

Association between Gestational Age, Birth Weight, Parental Age at Childbirth, Mode of Delivery, and Infantile Esotropia

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SIGNIFICANCE: This study investigated the potential perinatal risk factors associated with infantile esotropia in a Chinese population, including advanced parental age at childbirth and mode of delivery. The findings may be significant in developing better intervention strategies for infantile esotropia.

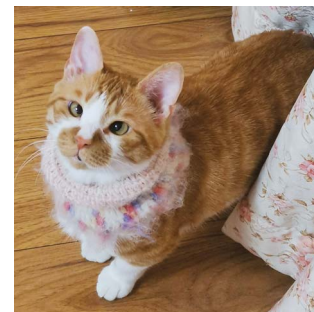
PURPOSE: This study aimed to investigate the associations between gestational age, birth weight, parental age at childbirth, mode of delivery, family history of strabismus, and infantile esotropia in the Chinese population.

METHODS: Ninety-nine patients with infantile esotropia and 117 control subjects were enrolled between March 2018 and March 2021. Detailed questionnaires were administered to parents to collect relevant information. Univariate and multivariate logistic regression models were used to identify possible risk factors of infantile esotropia. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated.

RESULTS: Infantile esotropia was associated with low birth weight (<2500 g; OR, 4.235; 95% CI, 1.460 to 12.287; $P = .008$) and emergency cesarean delivery (OR, 2.230; 95% CI, 1.127 to 4.413; $P = .02$).

CONCLUSIONS: The findings suggest that low birth weight and emergency cesarean deliveries are risk factors for infantile esotropia, highlighting a need for collaborative care between obstetricians, pediatricians, and vision care providers.

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Infantile esotropia is a binocular misalignment that arises within 6 months after birth with an estimated incidence of 0.1 to 1.0%.^{1,2} It is nonaccommodative, constant, moderate to large angle, and with no or mild amblyopia and may include dissociated vertical deviation and nystagmus.^{3,4} Infantile esotropia not only affects one's appearance but is also accompanied by binocular vision abnormalities, such as severe maldevelopment of stereopsis, movement processing, and eye tracking.⁵ The etiology of infantile esotropia is still unknown, but mutations or perturbations that prolong subcortical neuroplasticity may be a potential cause.⁶ Perinatal risk factors associated with infantile esotropia include preterm birth, low birth weight, low Apgar scores, gestational complications, and use of supplemental oxygen as a neonate.^{3,7,8}

China had the second highest number of preterm births worldwide in 2010.⁹ Moreover, according to China's 2017 National Fertility Survey, the average women's age at first childbirth increased from 24.3 years in 2006 to 27.3 years in 2017. In some populous cities (e.g., Shanghai), the average childbearing age in 2020 was 31.74 years. Since the implementation of the universal two-child policy in 2015, live births of parents with an advanced age (≥ 35 years) have increased rapidly, and age-related anomalies are also increasing,¹⁰ affecting the choice of delivery mode.^{11,12} An emergency cesarean delivery is defined as an immediate intervention after attempted vaginal delivery.¹³ However, elective cesarean delivery upon maternal request without medical indications has rapidly increased.¹⁴ Elective

cesarean delivery may increase the risk of certain diseases, such as pulmonary disorders in children, and jeopardize neonatal outcomes.¹⁵ One study found that elective cesarean delivery increased the risk of severe astigmatism in childhood.¹⁶

To further assess risk factors for the development of infantile esotropia, we analyzed the associations between gestational age, birth weight, parental age at childbirth, mode of delivery, family history of strabismus, and infantile esotropia within a Chinese population.

METHODS

Ethical Review

This research was reviewed by an independent ethical review board. It conforms to the principles and applicable guidelines for the protection of human subjects in biomedical research. Ethical approval was obtained from the Ethics Committee of the West China Hospital, Sichuan University. The procedures were performed in accordance with the ethical standards of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Participants were recruited from inpatient wards and the Department of Optometry and Visual Science, West China Hospital, Sichuan. Infantile esotropia was defined as an esotropia of more than 30 prism diopters occurring before 6 months of age. The exclusion criteria were

as follows: (i) other types of strabismus, (ii) high or low accommodative convergence over accommodation (AC/A), (iii) esotropia reduced by more than 15 prism diopters after full-time refractive correction, and (iv) neurodevelopmental disorder. The noninfantile esotropia group included randomly selected age- and sex-matched healthy children without a diagnosis of strabismus.

Participants and Data Collection

In total, 236 children were recruited between March 2018 and March 2021, and 216 children were enrolled after considering the exclusion criteria. All children were screened with the cover-uncover test, and cycloplegic retinoscopy was used to assess refractive error. Children with infantile esotropia received full refractive error correction for at least 1 month. At the follow-up visit, the strabismus magnitude was measured using the simultaneous prism and cover test at near (33 cm) and distance (6 m). The AC/A ratio was determined using the calculated method (with normal AC/A ratio defined as 2 to 6).

The parents of the patients with definitive diagnosis of infantile esotropia who provided informed consent to participate in the study completed questionnaires to provide relevant information on the age at disease onset, parental age, family history of strabismus, mode of delivery, and birth information including parental age at childbirth, gestational age, and the infant's birth weight. Birth information was collected from the birth certificate. The examination findings and questionnaire records were reviewed, and eligible participants were included. Gestational age was classified into very to moderate preterm (<34 weeks), late preterm (34 to 36 weeks), full-term (37 to 41 weeks), and late (≥ 42 weeks). Birth weight was classified into very low birth weight (<1500 g), low birth weight (1500 to 2499 g), normal birth weight (2500 to 3999 g), and high birth weight (≥ 4000 g). Cesarean delivery was divided into elective cesarean delivery and emergency cesarean delivery.

Statistical Analysis

Statistical analyses were performed using SPSS software version 25.0 (SPSS Inc., Chicago, IL). Categorical variables were expressed as frequencies (percentages) and analyzed with χ^2 tests, and rank variables were analyzed using the Mann-Whitney *U* test. Univariate logistic regression analysis was performed to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for each exposure factor. Variables with $P < .05$ in the univariate analysis were entered into a backward multivariate logistic regression analysis, and ORs for each variable were calculated when controlling for the other factors. All tests were two-tailed, with $P < .05$ considered as statistically significant.

RESULTS

Demographics and Perinatal Risk Factors

A total of 99 Chinese patients with infantile esotropia and 117 control subjects were included. There was no significant difference in sex and age between the two groups ($P > .05$). The mean magnitude of esotropia, mean gestational age, and mean birth weight in the infantile esotropia group were 61.09 ± 23.73 prism diopters, 38.3 ± 2.8 weeks (range, 28 to 44 weeks), and 3112 ± 616 g (range, 1600 to 4750 g), respectively. The mean maternal and paternal ages at childbirth were 28.7 ± 5.9 and 29.5 ± 3.7 years, respectively. In the noninfantile esotropia control subjects, the mean gestational age was 38.4 ± 1.7 weeks (range, 30 to 41 weeks), and the mean birth weight was 3228 ± 520 g (range, 1160 to 4700 g).

The mean maternal and paternal ages at birth were 29.5 ± 3.7 and 31.4 ± 4.2 years, respectively. The detailed stratified data are shown in Table 1, and the distribution of individual values is shown in Fig. 1. Significant differences were found in birth weight, gestational age, and mode of delivery between the infantile esotropia and noninfantile esotropia groups ($P < .05$). No significant differences were found in parental age at birth and family history of strabismus between the two groups.

Univariate Logistic Regression Analysis of Related Factors for Infantile Esotropia

Because of their small frequencies, the stratification of very low birth weight (<1500 g) was combined with low birth weight (1500 to 2499 g) in the univariate logistic regression analysis. Similarly, the stratification of late birth (gestational age ≥ 42 weeks) was combined with full-term birth (≥ 37 weeks). Table 2 presents the univariate analyses of each risk factor for infantile esotropia. Low birth weight (<2500 g; OR, 4.725; $P = .003$) and late preterm birth (34 to 36 weeks; OR, 4.192; $P = .008$) had increased the risk of infantile esotropia compared with normal birth weight (2500 to 3999 g) and full-term birth (≥ 37 weeks), respectively. Emergency cesarean delivery was also a significant risk factor for infantile esotropia (OR, 2.535; $P = .006$). However, the estimated ORs for high birth weight (≥ 4000 g; OR, 1.39; $P = .61$), very to moderate preterm birth (<34 weeks; OR, 2.795; $P = .16$), or elective cesarean delivery (OR, 1.572; $P = .18$) were not statistically significant.

Multivariate Logistic Regression Analysis of Related Factors and Infantile Esotropia

We further used a multivariate logistic regression analysis to investigate the three significant factors (birth weight, gestational age, and mode of delivery) in the univariate logistic regression models. As shown in Table 3, after controlling for other factors, the risk of infantile esotropia was 4.235-fold (OR; 95% CI, 1.460 to 12.287; $P = .008$) higher for low birth weight (<2500 g) than for normal birth weight (2500 to 3999 g). Emergency cesarean delivery was associated with 2.230 (OR; 95% CI, 1.127 to 4.413; $P = .02$) times the risk of infantile esotropia compared with vaginal delivery.

DISCUSSION

To identify the risk factors and susceptible populations for infantile esotropia, we investigated the association between infantile esotropia and gestational age, birth weight, parental age, mode of delivery, and family history of strabismus.

Previous studies that used univariate analysis have reported that preterm birth (<37 weeks) and low birth weight (<2500 g) increased the risk of infantile esotropia.^{3,7} Using finer classification of gestational age and birth weight, our study showed that preterm birth (34 to 36 weeks) and low birth weight (<2500 g) were associated with infantile esotropia. Children born very and moderately preterm were found to have high incidence rate for neuropsychiatric disorders.¹⁷ Because we excluded children with neurodevelopmental disorders from this study, it is likely that we simultaneously excluded individuals with accompanying infantile esotropia, which may explain why we did not observe an association between very to moderate preterm birth (<34 weeks) and infantile esotropia. Neurodevelopmental disorders may result in abnormal innervation of individual extraocular muscles by the central nervous system, which eventually manifests as strabismus.⁶

TABLE 1. Demographics characteristics of children with infantile esotropia and noninfantile esotropia

	Non-IE (n = 117), n (%)	IE (n = 99), n (%)	Statistics	P
Sex				
Female	62 (52.99)	43 (43.43)	1.961*	.16
Male	55 (47.01)	56 (56.57)		
Age (y), median (Q ₁ , Q ₃)	3.0 (2.5, 5.0)	2.9 (1.7, 4.9)	1.334†	.18
Birth weight (g)				
<1500	1 (0.85)	0	-2.349†	.02
1500–2499	4 (3.42)	17 (17.17)		
2500–3999	107 (91.45)	77 (77.78)		
≥4000	5 (4.27)	5 (5.05)		
Gestational age (wk)				
<34	3 (2.56)	6 (6.06)	-2.300†	.02
34–36	5 (4.27)	15 (15.15)		
37–41	109 (93.16)	75 (75.76)		
≥42	0	3 (3.03)		
Maternal age at birth (y)				
<35	105 (89.74)	81 (81.82)	2.816*	.09
≥35	12 (10.26)	18 (18.18)		
Paternal age at birth (y)				
<35	92 (78.63)	71 (71.72)	1.385*	.24
≥35	25 (21.37)	28 (28.28)		
Mode of delivery				
VD	57 (48.72)	32 (32.32)	7.747*	.02
ECD	34 (29.06)	30 (30.30)		
EMCD	26 (22.22)	37 (37.37)		
Family history of strabismus				
Unknown	9 (7.69)	12 (12.12)	5.241*	.07
No	106 (90.60)	80 (80.81)		
Yes	2 (1.71)	7 (7.07)		

* χ^2 Test. †Mann-Whitney *U* test. ECD = elective cesarean delivery; EMCD = emergency cesarean delivery; IE = infantile esotropia; VD = vaginal delivery.

In our multivariate regression model, low birth weight (<2500 g) was associated with a higher risk of developing infantile esotropia than normal birth weight (2500 to 3999 g), but preterm birth (34 to 36 weeks) was not associated with infantile esotropia. These results are consistent with those of a study in a large Danish population-based cohort.⁸ In this cohort study, birth weight <2000 and 2000 to 2499 g increased the risk of infantile esotropia 2.66 and 3.58 times, respectively, compared with normal birth weight. No association was found between gestational age and infantile esotropia.

A previous study found an association between birth by cesarean delivery and infantile esotropia.⁷ After classifying cesarean deliveries as either elective or emergency, our study found that emergency cesarean delivery was a risk factor for infantile esotropia. Emergency cesarean delivery is a composite outcome of abnormalities in pregnancy with one or more serious adverse events in the mother and/or fetus, such as pre-eclampsia, placenta previa, and fetal distress.¹⁸ These adverse events may have deleterious effects

on the development of the fetal central nervous system,¹⁹ which may lead to infantile esotropia. Further research is needed to investigate the association between different adverse events and infantile esotropia.

Some studies found that higher maternal age at childbirth increased the odds of infantile esotropia. However, the upper limit of maternal age included in these studies was 35 years, and paternal age was not explored.^{3,7} The risk of adverse infant outcomes increased with advanced parent age.^{20–22} In a study of school-aged children in Hong Kong, children with mothers who gave birth at an advanced age were generally prone to higher risks of strabismus, although there was no classification of subtypes of strabismus.²³ Our data indicated a higher frequency of advanced maternal age at childbirth (>35 years) in the infantile esotropia group than the noninfantile esotropia group, but it was not statistically significant (*P* = .09), which may be due to the relatively small sample size. The associations with advanced age in pregnancy may reflect the well-known association with adverse pregnancy outcomes including miscarriage, low birth

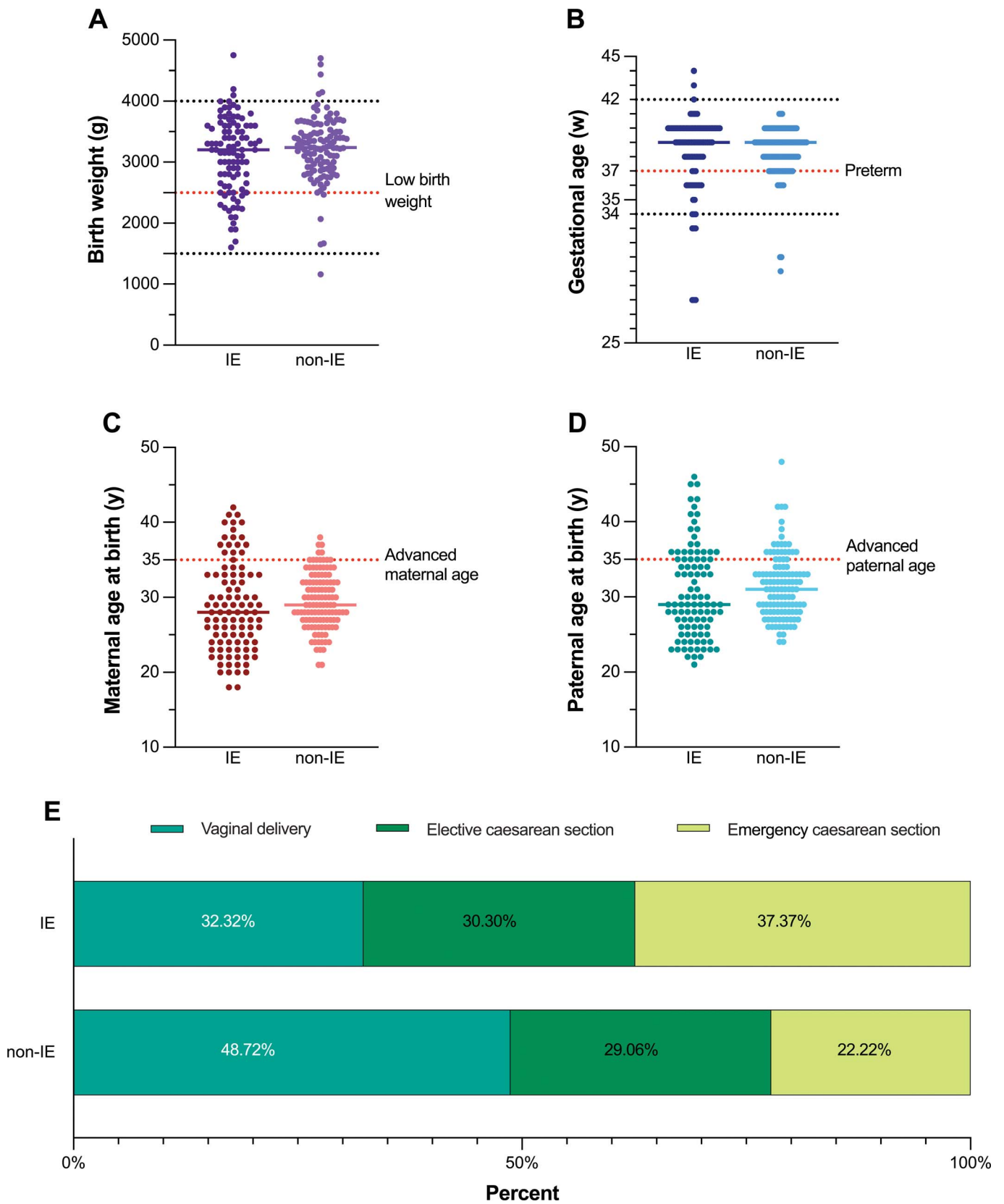


FIGURE 1. Perinatal risk factors of IE (n = 99) and non-IE (n = 117). (A–D) Each dot represents the data of one participant. (E) The shaded areas are expressed as percentages of the different delivery modes. IE = infantile esotropia; w = weeks.

TABLE 2. Univariate logistic regression analysis of the perinatal risk factors

	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>P</i>	<i>OR (95% CI)</i>
Birth weight (g)					
<2500	1.553	0.530	8.576	.003	4.73 (1.7–13.36)
2500–3999					1 (Reference)
≥4000	0.329	0.650	0.256	.61	1.39 (0.39–4.97)
Gestational age (wk)					
<34	1.028	0.722	2.024	.16	2.80 (0.68–11.52)
34–36	1.433	0.537	7.116	.008	4.192 (1.46–12.02)
≥37					1 (Reference)
Mode of delivery					
VD					1 (Reference)
ECD	0.452	0.334	1.833	.18	1.57 (0.82–3.02)
EMCD	0.930	0.338	7.570	.006	2.54 (1.31–4.92)

B = coefficient estimation; *CI* = confidence interval; *ECD* = elective cesarean delivery; *EMCD* = emergency cesarean delivery; *OR* = odds ratio; *SE* = standard error; *VD* = vaginal delivery; *Wald* = Wald test.

weight, preterm delivery, perinatal mortality, placenta previa, postpartum hemorrhage, and congenital malformations.^{24,25} The association between parental age at childbirth and infantile esotropia needs to be studied in a larger sample. Prior studies suggest that family history of strabismus increases the risk of strabismus,²⁶ but there are few studies specific to infantile esotropia.^{3,7} In this study, family history of strabismus was not found to be associated with infantile esotropia. Matsuo et al.²⁷ reported that family history was significantly higher in accommodative/partially accommodative esotropia and intermittent/constant exotropia than infantile esotropia. Also, probably because of the relatively inadequate eye care system in China,²⁸ potential patients with strabismus, especially older adults, are often undiagnosed.

Recent literature demonstrated that early surgery, even very early surgery within 6 months of infantile esotropia onset, results in better

outcomes in infantile esotropia.²⁹ Moreover, the risk factors during pregnancy and delivery are related to the prognosis of infantile esotropia, including a higher rate of surgical failure.^{30–32} These results will be helpful for obstetricians and pediatricians to improve awareness of the association of these risk factors with infantile esotropia and to recommend early eye examinations for high-risk infants. Vision care providers must diagnose infantile esotropia as early as possible and make informed decisions regarding the management of children with this condition.

There are several limitations in this study. First, the data used to identify eligible participants were collected retrospectively, and the accuracy of some information from the questionnaire was not easily verifiable. Moreover, the participants were from a single center, and the sample size was relatively small, leading to possible statistical bias. Data on socioeconomic status, education level, Apgar

TABLE 3. Multivariate logistic regression model of the perinatal risk factors

	<i>B</i>	<i>SE</i>	<i>Wald</i>	<i>P</i>	<i>OR (95% CI)</i>
Birth weight (g)					
<2500	1.443	0.543	7.053	.008	4.24 (1.46–12.29)
2500–3999					1 (Reference)
≥4000	0.267	0.666	0.160	.69	1.31 (0.35–4.82)
Gestational age (wk)					
<34	−0.188	0.963	0.038	.85	0.83 (0.13–5.47)
34–36	0.901	0.591	2.326	.13	2.46 (0.77–7.84)
≥37					1 (Reference)
Mode of delivery					
VD					1 (Reference)
ECD	0.508	0.334	2.182	.14	1.66 (0.85–3.26)
EMCD	0.802	0.348	5.305	.02	2.23 (1.13–4.41)

B = coefficient estimation; *CI* = confidence interval; *ECD* = elective cesarean delivery; *EMCD* = emergency cesarean delivery; *OR* = odds ratio; *SE* = standard error; *VD* = vaginal delivery; *Wald* = Wald test.

scores, placental weight, diseases during pregnancy, and parental behavioral factors such as smoking, medicine, or alcohol consumption were not analyzed. Finally, our study sample was limited to infantile esotropia, and the research methods and results may not be applicable to other types of strabismus.

In conclusion, we investigated the associations between infantile esotropia and gestational age, birth weight, parental age, mode

of delivery, and family history of strabismus. Our findings suggest that low birth weight and emergency cesarean delivery are risk factors for infantile esotropia. Although the mechanisms linking these risk factors to infantile esotropia are unclear, these findings highlight a need for collaborative care between obstetricians, pediatricians, and vision care providers to develop feasible and effective intervention strategies for infantile esotropia.

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JH and QZ contributed equally to this work and are considered first coauthors.

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