

Gender-specific associations of different birth weights with neonatal moderate or severe hypoxic ischemic encephalopathy: a cross-sectional study

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Abstract

To investigate the associations of different birth weights with neonatal moderate or severe hypoxic ischemic encephalopathy (HIE) according to different gender, and explore the interactions among the related risk factors. T-test and Chi-square test were used to analyze data. Multiple logistic regression analysis was used to estimate the odds ratios (OR_s) and corresponding 95% confidence intervals (CI_s) between different birth weights and risk of moderate or severe HIE stratified by gender. The relative excess risk due to interaction and the attributable proportion of interaction indices were used to measure additive interactions. In the adjusted logistic regression models, the overall population with low birth weight (adjusted OR:4.329,95%CI:1.587–5.138) had an increased risk of moderate or severe HIE, and the associations differed by gender-specific. The results of these multiplicative and additive interactions were consistent according to different gender groups. Low birth weight was independently positively associated with an increased risk of moderate or severe HIE, and the associations differed by gender-specific. Notably, low birth weight possibly interplayed synergistically with umbilical cord around the neck as well as low birth weight and amniotic fluid contamination to increase the risk of moderate or severe HIE across gender.

1. Introduction

Hypoxic ischemic encephalopathy (HIE) is a critical condition in neonatal medicine due to its potential to cause long-term neurological deficits. It significantly contributes to both morbidity and mortality in neonates^[1–6]. HIE results from brain damage caused by a hypoxic-ischemic event during the prenatal, intrapartum, or postnatal period, leading to restricted blood flow to the infant's brain^[7–11]. Despite significant improvements in neonatal therapy, neonatal HIE continues to exist in developed countries and a disproportionately high burden remains in developing countries currently. In developed countries, it is estimated to occur in one to eight per 1000 live births, while in developing countries, the incidence can be as high as 26 per 1000. In China, about 100,000 neonates are affected by HIE^[12–15]. Depending on the neurological symptoms of the neonates, HIE is classified into three categories: mild, moderate or severe. Neonates with mild HIE are more likely to survive without developmental disabilities, whereas neonates with moderate or severe HIE can suffer serious consequences, such as death, cerebral palsy, epilepsy and cognitive disability^[16–19]. Clinically, it is not only necessary to take appropriate preventive and therapeutic measures, but also to identify the relevant risk factors of moderate or severe HIE to inform new strategies and tailor-specific therapies before they occur.

It is in urgent need to understand both timing, pathophysiology, and the risk factors underlying the incidence of moderate or severe HIE. The etiology of moderate or severe HIE is not fully understood, but it is likely to involve complex interactions between environmental and genetic factors. At present, the risks of moderate or severe HIE are mainly based on the characteristics of pregnant women and fetuses during pregnancy and delivery. Due to maternal or fetal abnormalities, fetal low birth weight leads to fetal brain asphyxia leading to neuronal destruction, which may evolve into moderate or severe HIE. Similarly,

the etiology for different birth weights are also exceeding broad and wide-ranging. Some epidemiological studies have shown that there is an association between moderate or severe HIE and low birth weight, which is a known risk factor of moderate or severe HIE^[20–22]. However, there are still some inconsistent results in studies examining the associations between different birth weights and moderate or severe HIE, which may be related to the differences in study design, study population or sample size. In addition, the potential interactions between different birth weights and other risk factors were described to contribute to the increased risk factors of moderate or severe HIE, which may be another possible reasons for inconsistent results across studies.

In current literature, there is limited information on the association between different birth weights and moderate or severe HIE by the gender-specific effect. Additionally this association remains obscure in Henan Province population, which is an important central city in central China. Region research is necessary in order to establish a presentative study population and to provide evidence as justification for the design of preventive strategies against moderate or sever HIE in Henan's hospitals. Besides, there is limited information on how gender can be a risk factor for moderate or severe HIE. Thus, we conducted a cross-sectional study to analyze different birth weights related with neonatal moderate or severe HIE, using the neonatal HIE database containing detailed clinical data according to gender-specific differences. Additionally, we also used an additive model to analyze possible interactions between different birth weights and the risk factors of moderate or severe HIE across gender, in order to provide a basis for the primary prevention for moderate or severe HIE in early clinical stage.

2. Methods

2.1 Study population

This cross-sectional study included 178 neonates diagnosed with HIE who were admitted to Henan Children's Hospital between 2017 and 2023. The diagnosis of HIE was established according to “the Diagnosis of Hypoxic-ischemic Encephalopathy in Term Infants”^[23]. The diagnostic criteria for HIE issued by the Neonatal Group of the Pediatric Society of the Chinese Medical Association were applied as follows: (a) a definite history of abnormal obstetrics capable of inducing fetal distress, accompanied by severe manifestations of fetal distress (fetal heart rate < 100 beats/min lasting more than 5 min, and/or grade III amniotic fluid contamination), or a marked history of asphyxia during delivery; grade III amniotic fluid contamination here denotes amniotic fluid that is more viscous and turbid, which exerts a stronger adverse influence on fetal respiration and, in severe cases, readily results in intrauterine hypoxia and fetal asphyxia; (b) severe asphyxia at birth, defined as an Apgar score ≤ 3 at 1 min and ≤ 5 at 5 min,, and/or umbilical cord arterial acidemia (pH < 7); (c) neurological symptoms emerging shortly after birth and persisting for more than 24h, such as altered consciousness (hyperexcitability, lethargy, or coma), changes in muscle tone (increased or decreased), abnormal primitive reflexes (weakened or absent sucking and embrace reflexes), seizures in severe cases, brainstem signs (altered respiratory rhythm, pupillary changes, and delayed response to light), and increased anterior fontanelle tension; and (d)

exclusion of convulsions attributable to electrolyte imbalance (hypocalcemia, hypoglycemia, etc.), birth trauma, or intracranial hemorrhage, as well as brain injury caused by intrauterine infection, inherited metabolic disease, or other congenital conditions. Among the enrolled neonates, 62 were diagnosed with mild HIE and 116 with moderate or severe HIE.

All enrolled cases fulfilled the following inclusion criteria: (a) meeting the HIE diagnostic criteria formulated by the Neonatal Group of the Pediatric Society of the Chinese Medical Association; (b) admission to the Neonatal Intensive Care Unit of Henan Children's Hospital with typical clinical manifestations confirmed by computed tomography, magnetic resonance imaging, and other examinations; and (c) complete demographic information and clinical characteristics. The exclusion criteria were: (a) severe cardiac, hepatic, or renal dysfunction at birth; (b) hematological or congenital diseases; and (c) convulsions caused by birth injury or intracranial hemorrhage.

2.2 Data Sources

The data collection procedures followed those described in our previous study^[24], with modifications as detailed below. Neonatal basic demographic information and clinical characteristics were documented from the neonatal HIE database. This database center was established by a university-affiliated children's hospital in Henan Province, China (a Grade A, Level III children's public hospital in Zhengzhou, Henan), and is recognized as a province-wide, clinically oriented, computerized disease-specific database. The neonatal HIE database was connected to the physician's medical record system, which allowed simultaneous acquisition of neonatal birth information, medical treatment, and record data. Maternal sociodemographic information was collected by the investigator through questionnaires and imported into the database in real time. Data on maternal and neonatal characteristics were collected for the mild HIE and moderate or severe HIE groups, comprising neonatal age at diagnosis, gender, residential region, birth weight, gestational age at birth, feeding pattern, maternal age, delivery mode, gestational diabetes, gestational hypertension, anemia during pregnancy, intrauterine distress, umbilical cord around the neck, and amniotic fluid contamination. All data were collected prospectively by the hospital data management center, which was staffed with ten data management specialists for real-time data quality inspections; a supervisor then completed the review before the data were locked annually to ensure the accuracy of the information. When data were found to be inconsistent, the hospital number, recorded names, variables, and errors were listed to facilitate subsequent inspection and correction. The studies involving humans were approved by Ethics Committee of Henan Children's Hospital. All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all subjects and/or their legal guardian(s).

2.3 Ascertainment of variables

The definitions of the variables followed those described in our previous study^[24], with modifications as detailed below. Neonatal birth weight was obtained from the birth certificate, or the weight was measured directly: after birth, the body was dried, the wrapping removed, and the naked body placed on an electronic scale until stable readings were obtained, with an accuracy of 1g. In this study, neonatal

birth weight was categorized into three groups: 1500–2499 g was defined as low birth weight (LBW); 2500–4000 g as normal birth weight (NBW); and > 4000 g as high birth weight (HBW). Neonatal gestational age at birth was classified as premature infant (< 37 weeks), term infant (37–42 weeks), and postterm infant (> 42 weeks). Neonatal feeding pattern was classified as breastfeeding, artificial feeding, and mixed feeding. Maternal delivery mode was categorized as natural delivery and cesarean section. Neonatal and maternal gestational diabetes, gestational hypertension, anemia during pregnancy, intrauterine distress, umbilical cord around the neck, and amniotic fluid contamination were all treated as dichotomous variables consisting of "Yes" or "No".

2.4 Statistical analysis

The statistical analysis followed the approach described in our previous study^[24], with modifications as detailed below. Continuous and categorical baseline maternal and neonatal demographic characteristics were statistically described as mean±standard deviation and as frequencies and percentages, respectively, stratified by group. Statistical differences between the moderate or severe HIE group and the mild HIE group were compared using the t-test or Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. A gender-based stratified analysis was conducted to examine the proportions of different birth weight groups among neonates with HIE. Multiple logistic regression analysis was used to identify associations between different birth weights and the risk of moderate or severe HIE, stratified by gender. The occurrence of moderate or severe HIE served as the dependent variable, with mild HIE as the reference group. Risks were estimated using unadjusted and adjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for moderate or severe HIE versus mild HIE. Unadjusted ORs were first estimated in model 1. In model 2, ORs were adjusted for neonatal age at diagnosis, gender, residential region, gestational age at birth, feeding pattern, maternal age, delivery mode, gestational diabetes, gestational hypertension, anemia during pregnancy, intrauterine distress, umbilical cord around the neck, and amniotic fluid contamination.

In addition, an additive model was used to test for possible interactions between neonatal birth weight and umbilical cord around the neck, and between birth weight and amniotic fluid contamination, according to gender. In this process, normal birth weights and high birth weights were merged as non-LBW to achieve adequate power for the interaction analysis. The relative excess risk due to interaction (RERI) and the attributable proportion due to interaction (AP) were evaluated to measure additive interaction based on the additive model. To estimate multiplicative interaction, the product term was included in the logistic regression model, and the interaction odds ratio (IOR) with its 95% CI was calculated. All statistical analyses were performed using IBM SPSS Statistics (version 22, Chicago, IL, USA). Two-sided P values less than 0.05 were considered statistically significant.

3. Results

3.1 Demographic characteristics of the study population

A total of 178 neonates diagnosed with HIE were included in the cross-sectional study, including 103 (57.9%) male neonates and 75 (42.1%) female neonates. Among the study population, 62 (34.8%) neonates were diagnosed with mild HIE, 116 (65.2%) neonates were diagnosed with moderate or severe HIE. Maternal and neonatal demographic characteristics of mild HIE and moderate or severe HIE were summarized in Table 1. In the overall neonates, 91 (51.1%) neonates were categorized as low birth weight (1500-2499g), 34 (19.1%) neonates were categorized as normal birth weight (2500-4000g), 53 (29.8%) neonates were categorized as high birth weight (>4000g), and there was statistically significantly difference between the two groups with respect to neonatal birth weight ($P = 0.025$). The proportion of neonatal intrauterine distress in the moderate or severe HIE group was significantly higher compared with the mild HIE group (53.6% vs. 46.4%, $P = 0.028$). Neonatal umbilical cord around the neck occurred in 80 (70.8%) of the moderate or severe HIE group was significantly higher compared with 33 (29.2%) in the mild HIE group ($P = 0.038$). The proportion of neonatal amniotic fluid contamination in the moderate or severe HIE group had a statistically significantly higher compared with the mild HIE group (74.0% vs. 26.0%, $P = 0.040$). However, there were no statistically significant differences between the two groups in proportions of the neonatal age at diagnosis, gender, residential region, gestational age at birth, feeding pattern, maternal age, delivery mode, gestational diabetes, gestational hypertension and anemia during pregnancy (all $P > 0.05$).

Table 1
Maternal and neonatal demographic characteristics of neonates with different levels of hypoxic ischemic encephalopathy

Variables	Total (n = 178)	Mild HIE (n = 62)	Moderate or severe HIE (n = 116)	P-value
Age at diagnosis(days)	13.5 ± 5.1	13.6 ± 5.2	13.3 ± 5.0	0.703
Gender				
Male	103(57.9)	33(53.2)	70(60.3)	0.359
Female	75(42.1)	29(46.8)	46(39.7)	
Residential region				
Urban	53(29.8)	14(22.6)	39(33.6)	0.125
Rural	125(70.2)	48(77.4)	77(66.4)	
Birth weight (g)				
1500–2499	91(51.1)	31(50.0)	60(51.7)	0.025
2500–4000	34(19.1)	18(29.0)	16(13.8)	
>4000	53(29.8)	13(21.0)	40(34.5)	
Gestational age at birth (weeks)				
<37	86(48.3)	33(53.2)	53(45.7)	0.377
37–42	53(29.8)	19(30.7)	34(29.3)	
>42	39(21.9)	10(16.1)	29(25.0)	
Feeding pattern				
Breastfeeding	75(42.1)	22(35.5)	53(45.7)	0.172
Artificial feeding	64(36.0)	28(45.2)	36(31.0)	
Mixed feeding	39(21.9)	12(19.3)	27(23.3)	
Maternal age (years old)				
<35	80(44.9)	29(46.8)	51(44.0)	0.720
≥ 35	98(55.1)	33(53.2)	65(56.0)	
Delivery mode				
Natural delivery	75(42.1)	23(37.1)	52(44.8)	0.320
Cesarean section	103(57.9)	39(62.9)	64(55.2)	

Variables	Total (n = 178)	Mild HIE (n = 62)	Moderate or severe HIE (n = 116)	P-value
Gestational diabetes				
Yes	59(33.1)	26(41.9)	33(28.4)	0.069
No	119(66.9)	36(58.1)	83(71.6)	
Gestational hypertension				
Yes	67(37.6)	26(41.9)	41(35.3)	0.387
No	111(62.4)	36(58.1)	75(64.7)	
Anemia during pregnancy				
Yes	75(42.1)	24(38.7)	51(44.0)	0.499
No	103(57.9)	38(61.3)	65(66.0)	
Intrauterine distress				
Yes	56(31.5)	26(41.9)	30(25.9)	0.028
No	122(68.5)	36(58.1)	86(74.1)	
umbilical cord around the neck				
Yes	113(63.5)	33(53.2)	80(69.0)	0.038
No	65(36.5)	29(46.8)	36(31.0)	
Amniotic fluid contamination				
Yes	73(41.0)	19(30.6)	54(46.6)	0.040
No	105(59.0)	43(69.4)	62(53.4)	

3.2 Subgroup analysis of different birth weights according to different gender

Neonates were divided into different gender groups to investigate the distributions in subgroups analyses of different birth weights. The proportions of different birth weights groups among neonatal HIE according to different gender were shown in Table 2. We found that the overall neonates showed statistically significantly difference with respect to neonatal different birth weights between mild HIE and moderate or severe HIE groups ($P = 0.025$). However, there were no statistically significantly differences detected between the two groups in the proportions of different birth weights in the male and female groups respectively (all $P > 0.05$).

Table 2

Proportions of different birth weights groups among neonatal hypoxic ischemic encephalopathy according to different gender

Variables	Total (n = 178)	Mild HIE (n = 62)	Moderate or severe HIE (n = 116)	P-value
Male				
LBW	53(51.5)	18(54.6)	35(50.0)	0.328
NBW	16(15.5)	7(21.2)	9(12.9)	
HBW	34(33.0)	8(24.2)	26(37.1)	
Female				
LBW	38(50.7)	13(44.8)	25(54.4)	0.068
NBW	18(24.0)	11(37.9)	7(15.2)	
HBW	19(25.3)	5(17.3)	14(30.4)	
Overall				
LBW	91(51.1)	31(50.0)	60(51.7)	0.025
NBW	34(19.1)	18(29.0)	16(13.8)	
HBW	53(29.8)	13(21.0)	40(34.5)	

3.3 Associations between different birth weights and risk of moderate or severe hypoxic ischemic encephalopathy stratified by gender

To be specific, the results of logistic regression analyses between different birth weights and risk of moderate or severe HIE stratified by gender were presented in Table 3. The unadjusted and adjusted OR_s and 95%CI were showed in model 1 and model 2 respectively. We found the associations between different birth weights and risk of moderate or severe HIE differed based on the gender-specific. In the male and female groups, we found that LBW was significantly associated with an increased risk of moderate or severe HIE compared with the mild HIE after adjusting for potential confounders, where the adjusted OR_s were 3.275 (95%CI:1.591–4.282) and 2.368 (95%CI:1.403–3.315) respectively. We also performed the analysis based on the overall neonates of the associations, the results also showed that LBW (adjusted OR:4.329, 95%CI:1.587–5.138) had a positively higher risk of moderate or severe HIE. However, there were no statistically significant associations between HBW and risk of moderate or severe HIE according to different gender and overall neonates subgroups.

Table 3
Logistic regression analyses between different birth weights and risk of moderate or severe hypoxic ischemic encephalopathy stratified by gender

Variables	Model 1 ^a		Model 2 ^b	
	Unadjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Male				
LBW	2.556(1.347–3.728)	0.027	3.275(1.591–4.282)	0.036
NBW	1.00(reference)*		1.00(reference)*	
HBW	1.969(0.769–2.861)		2.623(0.896–3.417)	
Female				
LBW	1.879(1.246–2.953)	0.033	2.368(1.403–3.315)	0.045
NBW	1.00(reference)*		1.00(reference)*	
HBW	1.564(0.623–2.487)		2.132(0.873–3.246)	
Overall				
LBW	3.358(1.389–4.675)	0.019	4.329(1.587–5.138)	0.026
NBW	1.00(reference)*		1.00(reference)*	
HBW	2.573(0.756–3.529)		3.167(0.971–4.033)	

^a Model 1: the unadjusted ORs; ^bModel 2: adjusted ORs for neonatal age at diagnosis, gender, residential region, gestational age at birth, feeding pattern, maternal age, delivery mode, gestational diabetes, gestational hypertension, anemia during pregnancy, intrauterine distress, umbilical cord around the neck and amniotic fluid contamination. *1.00(reference) meant the reference group.

3.4 Interaction analysis between different birth weights and the risk factors of moderate or severe hypoxic ischemic encephalopathy across gender

The interactions between different birth weights and the risk factors of moderate or severe HIE across gender were showed in Table 4. In this process, normal birth weights and high birth weights were merged as non-LBW to achieve power for the interaction analysis. In the overall neonates, we found that LBW with umbilical cord around the neck had significantly higher risk of moderate or severe HIE (adjusted OR:4.634,95%CI:1.718–5.695), when comparing to the non-LBW with umbilical cord around the neck. As expected, a significant additive interaction was found between LBW and umbilical cord around the neck (RERI:2.581,95%CI:1.497–3.768;AP:0.825,95%CI:0.569–1.917) based on the additive model. In addition, we also found that LBW with amniotic fluid contamination significantly increased the risk of moderate or severe HIE (adjusted OR:3.696,95%CI:1.573–4.892). Similarly, LBW and amniotic fluid

contamination (RERI:1.958,95%CI:1.412–3.126;AP:0.714,95%CI:0.625–1.698) also yielded cumulative effects by the additive model. The results of these multiplicative and additive interactions were consistent in the male and female groups respectively in Table 4.

Table 4

The interactions between different birth weights and the risk factors of moderate or severe hypoxic ischemic encephalopathy across gender

Variables	Birth weight	Adjusted OR(95%CI)	IOR(95%CI)	RERI(95%CI)	AP(95%CI)
Male					
umbilical cord around the neck			3.345(1.679–4.573)	2.375(1.572–3.651)	0.726(0.663–1.745)
Yes	LBW	4.276(1.875–5.328)			
No	Non-LBW	1.00(reference)*			
Amniotic fluid contamination			2.764(1.547–3.871)	1.896(1.337–2.965)	0.621(0.578–1.539)
Yes	LBW	3.561(1.689–4.652)			
No	Non-LBW	1.00(reference)*			
Female					
umbilical cord around the neck					
Yes	LBW	3.728(1.717–4.863)	2.872(1.634–3.985)	1.977(1.476–3.152)	0.558(0.416–1.673)
No	Non-LBW	1.00(reference)*			
Amniotic fluid contamination			2.237(1.382–3.516)	1.659(1.261–2.678)	0.493(0.387–1.472)
Yes	LBW	2.879(1.576–3.915)			
No	Non-LBW	1.00(reference)*			
Overall					
umbilical cord around the neck			3.512(1.543–4.716)	2.581(1.497–3.768)	0.825(0.569–1.917)
Yes	LBW	4.634(1.718–5.695)			
No	Non-LBW	1.00(reference)*			

Variables	Birth weight	Adjusted OR(95%CI)	IOR(95%CI)	RERI(95%CI)	AP(95%CI)
Amniotic fluid contamination			2.865(1.437–3.978)	1.958(1.412–3.126)	0.714(0.625–1.698)
Yes	LBW	3.696(1.573–4.892)			
No	Non-LBW	1.00(reference)*			

*1.00(reference) meant the reference group.

4. Discussion

Moderate or severe HIE is the leading cause of neonatal encephalopathy and ranking as the fifth leading cause of death in children under five. The development of moderate or severe HIE is caused by the interaction of multiple factors in the neonatal period. In this cross-sectional study, 178 neonates with HIE were included, of which 103 (57.9%) neonates were males and 75 (42.1%) neonates were females. Among the overall neonates, 33 (53.2%) neonates were males and 29 (46.8%) neonates were females in the 62 neonates with mild HIE, 70 (60.3%) neonates were males and 46 (39.7%) neonates were females in the 116 neonates with moderate or severe HIE respectively. Our study indicated that there was higher male susceptibility to neonatal moderate or severe HIE. In a similar study, Debillon et al.^[25] observed a similar 53.8% male prevalence. These findings remind us that gender can be regarded as specific stratified characteristic for further investigation. It has been reported that male neonates tend to have unfavorable outcomes of moderate or severe HIE compared to female ones, which has been demonstrated using radiological methods such as magnetic resonance imaging and ultrasound^[26–27]. There is a possibility that the variation in moderate or severe HIE between males and females is connected to the fact that males and females have different levels of steroid hormones and different levels of motor function.

In this study, we found that LBW was significantly associated with an increased risk of moderate or severe HIE in the overall population (adjusted OR:4.329,95%CI:1.587–5.138). When stratified by gender, we also found that LBW positively increased the risk of moderate or severe HIE in the male and female groups, where the adjusted OR_s were 3.275 (95%CI:1.591–4.282) and 2.368 (95%CI:1.403–3.315) respectively. Neonates who developed moderate or severe HIE had significantly lower birth weights than the neonates who did not develop moderate or severe HIE. Several studies have also verified the level of birth weight as one strong predictor of moderate or severe HIE among neonates. However, few studies in China, to our knowledge, were limited to one specific gender group in one provincial area, which cannot reveal the overall associations more broadly. In our study, we found the associations between LBW and the odds of moderate or severe HIE had gender-specific before and after adjusting for the covariables. Our findings suggest that LBW is an independent risk factor for the development of moderate or severe

HIE, which is consistent with several previous studies^[28–29]. Liljestrom L et al.^[8] revealed that birth weight less than 3000g (OR:1.61,95%CI:1.23–2.12) had a positively higher risk of moderate or severe HIE in the Swedish national cohort study. In one study, a cohort of infants with perinatal asphyxia was analyzed based on machine learning methods, and a predictive risk model for moderate or severe HIE was constructed using some clinical indicators such as infant birth weight^[30]. There are some possible explanations for the associations between LBW and moderate or severe HIE. LBW in neonate is often accompanied by imperfect organ development. Especially when the lung development is immature, it is prone to cause the occurrence of moderate or severe HIE. Although the underlying mechanisms have been proposed, how LBW affects moderate or severe HIE is a complex process within the life course and deserves further study.

More importantly, we also observed the significant multiplicative effects and additive effects in the interactions between LBW and umbilical cord around the neck as well as between LBW and amniotic fluid contamination stratified by gender respectively. In the overall population, we found that the LBW neonates with umbilical cord around the neck had much higher risk of moderate or severe HIE compared with non-low birth weight neonates with umbilical cord around the neck by the multiplicative and additive interactions (adjustedOR:4.634,95%CI:1.718–5.695;RERI:2.581,95%CI:1.497–3.768;AP:0.825,95%CI:0.569–1.917). Interestingly, we also observed that LBW with amniotic fluid contamination significantly increased the risk of moderate or severe HIE based on the multiplicative and additive effects (adjustedOR:3.696,95%CI:1.573–4.892;RERI:1.958,95%CI:1.412–3.126;AP:0.714,95%CI:0.625–1.698). The results of these multiplicative and additive interactions were consistent according to different gender groups. The associations of the multiplicative and additive interactions among umbilical cord around the neck and amniotic fluid contamination of LBW with moderate or severe HIE may be multifactorial^[31–33]. Abnormalities of the umbilical cord can affect the blood circulation of fetus. Especially when the umbilical cord is wrapped around the neck, the blood supply is significantly blocked or even interrupted, which can cause intrauterine distress, resulting in neonatal hypoxia and ischemia. Umbilical cord around the neck is a common high risk factor for acute fetal distress in utero during the delivery period. At present, amniotic fluid contamination is a risk factor leading to fetal intrauterine hypoxia or distress, and the degree of amniotic fluid contamination is positively correlated with neonatal moderate or severe HIE^[34–36]. The higher degree of amniotic fluid contamination, the higher probability of neonates with moderate or severe HIE. Intrauterine distress is the manifestation of acute or chronic fetal hypoxia. Long term hypoxia can cause acidosis, inhibit respiratory center and lead to neonatal moderate or severe HIE^[37–38]. Therefore, regarding LBW neonates with the umbilical cord around the neck and amniotic fluid contamination, we should enhance the standardization of prenatal examinations, conduct fetal heart rate monitoring weekly and closely monitor whether the pregnant women have amniotic fluid contamination, so as to detect abnormal conditions of pregnant women and fetuses as early as possible. Once intrauterine distress of the fetus is detected, clinicians should strengthen the monitoring of the whole labor process and take countermeasures timely, thus reduce the brain damage caused by asphyxia in neonatal moderate or severe HIE with LBW.

The main strengths of this study are the enrolled population of neonatal moderate or severe HIE came from a single hospital institution and the possible confounding factors are controlled as much as possible during the analysis to increase the reliability of the conclusion. The research data management personnel are of high quality, the data collection work is organized and planned, and the data collected is relatively accurate, thus minimizing information bias. However, there are still some limitations that should be considered in this study. Firstly, given that this was a cross-sectional design and we were unable to establish a causal relationship between different birth weights and moderate or severe HIE. Secondly, although we tried our best to identify relevant factors that may affect different birth weights and moderate or severe HIE, our data are still far from perfect. We cannot fully monitor all factors that affect different birth weights and moderate or severe HIE. Peri-pregnancy factors of maternal are acquired through recall, which has a certain recall bias. Thirdly, this study was comprised of a sample within a limit range in the central region of China, which may not be representative of the total Chinese population. Whether the findings of the study are generalised to the broader population in other geographical regions with different living habits remains to be answered. Comparisons with national-level data or other regions should be included to strengthen the argument for representativeness in the follow-up study.

5. Conclusions

In conclusion, LBW was independently positively associated with an increased risk of moderate or severe HIE, and the associations differed by gender-specific. Notably, LBW possibly interacted synergistically with umbilical cord around the neck as well as LBW and amniotic fluid contamination to increase the risk of moderate or severe HIE across gender. Therefore, intensive attention should be paid earlier in life for the neonates born with LBW and reduce the incidence of moderate or severe HIE in early neonatal period.

Abbreviations

ORs: Odds Ratios; CIs: Confidence Intervals; RERI: relative excess risk due to interaction; AP: attributable proportion due to interaction; IOR: Interaction of Odd Ratio.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability statement

The datasets generated and/or analysed during the current study are not publicly available due to privacy and ethical restrictions regarding neonatal and maternal identifiable information but are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

Yiran Wang wrote the first draft and final article versions of this paper. Yaodong Zhang and Shuying Luo participated in data collection. Kaijuan Wang was responsible for data cleaning and analysis. All authors read and approved the final manuscript.

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