schools. In this study, in addition to other commonly recognized risk factors, we took into account parental personality and daily TV time of children.

Methods

Study Design and Sampling

Our data derived from a study of children aged 3 to 12 years in Shanghai. The specific study design and sampling method has been described in our previous publications(Jin et al., 2018; Chen et al., 2016). We randomly sampled three of the eight urban districts and four of the nine suburban districts. In Shanghai, children are routinely assessed before a kindergarten accepts them. If children have serious cognitive or behavioral problems, they are transferred to special need schools after comprehensive evaluation by educational experts and physicians. Therefore, we conducted a sample survey of general education kindergartens and primary schools and a census of special need schools. Firstly, all parents were requested to fill out the Social and Communication Questionnaire (SCQ) and our self-designed questionnaire. Secondly, the teachers of children who screened positive by their parents were asked to complete the SCQ. Finally, children who screened positive by both parents and teachers were referred to the Department of Developmental and Behavioral Pediatrics at Shanghai Children's Medical Center and ASD cases were identified based on DSM-5 diagnostic criteria by at least two experienced developmental and behavioral pediatricians independently. If disagreement occurred between the two pediatricians, a third experienced pediatrician was involved, and all pediatricians discussed the case until consensus was reached. This study was approved by the Institutional Review Board of the Shanghai Municipal Commission of Health and Family Planning.

It should be noted that we did not include children in orphanages here. The reasons for not including orphans were as follows: First, according to the Shanghai Statistical Yearbook 2016, there were only 1863 orphans in Children Welfare Homes, accounting for about 0.2% of children in

Shanghai(Shanghai Municipal Statistics Bureau, 2016a). Second, over the years, China was speeding up establishing a preschool education subsidy system to subsidize children from families with financial difficulties, orphans and children with disabilities to receive universal preschool education. In 2015, according to a statistical bulletin on the development of disabled persons in Shanghai, there were only 30 disabled children who had reached school age and were not in school(Shanghai Municipal Statistics Bureau, 2016b). That is, we were able to include the vast majority of disabled children through a census of special-needs school. Third, the parents of orphans were not available to answer questions about pregnancy or family history in survey.

In 2011, the results of the Sixth National Census in Shanghai showed that among the city's resident population, the Han population was 22.7433 million, accounting for 98.80%, and the population of various ethnic minorities was 275, 800, accounting for 1.2%(Shanghai Municipal Statistics Bureau, 2011). Therefore, we did not take ethnic background into account.

Measures

The Social and Communication Questionnaire (SCQ)

The SCQ is derived from the Autism Diagnostic Interview-Revised and was developed as a screening tool for children with a high risk for developmental problems(Rutter et al., 2003). It has 40 yes/no questions. Usually, parents can finish it in 10 min. We took 15 as the cut-off score recommended in the manual. The Chinese SCQ has satisfactory reliability and validity. The sensitivity and specificity of the questionnaire were found to be 0.74 and 0.93, respectively(Jing & Xiu, 2015).

Self-designed Questionnaire

The questionnaire for family and social environmental factors was developed based on relevant literature(Lyall et al., 2014; Kolevzon et al., 2007; Gardener et al., 2009). Variables used in this study include age (continuous), gender (male, female), birth weight (2500-4000 g, <2500 g, ≥ 4000 g), gestational period (37–42 weeks, <37 weeks, ≥ 42 weeks), type of delivery (vaginal, caesarean), the presence of anoxia or asphyxia at birth (yes, no), one child (yes, no), mode of feeding (breast feeding, artificial feeding, mixed feeding), parental age during pregnancy (<35 years, ≥ 35 years), history of assisted reproduction (yes, no), maternal psychological status during pregnancy (good, anxious or depressed, nervous), complications during pregnancy (yes, no), family history of mental disorders (yes, no), parental personality type (introverted, extroverted), amount of daily TV viewing (<1 h, 1-2 h, 2-3 h, ≥ 3 h), parental education (below bachelor degree, bachelor degree and above), and household income ($<20{,}000$RMB, $\geq 20{,}000$RMB). Family history of mental disorders, parental personality, and amount of daily TV viewing were based on the time the survey was conducted.

To further explore the association between adverse maternal psychological status and the presence of ASD, if mothers experienced adverse maternal psychological status during pregnancy, they were asked to answer the following questions: please choose the occurrence period (first-trimester, second-trimester, third-trimester, note: multiple selection), and please choose the duration of time of symptoms(<1 weeks, 1 week-1 month, 1month-3 months, ≥ 3 months).

We reported the presence or absence of complications during pregnancy and family history of mental disorders. Complications during pregnancy included any one or more of the following based on parent report: threatened abortion, use of medication, high fever (39°C), heart disease, hyperemesis gravidarum and anemia. Family history of mental disorders included any one or more of the following based on parent report: schizophrenia, depression, intellectual disability and language disorders. No analysis was done on sub-types due to the small sample size for each.

Procedures and Quality Control

We informed all parents about the study and obtained consent prior to distributing the surveys to reduce the non-response bias. After completing the survey form, parents returned them to their child's teacher in a sealed envelope. They were then coded and deidentified to protect privacy rights. After completing data entry, 15% of the samples were taken randomly and entered repeatedly. The consistency was 96%.

Statistical Analyses

The Epidata 3.1 was used to establish the database and all analyses were conducted with through R version 4.1.2. Univariate and multivariate logistic regression analyses were used to determine risk factors for ASD. The variables with $P<0.1$ in univariate analysis were entered a multivariate single-level logistic regression model. The Akaike Information Criterion (AIC) was used to evaluate model fit. The best-fit model was the one having the smallest AIC. $P<0.05$ was accepted as statistically different.

Intraclass correlation coefficient (ICC) for children nested in districts was 0.024. That is, 2.4% of the residual variation is attributable to unobserved district characteristics. Two-level logistic regression models (level 1: children; level 2:

districts) were used to analyze factors associated with the dependent variables. We compared a single-level and two-level model to see the impact of adding the district-level random effect. However, it was found that the differences between the two models were not statistically significant (P = 0.08; AIC of single-level model was 1736.4 and AIC of two-level model was 1736.1; all significant factors for the risk of ASD in single-level model were consistent with those of two-level model.) Therefore, we only reported the outcomes of single-level models in this manuscript and all models were adjusted by "district". Models did not account for school-level clustering. The reason was twofold. First, the sample consisted of children in the mainstream schools and special need schools and most of the cases came from

Table 1 Univariate logistics regression analysis of risk factors for ASD

	Control, *N (%)*	ASD, *N (%)*	Odds ratio (95% CI)	*P*
Age (months, *mean* ± SD)	91.10 ± 27.78	98.40 ± 29.26	1.01 (1.00-1.02)	< 0.001
Gender (Male)	38,888 (52.3)	145 (76.3)	2.84 (2.03–3.96)	< 0.001
Birth weight (grams)				
< 2500	3482 (4.9)	10 (5.3)	1.06 (0.56–2.02)	0.849
≥ 4000	7697 (10.8)	15 (8.0)	0.72 (0.43–1.23)	0.228
Gestational period (weeks)				
< 37	4322 (5.9)	18 (9.5)	1.66 (1.02–2.70)	0.042
≥ 42	2780 (3.8)	6 (3.2)	0.86 (0.38–1.94)	0.714
Caesarean	38,305 (52.4)	112 (59.6)	1.34 (1.00-1.80)	0.049
Anoxia or Asphyxia at Birth	2655 (3.6)	34 (17.8)	5.72(3.94–8.30)	< 0.001
One child	52,249 (71.1)	137 (71.7)	1.03 (0.75–1.42)	0.837
Mode of feeding				
Breast feeding	36,292 (49.5)	69 (36.1)	Reference	
Artificial feeding	11,771 (16.1)	46 (24.1)	2.06 (1.42–2.99)	< 0.001
Mixed feeding	25,233 (34.4)	76 (39.8)	1.58 (1.14–2.20)	0.006
Advanced maternal age[a]	3551 (5.0)	11 (5.8)	1.18 (0.64–2.17)	0.593
Advanced paternal age[a]	8744 (12.8)	30 (17.2)	1.42 (0.96–2.10)	0.083
History of assisted reproduction	647 (0.9)	2 (1.1)	1.17 (0.29–4.72)	0.826
Maternal psychological status				
Anxious or Depressed	2393 (3.3)	18 (9.7)	3.44 (2.11–5.63)	< 0.001
Nervous	3426 (4.7)	23 (12.4)	3.07 (1.98–4.78)	< 0.001
Complications during pregnancy[b]	16,164 (21.8)	75 (39.1)	2.30 (1.71–3.07)	< 0.001
Family history of mental disorders	1308 (1.8)	10 (5.2)	3.06 (1.61–5.79)	0.001
Introverted mother	6226 (8.6)	27 (14.5)	1.81 (1.20–2.72)	0.004
Introverted father	10,623 (14.6)	53 (28.5)	2.33 (1.69–3.20)	< 0.001
Daily TV viewing (hours)				
< 1	41,267 (56.9)	103 (56.6)	Reference	
1–2	24,237 (33.4)	56 (30.8)	0.93 (0.67–1.28)	0.642
2–3	5339 (7.4)	11 (6.0)	0.82 (0.44–1.54)	0.546
≥ 3	1692 (2.3)	12 (6.6)	2.84 (1.56–5.18)	0.001
High maternal education[c]	19,896 (27.0)	71 (37.2)	1.60 (1.19–2.14)	0.002
High paternal education[c]	22,681 (30.8)	90 (47.4)	2.02 (1.52–2.69)	< 0.001
High household income[d]	11,975 (16.6)	33 (17.6)	1.07 (0.74–1.56)	0.718
First-trimester[e]	4815 (6.5)	23 (12)	1.96 (1.27–3.03)	0.003
Second-trimester[e]	3276 (4.4)	20 (10.4)	2.51 (1.58-4.00)	< 0.001
Third-trimester[e]	3118 (4.2)	10 (5.2)	1.25 (0.66–2.37)	0.493
Duration[f]				
<1 week	57,845 (85.1)	108 (67.9)	Reference	
1week – 1 month	5364 (7.9)	23 (14.5)	2.50 (1.50–4.17)	< 0.001
1 month – 3 months	3137 (4.6)	17 (10.7)	2.84 (1.70–4.73)	< 0.001
≥ 3 months	1658 (2.4)	11 (6.9)	3.47 (1.87–6.46)	< 0.001

[a]Advanced age means ≥ 35 years; [b]Complications during pregnancy means if any one or more of the following was present: threatened abortion, medication, high fever (39°C), heart disease, hyperemesis gravidarum and anemia; [c]High education means having a bachelor's degree and above; [d]high household income means annual family income ≥¥20,000); [e]adverse psychological status appeared at dissimilar stages of pregnancy; [f]duration of adverse psychological status

special need schools. Second, not each school had both cases and controls.

Result

Univariate Logistics Regression Analysis of Risk Factors for ASD

As shown in Table 1, the following factors were associated

Table 2 Multivariate logistics regression analysis of risk factors for ASD

	Model 1 Odds ratio (95% CI)	Model 2 Odds ratio (95% CI)	Model 3 Odds ratio (95% CI)
Gender (Male)	2.75 (1.92–4.01) ***	2.77 (1.91–4.13) ***	2.77 (1.86–4.24) ***
Gestational period (weeks)			
< 37	0.98 (0.54–1.67)	1.13 (0.62–1.93)	1.05 (0.54–1.89)
≥ 42	1.05 (0.41–2.18)	1.17 (0.46–2.45)	1.33 (0.52–2.80)
Caesarean	1.25 (0.90–1.74)	1.26 (0.89–1.79)	1.12 (0.78–1.62)
Anoxia or Asphyxia at Birth	3.71 (2.35–5.66) ***	3.00 (1.82–4.73) ***	3.19 (1.89–5.15) ***
Mode of feeding			
Breast feeding		Reference	Reference
Artificial feeding	1.76 (1.15–2.67) **	1.74 (1.11–2.71) *	1.94 (1.21–3.08) **
Mixed feeding	1.27 (0.88–1.85)	1.33 (0.91–1.97)	1.32 (0.87–2.01)
Advanced paternal age[a]	1.27 (0.82–1.92)	1.23 (0.78–1.89)	1.24 (0.75–1.96)
Maternal psychological status			
Anxious or Depressed	2.57 (1.44–4.31) ***	2.13 (1.16–3.67) **	
Nervous	2.31 (1.36–3.71) **	2.01 (1.15–3.30) **	
Complications during pregnancy[b]	1.87 (1.33–2.61) ***	1.75 (1.23–2.48) **	1.52 (1.02–2.22) *
High maternal education[c]	1.01 (0.67–1.54)	1.06 (0.69–1.64)	1.18 (0.74–1.90)
High paternal education[c]	2.45 (1.62–3.69) ***	2.69 (1.73–4.14) ***	2.41 (1.49–3.85) ***
Family history of mental disorders		1.71 (0.75–3.41)	1.44 (0.55–3.13)
Introverted mother		1.32 (0.81–2.07)	1.38 (0.82–2.20)
Introverted father		1.92 (1.32–2.75) ***	2.01 (1.35–2.94) ***
Daily TV viewing (hours)			
< 1		Reference	Reference
1–2		1.34 (0.92–1.93)	1.40 (0.94–2.07)
2–3		1.13 (0.52–2.17)	1.24 (0.57–2.42)
≥ 3		2.84 (1.29–5.54) **	3.00 (1.29–6.09) **
First-trimester[e]			1.79 (1.04–2.94) *
Second-trimester[e]			1.70 (0.89-3.00)
Third-trimester[e]			0.70 (0.29–1.44)
Duration[f]			
<1 week			Reference
1week – 1 month			1.77 (0.95–3.09)
1 month – 3 months			1.72 (0.91–3.06)
≥ 3 months			1.31 (0.53–2.82)
AIC	2094	1943	1736

**P<0.05, **P<0.01, ***P<0.001; All models were adjusted by age, district*

[a]Advanced age means ≥ 35 years; [b]Complications during pregnancy means if any one or more of the following was present: threatened abortion, medication, high fever (39°C), heart disease, hyperemesis gravidarum and anemia; [c]High education means having a bachelor's degree and above; [d]high household income means annual family income ≥¥20,000); [e]adverse psychological status appeared at dissimilar stages of pregnancy; [f]duration of adverse psychological status

with the diagnosis of ASD. Age (in months) [odds ratio (OR) = 1.01, 95% confidence interval (CI) = 1.00-1.02, $P < 0.001$], male [OR = 2.84, 95% CI = 2.03–3.96, $P < 0.001$], preterm birth (< 37 weeks) [OR = 1.66, 95% CI = 1.02–2.70, $P = 0.042$], cesarean [OR = 1.34, 95% CI = 1.00-1.80, $P = 0.049$], the presence of anoxia or asphyxia at birth [OR = 5.72, 95% CI = 3.94–8.30, $P < 0.001$], artificial feeding [OR = 2.06, 95% CI = 1.42–2.99, $P < 0.001$], mixed feeding [OR = 1.58, 95% CI = 1.14–2.20, $P = 0.006$], maternal psychological status [anxiety or depression : OR = 3.44, 95% CI = 2.11–5.63, $P < 0.001$; maternal nervousness: OR = 3.07, 95% CI = 1.98–4.78, $P < 0.001$; present in first-trimester: OR = 1.96, 95% CI = 1.27–3.03, $P = 0.003$; present in second-trimester: OR = 2.51, 95% CI = 1.58-4.00, $P < 0.001$; duration ranged from 1 week to 1 month: OR = 2.50, 95% CI = 1.50–4.17, $P < 0.001$; duration ranged from 1 month to 3 months: OR = 2.84, 95% CI = 1.70–4.73, $P < 0.001$; duration over 3 months: OR = 3.47, 95% CI = 1.87–6.46, $P < 0.001$], complications during pregnancy [OR = 2.30, 95% CI = 1.71–3.07, $P < 0.001$], family history of mental disorders [OR = 3.06, 95% CI = 1.61–5.79, $P = 0.001$], introverted parents [mother: OR = 1.81, 95% CI = 1.20–2.72, $P = 0.004$; father: OR = 2.33, 95% CI = 1.69–3.20, $P < 0.001$], longer daily TV viewing time [≥ 3 h : OR = 2.84, 95% CI = 1.56–5.18, $P = 0.001$], higher parental education [mother: OR = 1.60, 95% CI = 1.19–2.14, $P = 0.002$; father: OR = 2.02, 95% CI = 1.52–2.69, $P < 0.001$].

However, birth weight, having siblings, parental ages at the time of the pregnancy, history of assisted reproduction, and household income were not associated with ASD.

Multivariate Logistics Regression Analysis of Risk Factors for ASD

The variables with $P < 0.1$ in the univariate analysis were entered a multivariate logistic regression model. These included gender, gestational period, caesarean, the presence of anoxia or asphyxia at birth, mode of feeding, advanced paternal age ($P = 0.08$), maternal psychological status, complications during pregnancy, family history of mental disorders, introverted parents, daily TV viewing, higher parental education. However, because this was a cross-sectional study, we were not able to determine whether all factors in our study appeared before the onset of ASD. So, we constructed 2 models: factors that were present before the occurrence of ASD were entered into model 1, while those factors whose timing could not be identified were entered as confounders and included into model 2. $P < 0.05$ was considered to be statistically significant. To further understand the association between ASD and adverse psychological status during pregnancy (adverse psychological status appeared at dissimilar stages of pregnancy and duration of the status), we conducted model 3, which included the two variables above and all variables in model 2 except "Maternal psychological status". All models were adjusted by continuous age and districts (see details in Table 2). Variance inflation factor (VIF) was used to assess collinearity. All square roots of VIF were below 2.

As depicted in Table 2, male, the presence of anoxia or asphyxia at birth, artificial feeding, adverse maternal psychological status, complications during pregnancy and higher paternal education were associated with ASD (Model 1). The results persisted even after adjusting for family history of mental disorders, parental personality and daily TV viewing time (Model 2). We further explored the association between the time adverse maternal psychological status was present and ASD (Model 3). We found that the presence of adverse maternal psychological status in the first-trimester remained a significant risk factor for ASD after controlling for the duration of adverse maternal psychological status. However, when the timing of adverse maternal psychological status was controlled, the duration was not association with ASD. On the other hand, as shown in Model 2 and 3, introverted parents and daily TV viewing ≥ 3 h may have had influences on ASD, although a causal relationship could not be established in this cross-sectional study.

Discussion

ASD is a serious neurodevelopmental disorder that occurs in the early developmental period with unclear pathogenesis. To date, there is still a lack of optimal treatment. Therefore, it is particularly important to identify its risk factors for effective prevention. This study found that male sex, the presence of anoxia or asphyxia at birth, artificial feeding, adverse maternal psychological status, complications during pregnancy, and higher paternal education were risk factors for ASD even after controlling by family history of mental disorders, parental personality, and excessive daily TV viewing time. The presence of adverse maternal psychological status in the first trimester had an important impact on ASD, which is consistent with previously published studies(Yong et al., 2021; Lord et al., 2018).

Due to the cross-sectional nature of the study design, we were unable to disentangle the direction of the relationship between parental personality and ASD. On the one hand, some previous studies indicated that parents who have children with ASD themselves have ASD symptoms which suggests a potential hereditary basis for ASD (i.e., ASD symptoms may be passed from parents to their offspring.) (Li et al., 2017, Hurley et al., 2007). On the other hand, parents with children who have ASD may suffer more parenting stress than those with typically developing children(Kogan

et al., 2018). However, expressed emotion in families has also been shown to be associated with ASD(Romero-Gonzalez et al., 2018), and the quality of parent-child interactions has a significant influence on the development of children's language and social development(Oono et al., 2013; Wu et al., 2020). Previous studies of ASD have been limited to the role of mothers and it is unclear to what extent paternal symptoms may play a similar role. Our study indicates that paternal personality has a strong influence on the development of children, although the causality of the relationship cannot be identified. Fathers are known to make a specific contribution to the early neurodevelopment of children(van Steijn et al., 2013). The role of fathers in the child's intervention is critical because it reduces the mother's parenting stress and improves the children's socio-communicative skills(Rankin et al., 2019). In China, among care providers, 63.2% are mothers who serve as primary daytime caregivers(All-China Women's Federation, 2011). Fathers are less involved in parenting tasks than mothers, especially in families with a child with ASD(Hu et al., 2017). From the point of view of early intervention, it seems important to appeal to the fathers of children with ASD to participate more actively in the upbringing of their children, as this may have a positive impact on the improvement of their child's ASD symptoms, and on the sustained and healthy development of their families(Rankin et al., 2019).

This study found that the amount of TV exposure was associated with ASD. Specifically, compared to daily TV viewing of less than 1 h, more than 3 h had a negative impact on ASD symptoms. The result remained after controlling for other confounders. However, the association between excessive screen exposure and ASD was complex. On the one hand, excessive screen exposure has a negative effect on language development and social skills, so children exposed to prolonged daily screen time may develop some ASD symptoms, such as social withdrawal(Healy et al., 2019). On the other hand, parents of children with ASD may use screen time to calm their children. Excessive screen exposure may also decrease the quality of parent-child interactions that would otherwise improve ASD symptoms(Heffler et al., 2020).

In this study, 22% of mothers who had children with ASD reported that they had experienced adverse psychological conditions during pregnancy (e.g., anxiety, depression and nervousness), while only about 8% of mothers with typically developing children suffered from these conditions. Although we simply asked mothers if they had psychological symptoms rather than probing for specific mental health diagnoses, our results corroborate the findings of a great deal of the previous work on maternal mental health and ASD(Beversdorf et al., 2005; Zhang et al., 2010; Chen et al., 2020). The mother's psychological status during pregnancy may have a significant impact on the child's endocrine, immune, neurodevelopmental, and behavioural and emotional development(Chan et al., 2018). For example, maternal stress enhances the generation and signal transduction of placental corticotropin-releasing factor, which in turn changes the feedback and development of the fetal hypothalamus-pituitary-adrenal axis(Mastorakos & Ilias, 2003).

We found that ASD has an increased incidence in families with higher level of education but has no association with household income. These results are consistent with some(Durkin et al., 2010, 2017; Thomas et al., 2012) and inconsistent with other previous studies(Rai et al., 2012; Bosch et al., 2021; Yu et al., 2021). It has been suggested that differences in health insurance plans might be one reason for this discrepancy, as this phenomenon has not been observed in countries with equitable and equal access to health care(Rai et al., 2012; Bosch et al., 2021). On the other hand, the prevalence of ASD is associated with increased awareness of the disorders by parents and physicians(Lung et al., 2017). Families with higher socioeconomic status (SES) are more likely to identify their child's abnormal behaviors and to receive an early ASD diagnosis and treatment. Also, about 80% of children with ASD in our sample came from special education schools. Often, parents with high SES are more likely to allow their children to receive education in special schools.

We found no association between the presence of siblings and ASD. This may be partially explained by China's one-child policy starting in the 1970s. About 70% of our sample were from one child families either with or without ASD. So we might not have been able to observe the real association between the number of siblings and ASD in this cohort(McCabe and Barnes, 2012).

Our study had a number of strengths. First, it was population based with a large representative sample instead of A small sample from a clinical setting. Second, final case identification was based on the opinions of at least two experienced experts rather than on the outcome of screening tools alone. Third, we included children in special need schools which may have helped us to include the vast majority of children with ASD in Shanghai. Finally, we took daily TV viewing time into account which was considered to be associated with ASD symptoms such as social withdrawal. Although we cannot identify a causal relationship, it seems meaningful to explore the relationship between daily TV viewing time and ASD symptoms in future studies.

Several limitations of our studies are worth noting. First, formal diagnostic tools for ASD were not used in our study due to limited resources. Unlike other countries that have established and well-designed screening and monitoring networks, we had to rely on judgments of at least two

experienced developmental and behavioral pediatricians independently to overcome this limitation. If disagreement occurred between the two pediatricians, a third experienced pediatrician was involved and all pediatricians discussed the case until consensus was reached. However, Wiggins et al., (2015) found that the use of Ohio State University Autism Rating Scale by clinicians resulted in acceptable diagnostic accuracy of ASD when compared to more in-depth evaluations. It is gratifying to see that there have some early ASD screening programs have been integrated into level three child healthcare networks in China(Li et al., 2018). Second, the cut-off score in the SCQ of 15 used in this study was considered too high to screen for ASD by Wiggins et al., (2007). Thus, some children with ASD who were in mainstream schools may have been missed. Third, the data mostly relied on parental report which may have introduced potential reporting biases and we cannot identify whether some factors were present before the diagnosis of ASD was made.

Conclusions

We found that male gender, the presence of anoxia or asphyxia at birth, artificial feeding, adverse maternal psychological status, complications during pregnancy and higher paternal education were associated with ASD even after controlling by family history of mental disorders, parental personality and daily TV viewing time were strong associated with ASD prevalence.

Author Contributions Xingming Jin, Hong Huang, Yiwen Zhang and Zhijuan Jin designed the study; You Yang, Hong Huang, Zhijuan Jin and Xingming Jin contributed to the conduct of the study; Yuanyuan Lin drafted the manuscript and performed statistical analyses; Yuanyuan Lin, Guanghai Wang, You Yang, Yiwen Zhang and Zhijuan Jin contributed to interpretation of the results and critically reviewed the manuscript; Zhijuan Jin had primary responsibility for final content. All authors have read and approved the final manuscript.

Funding The research leading to these results received funding from Shanghai Municipal Science and Technology Commission (Grant No. 21Y11905500) and Multi-disciplinary Project Cultivation Fund of Shanghai Jiao Tong University (Grant No. YG2021QN111).

Declarations

Conflicts of Interest/Competing Interests The authors have no relevant financial or non-financial interests to disclose.

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