

Neurodevelopment and Risk Factors in infants before, during and after COVID-19 Pandemic: A Cross-Sectional Study in Eastern China

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Abstract

Background: Emerging studies suggests that exposure to the COVID-19 pandemic may heighten risks of neurodevelopmental disorders in infants, however, population-based studies investigating these associations in Chinese contexts remain scarce, particularly including the post-pandemic phase.

Objective: To characterize dynamic changes in neurodevelopment among infants in eastern China during distinct phases of the COVID-19 pandemic, and identify critical risk factors associated with infant neurodevelopmental delays.

Methods: This cross-sectional study analyzed 17,621 Peabody Developmental Motor Scales-II (PDMS-II) assessments and 7,877 Bayley Scales of Infant Development-Chinese Cities Revised (BSID-CR) from infants who visited a tertiary maternal and children hospital for routine neurodevelopment assessment from January 2019 to July 2023. Multivariate logistic regression models were used to evaluate associations between COVID-19 pandemic phases, seasonal variations, and perinatal variables (e.g., delivery mode, birth weight, gender) with neurodevelopmental outcomes.

Results: Infants assessed at Stage II of the COVID-19 pandemic had a higher risk of neurodevelopmental delay compared to infants assessed at Stage I (total motor quotient: Odds Ratio (OR) =2.84, 95% confidential interval (CI): 2.17-3.72; fine motor quotient: OR=2.71, 95% CI: 1.99-3.68) and Stage III (total motor quotient: OR=2.52, 95% CI: 1.79-3.55; gross motor quotient: OR=1.65, 95% CI: 1.21-2.25; fine motor quotient: OR=3.40, 95% CI: 2.36-4.92). Infants assessed at stage III had the highest risk of mental development delay (OR=2.54, 95% CI: 1.91-3.36). In addition, cesarean section, male gender and low birth weight were independent risk factors of neurodevelopmental delay (P values < .05).

Conclusions: The COVID-19 pandemic exacerbated neurodevelopmental vulnerabilities in infants, persisting into the post-pandemic period. Public health strategies should prioritize developmental monitoring for high-risk subgroups (boys, cesarean-delivered, low birth weight infants) and mitigate long-term effects through early interventions.

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Original Paper

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Abstract

Background: Emerging studies suggests that exposure to the COVID-19 pandemic may heighten risks of neurodevelopmental disorders in infants, however, population-based studies investigating these associations in Chinese contexts remain scarce, particularly including the post-pandemic phase.

Objective: To characterize dynamic changes in neurodevelopment among infants in eastern China during distinct phases of the COVID-19 pandemic, and identify critical risk factors associated with infant neurodevelopmental delays.

Methods: This cross-sectional study analyzed 17,621 Peabody Developmental Motor Scales-II (PDMS-II) assessments and 7,877 Bayley Scales of Infant Development-Chinese Cities Revised (BSID-CR) from infants who visited a tertiary maternal and children hospital for routine neurodevelopment assessment from January 2019 to July 2023. Multivariate logistic regression models were used to evaluate associations between COVID-19 pandemic phases, seasonal variations, and perinatal variables (e.g., delivery mode, birth weight, gender) with neurodevelopmental outcomes.

Results: Infants assessed at Stage II of the COVID-19 pandemic had a higher risk of neurodevelopmental delay compared to infants assessed at Stage I (total motor quotient: Odds Ratio (OR) =2.84, 95% confidential interval (CI): 2.17-3.72; fine motor quotient: OR=2.71, 95% CI: 1.99-3.68) and Stage III (total motor quotient: OR=2.52, 95% CI: 1.79-3.55; gross motor quotient: OR=1.65, 95% CI: 1.21-2.25; fine motor quotient: OR=3.40, 95% CI: 2.36-4.92). Infants assessed at stage III had the highest risk of mental development delay (OR=2.54, 95% CI: 1.91-3.36). In addition, cesarean section, male gender and low birth weight were independent risk factors of neurodevelopmental delay (P values < .05).

Conclusions: The COVID-19 pandemic exacerbated neurodevelopmental vulnerabilities in infants, persisting into the post-pandemic period. Public health strategies should prioritize developmental monitoring for high-risk subgroups (boys, cesarean-delivered, low birth weight infants) and mitigate long-term effects through early interventions.

Keywords: Neurodevelopment; infants; risk factor; COVID-19; cross-sectional study

Introduction

The early childhood period represents a critical window of heightened neuroplasticity. However, globally, 8-15% of children under 5 years old experience neurodevelopmental delays, which has been increasing annually [1,2]. In United States, the prevalence rate of neurodevelopmental delay increased from 16.2% to 17.8% between 2009-2017[3]. While in rural China, around 30% infants experienced motor delays and approximately half of children aged 0-3 years exhibited cognitive, language, and social-emotional delays [4]. Early neurodevelopmental delay constitutes a major global public health challenge, with profound lifelong consequences, such as the increased risks of academic underperformance and cognitive impairment during adolescence. Longitudinal studies demonstrate that 38% of affected children exhibit reduced labor productivity in adulthood, contributing to 1.2-2.6% annual GDP loss in low/middle-income countries [5]. Alarming, 34.7% of children under five in developing regions fail to attain developmental potential due to intersecting poverty and neurodevelopmental impairments [5].

Early neurodevelopmental screening is a crucial public health intervention, providing children with timely access to support services [6]. Previous research consistently demonstrates that early intervention, particularly before the age of three, can significantly improve outcomes for children with developmental disorders [7,8]. Neurodevelopment is influenced by a complex interplay of genetic, environmental, and social factors [9]. While some factors, including perinatal factors, are amenable to intervention [10-12]. In addition, emerging evidence from high-income countries suggests that the COVID-19 pandemic has had a significant macro-social impact on early childhood development [13,14]. However, large-scale, population-based data from developing countries are needed to fully understand the pandemic's effects on children's neurodevelopment.

Since 2018, the city of Yiwu, located in Zhejiang Province, China, has rolled out a comprehensive, publicly - funded neurodevelopmental screening program targeting all children aged 0 - 3 years. This initiative is remarkable because it provides free screening services to around three thousand children each year. Such a large - scale and long - running program presents a distinctive opportunity for conducting real - world research with extensive data. Therefore, we conducted this study using the screening data as mentioned above, and aimed to evaluate the trends and characteristics of infant neurodevelopment after the implementation of such screening program. Moreover, we aimed to identify the key associated factors for infants' neurodevelopment and assess the influence of the COVID - 19 pandemic. Findings from the present study will contribute substantial evidence, which can be used to inform the formulation of public health policies and the design of interventions. These policies and interventions are crucial for promoting optimal child development in China.

Methods

Study population

This cross-sectional study retrospectively analyzed infants who underwent routine neurodevelopmental assessments at Yiwu Maternity and Children's Hospital (a tertiary Grade A hospital) between January 2019 and July 2023. Yiwu City, a metropolitan hub in central Zhejiang Province with 1.86 million residents, served as the study setting, representing urban populations in high-income eastern area of China. Data were extracted from two electronic health systems: (1) Neurodevelopmental Assessment System: providing evaluation scores, assessment dates, and living address; (2) Child Healthcare System: containing sociodemographic (e.g., parental age, education) and perinatal variables (delivery mode, birthweight, gestational age at birth, date of birth, and infant's sex).

Ethical Statement

This study was conducted in accordance with the Declaration of Helsinki[15], and was approved by the ethics committee of Yiwu Maternity and Children Hospital (approval number: 2024-Research-07). Because it utilized a secondary analysis of pre - existing anonymized data, which carried no privacy threats to individuals, the informed consent was waived. Given that the study did not include direct engagement with participants, no monetary compensation was offered.

Measurements of general and clinical characteristics

We extracted children's demographic data (e.g., infant's sex, date of birth, residence) and neurodevelopmental assessment data from the Neurodevelopmental Assessment System and linked it to the Child Healthcare System via a unique ID to obtain parental general characteristics (e.g., age, educational level, parity) and child birth characteristics (e.g., gestational age at birth, birth weight, delivery mode, date of birth).

Parental age when the child was born was determined by subtracting the parents' birthdays from the child's birthday. Given the limited sample size for parity exceeding four times, we grouped these cases as "four times and above." Preterm birth was defined as a gestational age at delivery of less than 37 weeks. Birthweight was categorized into three groups: Low birth weight (LBW, < 2500g), Normal birth weight (NBW, 2500-3999 g), and Macrosomia ($\geq$ 4000g). Seasons were divided into spring (March, April, and May), summer (June, July, and August), autumn (September, October, and November), and winter (December, January, and February). Based on the living address, residence of participants was categorized into urban and town/rural areas.

We categorized the timeline into three stages of COVID-19 pandemic in Zhejiang Province, China as below: Stage I (Pre-pandemic: 02 January, 2019 to 22 January, 2020), Stage II (Pandemic: 23 January, 2020 to 18 December, 2022), and Stage III (Post-pandemic: 19 December 2022 to 31 July 2023).

Assessment of neurodevelopment

In 2018, Yiwu City was one the first municipalities in Zhejiang Province to implement a regional early childhood development screening program for infants aged 0-3 years, incorporating standardized developmental assessments into routine pediatric care at the Yiwu Maternity and Children's Hospital. Neurodevelopmental evaluations were routinely administered to infants starting from January 2019. Two validated instruments were administered: Peabody Developmental Motor Scales-II (PDMS-II) and Bayley Scales of Infant Development-Chinese Cities Revised (BSID-CR). PDMS-II was employed to assess the gross motor quotient (GMQ) and fine motor quotient (FMQ) for infants aged two to six months. The total motor quotient (TMQ) is calculated as $(GMQ + FMQ)/2$. BSID-CR was applied to assess development in infants aged eight to 12 months, and it encompasses two subscales- Mental Development Index (MDI) and Psychomotor Development Index (PDI) to measure cognitive/language abilities and gross/fine motor skills, respectively. All assessments followed standardized protocols: (1) being conducted in distraction-free rooms after 10-minute infant acclimation; (2) Performed by pediatric professionals certified in developmental assessment tools (inter-rater reliability $\kappa > 0.85$); (3) Double-checked data entry to minimize recording errors.

Developmental outcomes were classified using validated cut-off criteria aligned with Chinese norms for early childhood assessment, with scores below 90 on any indicator defined as neurodevelopmental delay [16]. For the PDMS-II, scores of $TMQ < 90$ were classified as total motor delay, encompassing both gross motor delay ($GMQ < 90$) and fine motor delay ($FMQ < 90$). For the BSID-CR, scores of $MDI < 90$ indicated below-average cognitive and language development, defined as mental development delay, and scores of $PDI < 90$ signified motor skill deficits, particularly in coordination and object manipulation, defined as psychomotor development delay.

Composite neurodevelopmental delay was defined as having either MDI or PDI below 90.

Statistical Analysis

Firstly, we conducted the descriptive analysis. Continuous variables were assessed for normality using Shapiro-Wilk tests. Normally distributed data were expressed as mean $\pm$ standard deviation, while non-normally distributed data were summarized as median with interquartile range (IQR). Categorical variables were described using numbers and percentages. Secondly, we assessed the difference in the general characteristics between groups with and without neurodevelopmental delay. Two-sample independent t-tests was applied for normally distributed data, while Mann-Whitney U tests for non-normally distributed data. Chi-square tests was used for categorical variables, or Fisher's exact tests when expected cell counts < 5 . For multivariable analyses, variables showing significance indicated by P value $< .1$ in univariate analyses were entered into logistic regression models. Lastly, we conducted multivariable logistic regression models to examine potential risk factors associated with neurodevelopmental delay (defined as scores < 90 on BSID-CR [MDI/PDI] or PDMS-II [TMQ]). All statistical analyses were carried out using R software (version 4.2.3). The statistical significance was set at P value $< .05$ (two-tailed).

Results

In this study, we included a total of 17,621 PDMS-II assessments and 7,877 BSID-CR assessments. Table 1 presented the parental and children's general characteristics. For infants assessed with the PDMS-II, 10,771 out of 17,621 (61.1%) were firstborn, 9,583 out of 17,621 (54.4%) were boys, 9,329 out of 17,621 (52.9%) were delivered vaginally, and 11,294 out of 17,621 (64.1%) were during COVID-19 pandemic stage II. Among infants assessed with the BSID-CR, 5,337 out of 7,877 (67.8%) were firstborn, 4,326 out of 7,877 (54.9%) were boys, 4,231 out of 7,877 (53.7%) were delivered vaginally, and 5,074 out of 7,877 (64.4%) were during COVID-19 pandemic stage II.

Table 1. The general characteristics of the study population^a

Variable	PDMS-II ^b (N=17,621)	BSID-CR ^c (N=7,877)
Parental characteristics		
Maternal age, year	30.27 $\pm$ 4.48	30.06 $\pm$ 4.47
Paternal age, year	31.92 $\pm$ 4.98	31.71 $\pm$ 4.95
Parity		
1	10771 (61.1)	5337 (67.8)
2	6252 (35.5)	2303 (29.2)
3	552 (3.1)	220 (2.8)
≥ 4	46 (0.3)	17 (0.2)
Maternal education		
Junior high school and below	964 (5.5)	393 (5.0)
Senior high school	6333 (35.9)	3181 (40.4)
College and above	9854 (55.9)	4102 (52.1)
Unknown	470 (2.7)	201 (2.6)
Paternal education		
Junior high school and below	945 (5.4)	395 (5.0)
Senior high school	6920 (39.3)	3496 (44.4)

College and above	9249 (52.5)	3764 (47.8)
Unknown	507 (2.9)	222 (2.8)
Infants' characteristics		
Age at check, day	109.99 ± 20.51	271.04 ± 29.82
Birthweight, g	3290.42 ± 479.57	3279.58 ± 488.58
Gestational age, week	38.58 ± 1.54	38.57 ± 1.64
Delivery mode		
Vaginal delivery	9329 (52.9)	4231 (53.7)
Cesarean section	8081 (45.9)	3541 (45.0)
unknown	211 (1.2)	105 (1.3)
Children's sex		
Girl	8038 (45.6)	3551 (45.1)
Boy	9583 (54.4)	4326 (54.9)
Preterm birth		
No	16323 (92.7)	7226 (91.8)
Yes	1287 (7.3)	648 (8.2)
Birthweight		
Low birth weight	848 (4.8)	432 (5.5)
Normal birth weight	15607 (89.2)	6969 (88.9)
Macrosomia	1032 (5.9)	439 (5.6)
Birth season		
Spring	3928 (22.3)	1803 (22.9)
Summer	4136 (23.5)	2060 (26.2)
Autumn	4904 (27.8)	2262 (28.7)
Winter	4653 (26.4)	1752 (22.2)
COVID-19 pandemic stages		
Stage I	3894 (22.1)	1094 (13.9)
Stage II	11294 (64.1)	5074 (64.4)
Stage III	2433 (13.8)	1709 (21.7)
Residence		
Town	6210 (35.2)	2649 (33.6)
City	11411 (64.8)	5228 (66.4)

^aValues presented in this table are means, standard deviations, numbers and percentages.

^bPDMS-II: Peabody Developmental Motor Scales-II.

^cPBSID-CR: Bayley scales of infant and toddler development revised in Chinese cities.

Supplementary Table S1 shows the comparison of general and clinical characteristics between infants with and without neurodevelopmental delay assessed by PDMS-II. There are statistically significant differences observed in maternal age, paternal age, maternal education, assessment age, delivery mode, preterm status, birth season, COVID-19 pandemic stages, and residence between infants with without neurodevelopmental delay assessed by PDMS-II. Similarly, significant differences were found in maternal age, paternal age, assessment age, birthweight, gestational age, delivery mode, gender, preterm status, birth season, COVID-19 pandemic stages, and residence between infants with and without neurodevelopmental delay assessed by BSID-CR (See Supplementary Table S2) .

Infant neurodevelopment trend from 2019 to 2023

As illustrated in Figure 1 and Figure 2, the neurodevelopmental levels of infants in Yiwu, assessed by BSID-CR and PDMS-II, exhibited fluctuations from January 2019 to July 2023. Specifically, the TMQ, GMQ, and FMQ, evaluated by PDMS-II, demonstrated a downward trend from October 2019 to October 2020. Figure 1 shows that since January 2021, there has been a cyclical fluctuation with an approximate one-year cycle, wherein the TMQ showed lesser variability. Figure 2 shows that both boys and girls followed similar patterns. However, in terms of mental and psychomotor development indices, as measured by BSID-CR, boys performed worse than girls. Figure 3 showed the prevalence of neurodevelopment delay at different stages of the COVID-19 pandemic. Across all evaluation indices (TMQ, GMQ, FMQ, MDI, PDI), Stage I showed the lowest prevalence of neurodevelopmental delay.

The associated factors of infant neurodevelopment delay

Table 2 and Table 3 presented the results of logistic regression analyses in terms of associated factors of infant neurodevelopmental delay assessed by PDMS-II and BSID-CR, respectively. Infants assessed at Stage II had a higher risk of neurodevelopmental delay compared to infants assessed at Stage I, even after adjusting for other variables (TMQ: OR=2.84, 95% CI: 2.17-3.72; FMQ: OR=2.71, 95% CI: 1.99-3.68) and Stage III (TMQ: OR=2.52, 95% CI: 1.79-3.55; GMQ: OR=1.65, 95% CI: 1.21-2.25; FMQ: OR=3.40, 95% CI: 2.36-4.92). Infants assessed at stage III had the highest risk of mental development delay (OR=2.54, 95% CI: 1.91-3.36). In addition, the results indicated that cesarean section, infant's sex as male, preterm birth, LBW and residing in town/rural areas were significantly associated with neurodevelopmental delay (P values $< .05$).

Table 2. Association between the influence factors and neurodevelopmental delay assessed PDMS-II^a.

Variable	TMQ ^b <90		GMQ ^c <90		FMQ ^d <90	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
COVID-19 pandemic stages						
Stage I	ref.	-	ref.	-	ref.	-
Stage II	2.84 (2.17-3.72)	<.001	1.11 (0.86-1.43)	0.43	2.71 (1.99-3.68)	<.001
Stage III	2.52 (1.79-3.55)	<.001	1.65 (1.21-2.25)	0.002	3.40 (2.36-4.92)	<.001
Maternal age, year	1.00 (0.97-1.03)	0.95	1.01 (0.97-1.04)	0.78	1.03 (0.99-1.06)	0.18
Paternal age, year	1.01 (0.98-1.04)	0.38	1.00 (0.97-1.03)	0.95	0.99 (0.96-1.02)	0.58
Parity						
1	ref.	-	ref.	-	ref.	-
2	1.13 (0.93-1.37)	0.21	0.95 (0.76-1.18)	0.64	1.07 (0.86-1.32)	0.55
3	1.51 (0.99-2.30)	0.06	1.22 (0.75-1.99)	0.43	1.39 (0.87-2.23)	0.17
≥4	1.38 (0.32-5.90)	0.66	/	/	0.75 (0.10-5.68)	0.78
Maternal education						

Junior school and below	high	ref.	-	ref.	-	ref.	-
Senior school	high	0.82 (0.58-1.15)	0.24	0.69 (0.47-1.01)	0.06	0.81 (0.55-1.20)	0.29
College above	and	0.77 (0.55-1.08)	0.13	0.73 (0.50-1.05)	0.09	0.83 (0.57-1.21)	0.33
Unknown		0.94 (0.46-1.90)	0.86	1.12 (0.56-2.25)	0.74	1.29 (0.63-2.63)	0.49
Check age, day		1.03 (1.03-1.03)	<.001	1.01 (1.01-1.02)	<.001	1.03 (1.03-1.04)	<.001
Delivery mode							
Vaginal delivery		ref.	-	ref.	-	ref.	-
Cesarean section		1.33 (1.12-1.58)	0.001	1.33 (1.10-1.61)	0.003	1.42 (1.17-1.73)	<.001
Unknown		1.57 (0.67-3.70)	0.30	1.10 (0.40-3.05)	0.85	2.04 (0.86-4.86)	0.11
Children's sex							
Girl		ref.	-	ref.	-	ref.	-
Boy		1.11 (0.94-1.32)	0.22	1.24 (1.02-1.49)	0.03	1.23 (1.02-1.49)	0.03
Preterm birth							
No		ref.	-	ref.	-	ref.	-
Yes		0.10 (0.05-0.22)	<.001	0.34 (0.20-0.56)	<.001	0.14 (0.07-0.27)	<.001
Birthweight							
Low birth weight	birth	1.64 (0.96-2.80)	0.07	2.79 (1.80-4.31)	<.001	2.44 (1.45-4.11)	<.001
Normal birth weight	birth	ref.	-	ref.	-	ref.	-
Macrosomia		0.54 (0.35-0.83)	0.005	0.62 (0.39-0.99)	0.04	0.50 (0.30-0.82)	0.006
Birth season							
Spring		ref.	-	ref.	-	ref.	-
Summer		0.87 (0.69-1.10)	0.24	1.24 (0.91-1.70)	0.17	1.11 (0.84-1.47)	0.46
Autumn		0.77 (0.61-0.97)	0.02	2.30 (1.75-3.03)	<.001	1.15 (0.88-1.49)	0.30
Winter		0.47 (0.36-0.61)	<.001	1.04 (0.76-1.43)	0.79	0.54 (0.40-0.74)	<.001
Address							
City		ref.	-	ref.	-	ref.	-
Town		1.29 (1.09-1.53)	0.003	1.09 (0.90-1.32)	0.37	1.47 (1.21-1.78)	<.001

^aPDMS-II: Peabody Developmental Motor Scales-II.

^bTMQ: Total motor score.

^cGMQ: Gross motor score.

^dFMQ: Fine motor score.

Table 3. Association between the influence factors and neurodevelopmental delay assessed by BSID-CR^a

Variable		Total score<90		MDI ^b <90		PDI ^c <90	
		OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
COVID-19 pandemic stages							
Stage I		ref.	-	ref.	-	ref.	-
Stage II		0.99 (0.84-1.17)	0.93	1.45 (1.13-1.87)	0.004	0.90 (0.76-1.06)	0.20
Stage III		1.15 (0.95-1.39)	0.16	2.54 (1.91-3.36)	<.001	1.00 (0.83-1.21)	0.99
Maternal age, year		0.99 (0.97-1.01)	0.34	0.99 (0.97-1.02)	0.67	0.99 (0.97-1.01)	0.56
Paternal age, year		1.01 (0.99-1.03)	0.18	1.02 (0.99-1.04)	0.15	1.01 (0.99-1.03)	0.28
Check age, day		1.03 (1.03-1.03)	<.001	1.03 (1.03-1.03)	<.001	1.03 (1.02-1.03)	<.001
Delivery mode							
Vaginal delivery		ref.	-	ref.	-	ref.	-
Cesarean section		1.20 (1.07-1.34)	0.001	1.12 (0.97-1.30)	0.13	1.23 (1.10-1.37)	<.001
Unknown		1.48 (0.88-2.49)	0.14	1.02 (0.48-2.21)	0.95	1.72 (1.03-2.88)	0.04
Child's sex							
Girl		ref.	-	ref.	-	ref.	-
Boy		1.34 (1.20-1.49)	<.001	1.56 (1.35-1.81)	<.001	1.32 (1.18-1.47)	<.001
Preterm birth							
No		ref.	-	ref.	-	ref.	-
Yes		0.48 (0.37-0.61)	<.001	0.44 (0.31-0.64)	<.001	0.51 (0.39-0.65)	<.001
Birthweight							
Low birth weight		1.36 (1.02-1.82)	0.04	1.37 (0.92-2.04)	0.12	1.39 (1.04-1.86)	0.03
Normal birth weight		ref.	-	ref.	-	ref.	-
Macrosomia		0.94 (0.75-1.19)	0.61	0.79 (0.57-1.10)	0.16	0.98 (0.77-1.23)	0.84
Birth season							
Spring		ref.	-	ref.	-	ref.	-
Summer		1.41 (1.22-1.64)	<.001	1.36 (1.11-1.67)	0.003	1.43 (1.23-1.66)	<.001
Autumn		0.82 (0.71-0.94)	0.00	1.31 (1.06-1.62)	0.01	0.72 (0.62-0.83)	<.001

	0.95)	7	1.62)		0.84)	1
Winter	0.48 (0.41-0.57)	<.001	1.05 (0.83-1.33)	0.69	0.41 (0.35-0.49)	<.001
Residence						
City	ref.	-	ref.	-	ref.	-
Town	1.05 (0.94-1.17)	0.42	1.00 (0.86-1.16)	0.98	1.02 (0.91-1.14)	0.70

^aBSID-CR: Bayley scales of infant and toddler development revised in Chinese cities.

^bMDI: Mental development index.

^cPDI: Psychomotor development index.

Discussion

Principal Findings

This study used a large-scale, retrospective dataset of publicly-funded neurodevelopmental screening program among infants since 2019 in Yiwu, China to evaluate the early childhood neurodevelopment after the implementation of this program. Our study revealed that the COVID-19 pandemic may have adverse impacts on infant neurodevelopment, persisting into the post-pandemic period. The scores obtained via BSID-CR and PDMS-II assessments among infants consistently demonstrated seasonal variations. Furthermore, infant's age, sex, birthweight, preterm birth and mode of delivery were significantly associated with the infants' neurodevelopment. To the best of our knowledge, this study bridges a crucial evidence gap on factors influencing infant neurodevelopment by providing population-level, neurodevelopmental data spanning pre-pandemic, pandemic, and post-pandemic periods.

This study found that the level of infant neurodevelopment fluctuated, especially in 2020, which might be related to the COVID-19 pandemic. Our study revealed that compared to infants in the Stage I of COVID-19 pandemic, those in Stage II demonstrated significantly higher risks of motor and mental delay. One study from Guangzhou, China in 2021 also demonstrated that the COVID-19 pandemic adversely affected infant neurodevelopment [17]. Another study conducted in New York also indicated that infants exposed and unexposed to the SARS-CoV-2 during the COVID-19 pandemic had considerably lower scores in gross motor, fine motor, and personal-social subdomains compared to historical cohorts born prior to the pandemic [18]. This adverse effect could be attributed to various factors. Firstly, the COVID-19 pandemic and related restrictions likely limited infants' opportunities for environmental exploration and peer engagement, which could adversely impact their neurodevelopmental outcomes [17]. Secondly, prolonged mask-wearing may reduce infants' exposure to facial expression recognition and other crucial social stimuli during critical developmental periods [19]. Notably, infants assessed at Stage III continued to demonstrate significantly lower neurodevelopmental level compared to those in Stage I. At present, there is a lack of relevant research to confirm. In our study, these infants at Stage III were born to mothers who were not only experienced pandemic-related stress during pregnancy but also had relatively high chance to be infected by the SARS-CoV-2. Related stress factors during pregnancy should be recognized as a potential contributing mechanism to these developmental delays [20,21]. Moreover, the infection itself might have played a role. A meta-analysis published in 2022, encompassing eight studies with 21,419 infants, demonstrated that maternal SARS-CoV-2 infection was associated with an increased risk of fine motor impairment in offspring (OR=3.46, 95% CI: 1.43-8.38) [22].

Even after adjusting for the effects of different stages of the COVID-19 pandemic on neurodevelopment, we still found several factors related to neurodevelopmental delay. In our study, we observed that boys exhibited poorer performance compared to girls, not only on the BSID-

CR but also on the PDMS-II. A cohort study conducted in Japan supported this finding, revealing a higher risk of developmental delay among boys under the age of two years (OR=2.5, 95% CI: 1.5–4.2) than girls [23]. Additionally, a 2024 review highlighted that boys are more prone to malnutrition and stunting, factors that could potentially impact neurodevelopment [24]. We hypothesized that these disparities may be linked to sex-based differences in utero exposure sensitivity. Elisa et al. also reported that exposure to inflammation in utero or early life can influence fetal neurodevelopment, with boys being more vulnerable than girls due to sex hormone differences [25]. Furthermore, early language development exhibits sexual dimorphism due to genetic and hormonal factors, with girls typically developing faster than boys, leading to earlier social awareness and superior neurodevelopment levels in girls [26-28].

Our study indicated that infants with LBW exhibited poorer neurodevelopmental outcomes. This observation aligned with that reported by Shu-I et al., demonstrating infants with marginally LBW (ranging from 2000 to 2499 g) with a higher risk of neurodevelopmental delays [29]. This may result from impaired brain connectivity and neuronal migration in LBW infants [30], where high-quality family environmental stimulation can partially mitigate the adverse neurodevelopmental impacts [31]. Consequently, timely parent-child interaction interventions should be prioritized for LBW infants to improve neurodevelopmental outcomes. Interestingly, our study found that preterm birth appeared to be a protective factor for infant neurodevelopment. This might be a chance finding due to the limited sample size of infants with preterm birth, especially very preterm birth in our study. Additionally, it was possible that the increased attention and care received by premature infants could have contributed to improved neurodevelopment by altering methylation levels [32]. We recommend that future studies replicate our protocol to support or refute our findings.

We also identified cesarean delivery as a risk factor for infant neurodevelopmental delay, consistent with prior epidemiological evidence [33]. The potential harm associated with cesarean delivery may be linked to microbiome disturbances. A blinded randomized controlled trial revealed that cesarean-born infants who received vaginal microbiota transfer showed significantly better neurodevelopment at six months compared to those who received saline [34].

Additionally, our study revealed seasonal variations in infants' neurodevelopment levels. We found that infants born in summer had a higher risk of mental and psychomotor development delay. This might be because most summer-born infants undergo the BSID-CR assessment in winter, when they received less sunlight exposure. Similar to what we found, a comprehensive multi-centers study encompassing Denmark, Finland, Norway, Sweden, and Western Australia has uncovered a seasonal trend in the occurrence of autism spectrum disorder [35]. This trend might be attributed to varying sunlight levels during early childhood [35]. Furthermore, recent research indicates a positive correlation between children's neurodevelopment and 25(OH)D levels [36,37]. This suggests that Vitamin D, closely linked to sunlight exposure, could be a crucial factor for explaining the seasonal disparity in neurodevelopment of infants.

Strengthens and Limitations

Our study possesses several strengths. Firstly, to our knowledge, this study represented one of the few large-scale real-world study evaluating neurodevelopment in infants from Eastern China, providing valuable population-based data. Secondly, we measured a comprehensive set of variables including parental and children's characteristics as potential influencing factors. Thirdly, by encompassing time periods both before, during and after the COVID-19 pandemic, this study enabled us to fully consider the impact of the COVID-19 pandemic on infant neurodevelopment. Nonetheless, there are some limitations worthy of mention. Firstly, as a cross-sectional design, this study could not establish causational relationships. We recommend future longitudinal follow-ups or birth cohort to replicate this study protocol in order to confirm or to refuse our findings. Furthermore, our data, derived from a single city, may not comprehensively reflect the situation in China. It is worth noting that Yiwu serves as a pilot city for various projects, including the National

Rural Early Childhood Development Project and the National Rural Revitalization Strategy-Grassroots Early Childhood Development Project, thereby possessing a certain degree of representativeness of areas with advanced child health care in China.

Conclusions

The COVID-19 pandemic exacerbated neurodevelopmental vulnerabilities in infants, persisting into the post-pandemic period. Public health strategies should prioritize developmental monitoring for high-risk subgroups (boys, cesarean-delivered, low birth weight infants) and mitigate long-term effects through early interventions.

Acknowledgements

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Conflicts of Interest

None declared.

Abbreviations

BSID-CR: Bayley scales of infant and toddler development revised in Chinese cities

FMQ: fine motor quotient

GMQ: gross motor quotient

MDI: mental development index

PDI: psychomotor development index

PDMS-II: Peabody developmental motor scales-II

TMQ: total motor quotient

OR: odds ratio

CI: confidential interval

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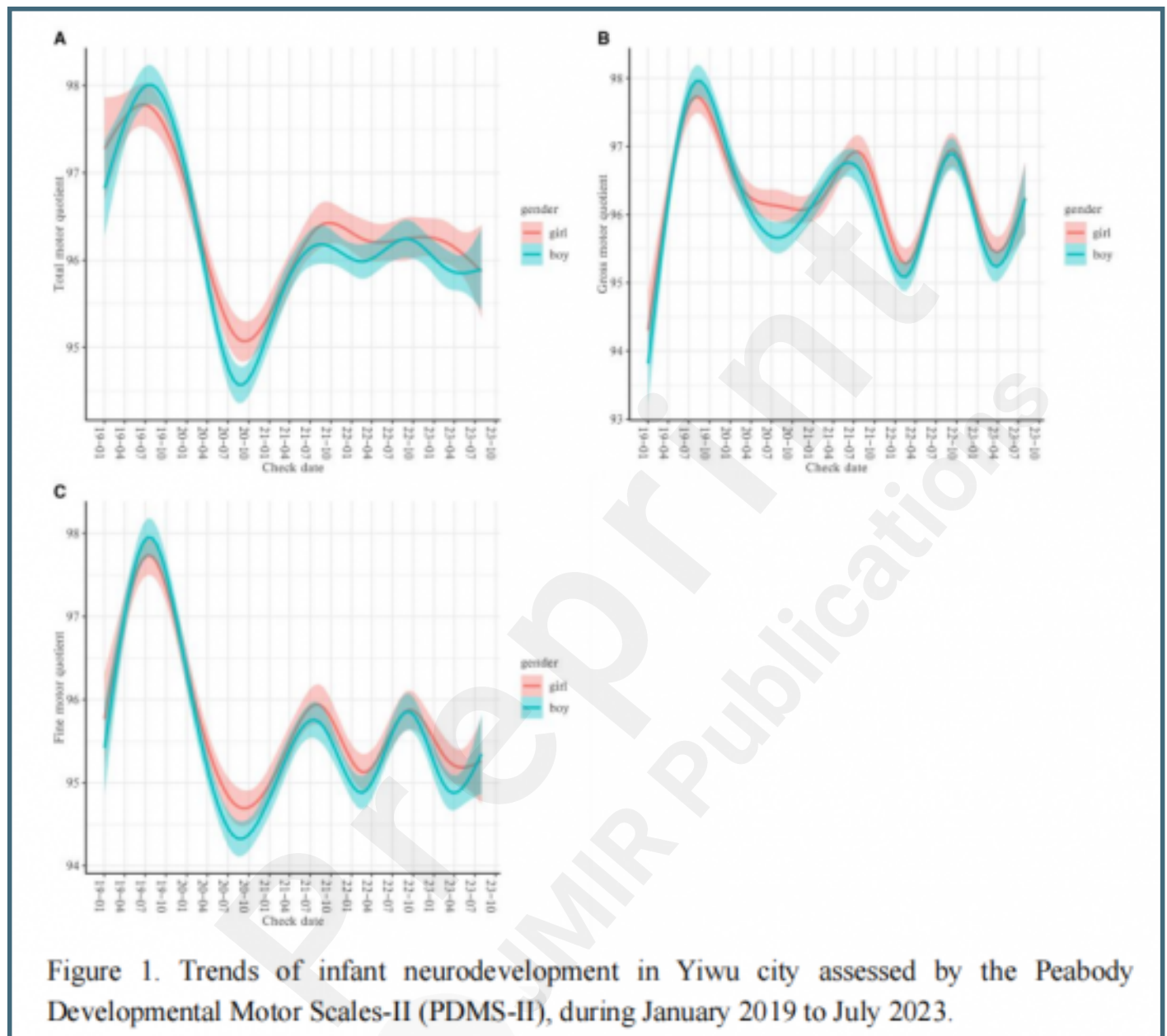
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Supplementary Files

Figures

Trends of infant neurodevelopment in Yiwu city assessed by the Peabody Developmental Motor Scales-II (PDMS-II), during January 2019 to July 2023.



Trends of infant neurodevelopment in Yiwu city assessed by the Bayley scales of infant and toddler development revised in Chinese cities (BSID-CR), during January 2019 to July 2023.

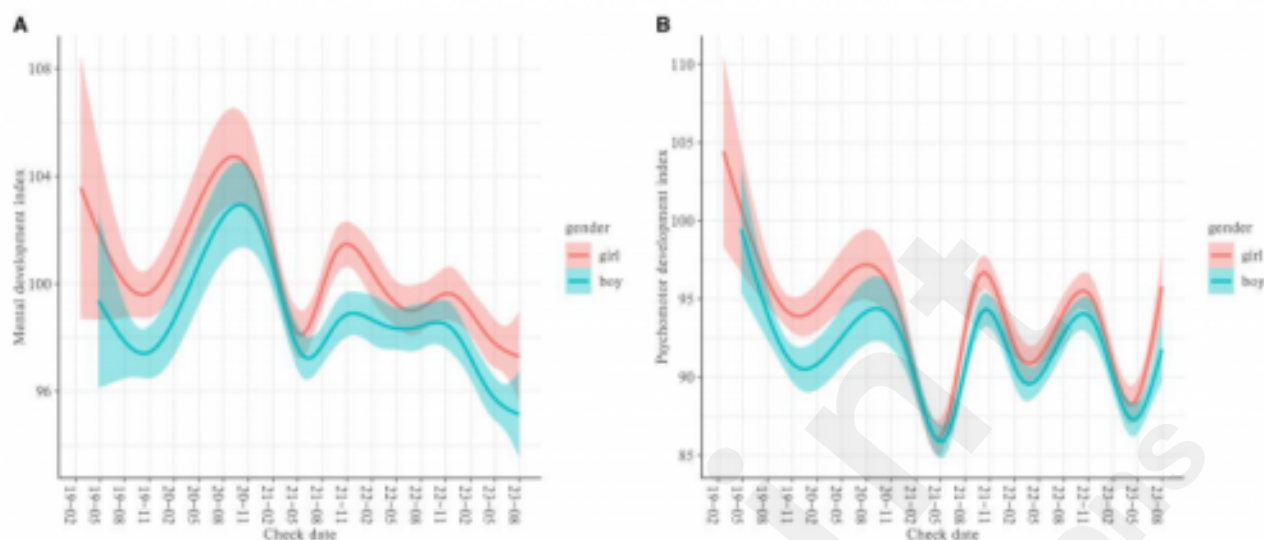


Figure 2. Trends of infant neurodevelopment in Yiwu city assessed by the Bayley scales of infant and toddler development revised in Chinese cities (BSID-CR), during January 2019 to July 2023

The prevalence of neurodevelopment delay of infant in Yiwu detected by PDMS-II (A) and BSID-CR (B), at different stages of the COVID-19 pandemic. BSID-CR, Bayley scales of infant and toddler development revised in Chinese cities; PDMS-II, Peabody Developmental Motor Scales-II; MDI, Mental development index; PDI, psychomotor development index; TMQ, total motor quotient; GMQ, gross motor quotient; FMQ, fine motor quotient.

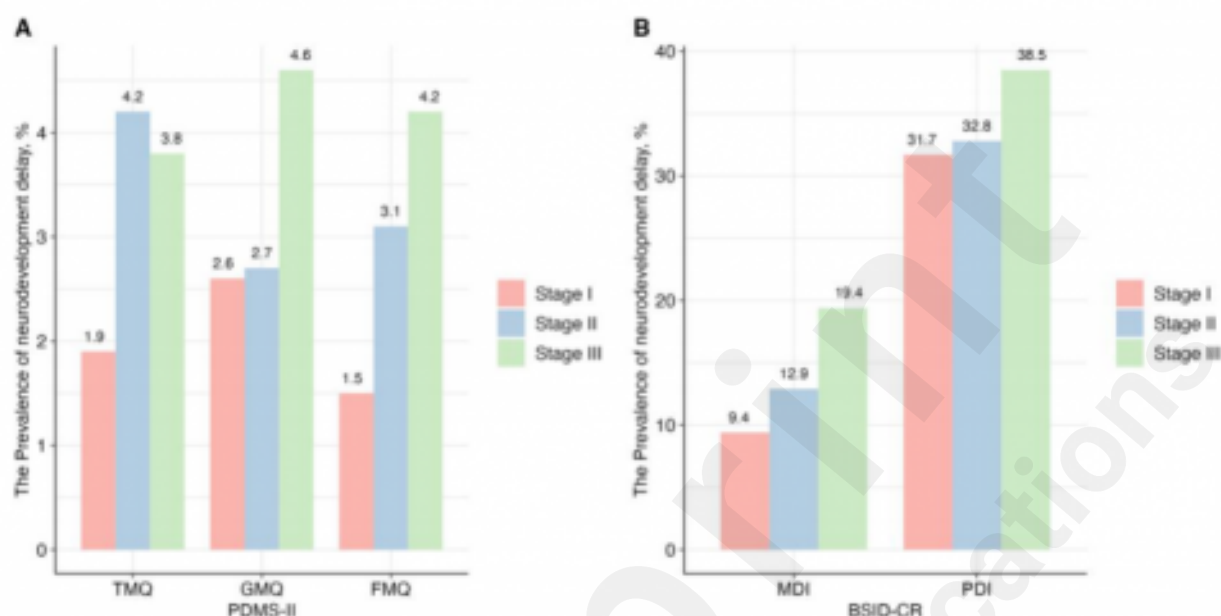


Figure 3. The prevalence of neurodevelopment delay of infant in Yiwu detected by PDMS-II (A) and BSID-CR (B), at different stages of the COVID-19 pandemic. BSID-CR, Bayley scales of infant and toddler development revised in Chinese cities; PDMS-II, Peabody Developmental Motor Scales-II; MDI, Mental development index; PDI, psychomotor development index; TMQ, total motor quotient; GMQ, gross motor quotient; FMQ, fine motor quotient.

Multimedia Appendixes

Two supplementary tables.

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