Risk factors for early wheezing in preterm infants: a retrospective cohort study

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Abstract

Background: The factors that cause recurrent wheezing in children are complex, and premature delivery may be one of these factors. Little is known about early wheezing in preterm infants.

Methods: Data were sourced from 1616 children born between 2007 and 2013 from 8 hospitals in Guangxi, China. All children were followed up by telephone or questionnaire through the sixth year of life. Children were grouped by gestational age (GA): Group A, GA ≤ 32 weeks; Group B, 32 weeks < GA < 37 weeks; and Group C, 37 weeks ≤ GA < 42 weeks.

Results: The incidences and risk factors for early wheezing in preterm infants were analysed. The incidences of early wheezing were as follows: Group A > Group B > Group C. The incidence of persistent early wheezing in Group A or Group B was significantly higher than that in Group C, respectively. SGA (*95% CI*: 1.097 to 7.519) was a risk factor for early wheezing in group A. Male sex (*95% CI*: 1.595 to 4.501) and family history of allergies (*95% CI*: 1.207 to 3.352) were risk factors for early wheezing in group B.

Conclusions: 1. New-borns with younger GAs had a higher risk of early wheezing. 2. The incidence of persistent early wheezing for preterm infants (GA ≤ 32 weeks and 32 weeks < GA < 37 weeks) was higher than that for full-term infants (37 weeks ≤ GA < 42 weeks). 3. SGA was a risk factor for early wheezing in preterm infants with a GA ≤ 32 weeks. 4. Male sex, personal history of allergies and family history of allergies were all possible factors affecting early wheezing in preterm infants with a GA > 32 weeks but < 37 weeks and full-term infants. Among them, male sex and family history of allergies were risk factors for early wheezing. 5. Mode of delivery, passive smoking, breastfeeding and invasive mechanical ventilation were not possible risk factors for early wheezing in infants of different GAs.

1 | Background

Asthma is the most common chronic respiratory disease in children, and wheezing is the most typical clinical manifestation of asthma in children. Approximately 57% of children have at least one attack of wheezing at the age of three years [1]. Recurring wheezing or asthma affects the growth of children, increases medical costs, and imposes a larger burden on the family and society [2]. According to the progression of the disease, children's wheezing is classified as one of two types: early wheezing (transient early wheezing and persistent early wheezing) and delayed wheezing (asthma) [3-5]. The related factors that cause recurrent wheezing and even asthma in children are complex, and premature delivery may be one of these factors. Studies have shown that the incidences of wheezing and abnormal lung function were higher among preterm infants than among full-term infants and that premature lung damage lasted for a long time [6]. In addition, preterm birth may be related to small airway disease and chronic obstructive pulmonary disease [7-10]. Therefore, it is extremely important to identify and prevent early wheezing in preterm infants. This study used stratified analysis and comparison with full-term infants to

determine the risk factors that caused early wheezing in preterm infants, with the aim of providing some guidance and help for early identification and effective avoidance of potential risk factors.

2 | Methods

2.1 | The sample population

A retrospective cohort study examined 1616 children (preterm and full-term infants) born between 2007 and 2013 from 8 provincial and municipal hospitals in Guangxi, China. All children were followed through the sixth year of life. Children were grouped by age: Group A, gestational age (GA) ≤ 32 weeks; Group B, 32 weeks < GA < 37 weeks; and Group C, 37 weeks ≤ GA < 42 weeks.

2.2 | Data collection

The clinical data were collected by telephone or questionnaire (Additional file 1) when the child was 6 years old. Early wheezing was defined as a diagnosis of wheezing once before the age of 3 years. Transient early wheezing was defined as a type of early wheezing that gradually disappeared before the age of 3 years, while persistent early wheezing continued to the age of 6 years. The diseases that caused early wheezing included bronchiolitis, asthmatic bronchitis, asthmatic bronchopneumonia, and bronchopulmonary dysplasia, and other conditions including tracheobronchial foreign bodies and other congenital diseases, such as congenital heart disease, tracheoesophageal fistula, laryngeal chondroplasia and mediastinal space occupying lesions, were excluded. Paediatrician and epidemiology experts were involved in the design and conduct of the questionnaire survey and telephone follow-up visits. we controlled the interviewee's enrollment by checking their medical records about wheezing. Besides, interviewer training was conducted to control the subjective influence. The questions about sex, birth weight, gestational age, mode of delivery, invasive mechanical ventilation, breastfeeding, passive smoking, and personal and family history of allergic disease were also necessary items for interviewees. Through a questionnaire survey or telephone follow-up, we could understand the risk factors for early wheezing in new-borns of different GAs. This questionnaire was designed specifically for this study. The original data of the questionnaire were also used only for the analysis in this study.

2.3 | Data analysis

Enumeration data are expressed as the number of cases or incidence. Each variable was assigned a value: dichotomous variables were used (0 = no, 1 = yes), and unordered multi-categorical variables were assigned by definition. SPSS version 23.0 was used to analyse the data of each group by analysis of variance, the chi-square test, the *Bonferroni* method for multiple comparisons, univariate analysis and multivariate analysis.

3 | Results

3.1 | Comparison of the incidence of early wheezing in each group

There was a significant difference in the incidence of early wheezing among each group ($P = 0.000$) (Table 1). The incidence of early wheezing in group A was significantly greater than that in group B ($P = 0.005$) or group C ($P = 0.000$) and the incidence in group B was significantly greater than that in group C ($P = 0.000$) (Additional file 2).

3.2 | The incidences of persistent and transient early wheezing in each group

There were significant differences in the incidence of persistent early wheezing ($P = 0.000$) and transient early wheezing ($P = 0.000$) among the groups (Table 2). The incidence of persistent early wheezing in group A ($P = 0.000$) and group B ($P = 0.000$) was significantly greater than that in group C, and the incidence of transient early wheezing in group A was significantly higher than that in group B ($P = 0.000$) or group C ($P = 0.000$) by pairwise comparison (Additional files 3, 4).

3.3 | Univariate analysis of early wheezing in each group

3.3.1 | Premature group: GA ≤ 32 weeks

The mean birth weight of preterm infants with a GA of less than 32 weeks is usually less than 2500 g. In this group, we used the relationship between birth weight and GA (small-for-gestational-age (SGA), appropriate-for-gestational-age (AGA)) instead of birth weight for evaluation. The results showed that the proportion of SGA infants in the early wheezing group was significantly higher than that in the non-wheezing group ($X^2 = 8.154$, $P = 0.005$) (Table 3).

3.3.2 | Premature group: 32 weeks < GA < 37 weeks

The proportion of males ($X^2 = 17.686$, $P = 0.000$), the positive rate of a personal history of allergies ($X^2 = 7.350$, $P = 0.007$), and the positive rate of a family history of allergies ($X^2 = 12.797$, $P = 0.000$) in the early wheezing group were significantly higher than those in the non-wheezing group (Table 4).

3.3.3 | Full-term group of 37 weeks ≤ GA < 42 weeks

The proportion of males ($X^2 = 8.486$, $P = 0.004$), the positive rate of a personal history of allergies ($X^2 = 3.949$, $P = 0.047$), and the positive rate of a family history of allergies ($X^2 = 6.126$, $P = 0.014$) in the early wheezing group were significantly higher than those in the non-wheezing group (Table 5).

3.4 | Multivariate analysis of early wheezing in each group

SGA (*OR* = 2.871, *95% CI*: 1.097 to 7.519) is a risk factor for early wheezing in preterm infants with a GA ≤ 32 weeks (Additional file 5).

Male sex (*OR* = 2.679, *95% CI*: 1.595 to 4.501) and family history of allergy (*OR* = 2.012, *95% CI*: 1.207 to 3.352) were risk factors for early wheezing in preterm infants with a GA > 32 weeks but < 37 weeks

(Additional file 6).

Male sex (*OR* = 2.568, *95% CI*: 1.363 to 4.836) and family history of allergies (*OR* = 2.009, *95% CI*: 1.117 to 3.612) were risk factors for early wheezing among full-term infants with GAs ≥ 37 weeks but < 42 weeks (Additional file 7).

4 | Discussion

It has been confirmed that premature birth can lead to immature lungs, low lung function, and immature immune system function, thereby increasing the risk of wheezing in children [11-14]. Enrico Lombard et al showed that GA and the development of the lung were closely related [15]. In this study, included new-borns were grouped and compared by GA, and the results confirmed that new-borns with a younger GA were at higher risk of early wheezing, which was consistent with the study of Unal et al. [16]. However, the incidences of early wheezing among different GA groups in this study were lower than those reported in the previous literature [17, 18], which might be related to the short follow-up and small sample size.

This study found that the incidence of persistent early wheezing among preterm infants (GA ≤ 32 weeks and 32 weeks < GA < 37 weeks) was significantly higher than that among full-term infants, which was consistent with previous literature reports [17]. In addition, this study also showed that the incidence of transient early wheezing among preterm infants with a GA ≤ 32 weeks was significantly greater than that among preterm infants with a GA > 32 weeks but < 37 weeks. However, there was no significant difference in the incidence of persistent early wheezing between the preterm infants with a GA ≤ 32 weeks and preterm infants with a GA > 32 weeks but < 37 weeks. The reasons might be as follows: first, the younger the gestational age of preterm infants was, the less mature their lungs were. Second, the respiratory system of the preterm infant gradually develops with age, resulting in a decrease in persistent early wheezing [19].

Birth weight is a well-established indicator of prenatal growth, intrauterine nutritional status and maternal health. It is a sensitive indicator of foetal respiratory and immune system development [20]. The Global Initiative for Asthma (GINA) also added low birth weight as a risk factor for persistent airflow limitation [2]. However, there was no significant correlation between birth weight and early wheezing in preterm and full-term infants in this study, which was inconsistent with the findings reported in the literature [21]. In the literature [21], the birth weight was used as the independent variable the analysis of relative factors of wheezing. However, the average birth weight of preterm infants in Group A was less than 2500 g in our study, which was not chosen as an independent variable. To reveal the relationship between premature birth and the symptom of wheezing, we set SGA and AGA as independent variables. On the other hand, some studies have shown that preterm infants with very low birth weight had a high incidence of impaired lung function, and the degree of impaired lung function was more severe in preterm infants with recurrent wheezing attacks [11, 22]. In our study, the results showed that SGA was a risk factor for early wheezing in preterm infants with a GA ≤ 32 weeks. This suggests that the lower the birth weight of a preterm infant at GA ≤ 32 weeks is, the more severe the impairment of lung function and the higher the

risk of early wheezing will be. In summary, we speculated that the younger the gestational age and the lower the birth weight is, the higher the risk of early wheezing will be. However, the results will be further verified with a large sample size in the future.

One thing worth noting is that because this study was a retrospective study, most of the included neonates lacked lung function data. The relationship between early wheezing and lung function in preterm infants is expected to be further evaluated with a large sample in prospective studies in the future.

Sex was another risk factor for early wheezing in infants. In this study, we found that the proportion of males in the early wheezing group was significantly higher than that in the non-wheezing group among both preterm infants with a GA of > 32 weeks but < 37 weeks and full-term infants with a GA ≥ 37 weeks but < 42 weeks. Additionally, the results of the univariate analysis and multivariate analysis showed that male sex was a possible influencing factor and risk factor for early wheezing, respectively. This was in line with previous studies [17, 23]. However, this study did not find an association between sex and early wheezing among preterm infants with a GA ≤ 32 weeks.

A personal history of allergies was a risk factor for wheezing in children. We also found that new-borns with a personal history of allergies had a higher risk of early wheezing regardless of whether they were preterm infants with a GA > 32 weeks but < 37 weeks or full-term infants with a GA ≥ 37 weeks but < 42 weeks, which was consistent with previous studies [24]. However, the history of personal allergy did not show a significant correlation in the multivariate analysis of early wheezing in preterm infants with a GA > 32 weeks but < 37 weeks or full-term infants with a GA ≥ 37 weeks but < 42 weeks. The reasons might be as follows: first, the results related to a personal history of allergies suggest that a larger sample size is needed. Second, the parents might have recall bias regarding whether or not their children had a personal history of allergies. Third, some children might be too young for allergy symptoms. On the other hand, the effect of personal history of allergies was not significant for early wheezing among preterm infants with a GA ≤ 32 weeks, suggesting that a personal history of allergies might not be associated with early wheezing in preterm infants with a GA ≤ 32 weeks. This suggested that the early wheezing of preterm infants with a GA ≤ 32 weeks may be related to the immaturity of their respiratory system.

A family history of allergies was also an important risk factor for wheezing in children [25]. The results of this study showed that a family history of allergies was a risk factor for early wheezing in preterm infants with a GA > 32 weeks but < 37 weeks, which was consistent with previous findings [24]. However, there was no correlation between family history of allergies and early wheezing among preterm infants with a GA ≤ 32 weeks in this study, which was consistent with previous reports [17]. This suggested that a family history of allergies might not be associated with early wheezing in preterm infants with a GA ≤ 32 weeks. The above results indicated that the main cause of early wheezing in preterm infants with a GA ≤ 32 weeks might be the immature respiratory system, rather than a personal history of allergies or a family history of allergies.

Previous studies have shown that caesarean section delays and alters the development of intestinal flora in infants, thereby increasing susceptibility to wheezing [26]**.** However, whether caesarean section increases the risk of wheezing in children is controversial. Some studies have demonstrated that the risk of asthma in preterm infants delivered by caesarean section was higher than that in preterm infants delivered vaginally [27]. It has also been proposed that although the proportion of caesarean sections has increased, there is no correlation between caesarean section and the risk of wheezing [28]. The results of this study showed that there was no significant difference between caesarean section and children's early wheezing. However, this did not indicate that caesarean section must not be a risk factor for early wheezing in children. Because the incidence of caesarean section in each group was greater in the early wheezing group than in the non-wheezing group, the failure to obtain statistically significant results might be related to the small sample size of cases.

Tobacco exposure increases the risk of wheezing by decreasing lung function and increasing airway hyperresponsiveness. A prospective birth cohort study showed that preterm infants whose mothers smoked during pregnancy had an increase in the number of wheezes and recurrent wheezing in early childhood [29]. Another study found that passive smoking was positively correlated with wheezing in preterm infants [16]. However, this study did not find a correlation between passive smoking and early wheezing in children in any group. Considering that with the long-term distribution of scientific information, an increasing number of parents were aware that smoking was harmful to their children's health, the amount and frequency of smoking have been reduced, and smoking has been increasing avoided at home. This reduced exposure of children to smoking exposure to some extent, thereby weakening the increased risk of early wheezing and its adverse effects by passive smoking.

It has been demonstrated that breastfeeding can reduce the risk of wheezing by preventing respiratory tract infection, promoting lung growth and development and supporting the maturation of the immune system. However, this study did not find that the feeding pattern was related to early wheezing in any group. This was inconsistent with the previous literature [30]. We speculated that this may be related to the improvement in the current processing of formula-based milk.

Some studies have shown that the use of invasive mechanical ventilation was associated with wheezing in preterm infants [16]. Preterm infants, especially those with bronchopulmonary dysplasia, required respiratory support due to immature lung development in the early postnatal period. While the use of mechanical ventilation plays a role in respiratory support, it might cause lung injury, leading to wheezing in children with bronchopulmonary dysplasia [31]. It has been found that preterm infants with a GA< 28 weeks are exposed to oxygen during the first 3 days of life or have frequent episodes of hypoxemia, which increases the risk of wheezing in children [32]. Although the rates of invasive mechanical ventilation use among preterm infants with a GA ≤ 32 weeks and a GA >32 but < 37 weeks was higher than that among infants in the non-wheezing group in this study, but this difference was not statistically significant. The reason might be related to the small sample size of cases using invasive mechanical ventilation.

5 | Limitations

This was a retrospective study, and most of the included neonates lacked lung function data. The short follow-up and the small sample size are also limitations.

6 | Conclusion

New-borns with younger GAs had a higher risk of early wheezing. 2. The incidence of persistent early wheezing for preterm infants (GA ≤ 32 weeks and 32 weeks < GA < 37 weeks) was higher than that for full-term infants (37 weeks ≤ GA < 42 weeks). 3. SGA was a risk factor for early wheezing in preterm infants with a GA ≤ 32 weeks. 4. Male sex, personal history of allergies and family history of allergies were all possible factors affecting early wheezing in preterm infants with a GA > 32 weeks but < 37 weeks and full-term infants. Among them, male sex and family history of allergies were risk factors for early wheezing. 5. Mode of delivery, passive smoking, breastfeeding and invasive mechanical ventilation were not possible risk factors for early wheezing in infants of different GAs.

7 | Abbreviations

GA: Gestational age

SGA: Small-for-gestational-age

BW: Birth weight

AGA: Appropriate-for-gestational-age

GINA: Global Initiative for Asthma

Declarations

Ethical approval and consent to participate

This study was ethically approved by the Medical Ethics and Human Subject Committee of First Affiliated Hospital of Guangxi Medical University (ID: 2015(028)). All parents or legal guardians provided written informed consent for infants to participate in the study.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XC, MY and SH: contributed equally to the study, conceived and designed the study, collected clinical data, prepared an analytical plan, analyzed data, and drafted the initial manuscript. GN: contributed for the conception and design of the study, supervised the study, analysed and interpreted data, drafted the manuscript and critically revised it. XQ, ZP, MZ, DZ, YH, TL, CL: collected clinical data and reviewed and revised the manuscript. All authors: commented on the manuscript and approved the final manuscript as submitted.

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Tables

Table 1. Comparison of the incidence of early wheezing among each group.

Groups	Early wheezing	Normal	Total	Incidence of early wheezing (%)
Group A	37	100	137	27.0
Group B	92	460	552	16.7
Group C	60	867	927	6.5
Total	189	1427	1616	11.7
χ^2				68.795
P				0.000*

"*" indicate significant results with *P* value < 0.05.

Grouped by characters of age. Group A: gestational age (GA) ≤ 32 weeks; Group B: 32 weeks < GA < 37 weeks; Group C: 37 weeks < GA < 42 weeks.

Table 2. Comparison of the incidence of persistent early wheezing and transient early wheezing among each group.

Groups	Persistent early wheezing		Transient early wheezing		Total
	number	%	number	%	
Group A	17	12.4	20	14.6	137
Group B	62	11.2	30	5.4	552
Group C	10	1.1	50	5.4	927
Total	89	5.5	100	6.2	1616
χ^2	82.234		18.240		
P	0.000*		0.000*		

"*" indicate significant results with *P* value < 0.05.

Grouped by characters of age. Group A: gestational age (GA) ≤ 32 weeks; Group B: 32 weeks < GA < 37 weeks; Group C: 37 weeks < GA < 42 weeks.

Table 3. Univariate analysis for risk associated with early wheezing in preterm infants (GA ≤ 32 weeks).

Independent variable	Early wheezing (%)	Normal (%)	χ^2	*P*
Gender			0.169	0.681
Male	20（54.1）	58（58.0）		
Female	17（45.9）	42（42.0）		
Mode of delivery			1.861	0.175
Natural labor	17（45.9）	59（59.0）		
Cesarean section	20（54.1）	41（41.0）		
BW-GA			8.154	0.005*
SGA	12（32.4）	12（12.0）		
AGA	25（67.6）	88（88.0）		
Breast feeding (< 3 months)			0.078	0.781
Yes	25（67.6）	65（65.0）		
No	12（32.4）	35（35.0）		
Personal history of allergy			2.897	0.091
Yes	16（43.2）	28（28.0）		
No	21（56.8）	72（72.0）		
Family history of allergy			1.248	0.266
Yes	8（21.6）	16（16.0）		
No	29（78.4）	84（84.0）		
Invasive mechanical ventilation			3.399	0.067
Yes	25（67.6）	50（50.0）		
No	12（32.4）	50（50.0）		
Passive smoking			0.200	0.656
Yes	21（56.8）	61（61.0）		
No	16（43.2）	39（39.0）		

"*" indicate significant results with *P* value < 0.05.

BW: birth weight, GA: gestational age, BW-GA: the relationship between BW and GA, SGA: small-for-gestational-age, AGA: appropriate-for-gestational age

Table 4. Univariate analysis for risk associated with early wheezing in preterm infants (32 weeks < GA < 37 weeks).

Independent variable	Early wheezing (%)	Normal (%)	χ^2	*P*
Gender			17.686	0.000*
Male	70（76.1）	242（52.6）		
Female	22（23.9）	218（47.4）		
Mode of delivery			0.254	0.615
Natural labor	35（38.0）	188（40.9）		
Cesarean section	57（62.0）	272（59.1）		
BW (< 2.5kg)			0.002	0.969
Yes	56（60.9）	279（60.7）		
No	36（39.1）	181（39.3）		
Breast feeding (< 3 months)			0.071	0.790
Yes	46（50.0）	237（51.5）		
No	46（50.0）	223（48.5）		
Personal history of allergy			7.350	0.007*
Yes	47（51.1）	166（36.1）		
No	45（48.9）	294（63.9）		
Family history of allergy			12.797	0.000*
Yes	33（35.9）	88（19.1）		
No	59（64.1）	372（80.9）		
Invasive mechanical ventilation			0.443	0.506
Yes	5（5.4）	18（3.9）		
No	87（94.6）	442（96.1）		
Passive smoking			0.000	1.000
Yes	48（52.2）	240（52.2）		
No	44（47.8）	220（47.8）		

'*' indicate significant results with *P* value < 0.05.

GA: gestational age, BW: birth weight

Table 5. Univariate analysis for risk associated with early wheezing in preterm infants (37 weeks ≤ GA < 42 weeks).

Independent variable	Early wheezing (%)	Normal (%)	χ^2	*P*
Gender			8.486	0.004*
Male	47（78.3）	515（59.4）		
Female	13（21.7）	352（40.6）		
Mode of delivery			0.123	0.726
Natural labor	41（68.3）	611（70.5）		
Cesarean section	19（31.7）	256（29.5）		
BW (< 2.5kg)			0.304	0.581
Yes	1（1.7）	25（2.9）		
No	59（98.3）	842（97.1）		
Breast feeding (< 3 months)			1.046	0.307
Yes	31（51.7）	389（44.9）		
No	29（48.3）	478（55.1）		
Personal history of allergy			3.949	0.047*
Yes	23（38.3）	230（26.5）		
No	37（61.7）	637（73.5）		
Family history of allergy			6.126	0.014*
Yes	18（30.0）	150（17.3）		
No	42（70.0）	717（82.7）		
Passive smoking			0.477	0.490
Yes	29（48.3）	459（52.9）		
No	31（51.7）	408（47.1）		

"*" indicate significant results with *P* value < 0.05.

GA: gestational age, BW: birth weight

Supplementary Files

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- Additionalfile1.doc
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