

# Perinatal Predictors of Wheezing in the First Year of Life a Prospective Study in the South of Brazil

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## Research Article

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# Abstract

**Introduction:** Prematurity has been associated with the occurrence of respiratory symptoms throughout childhood, such as bronchiolitis and pneumonia. The identification of factors related to respiratory morbidity in childhood has direct implications for management and prevention.

**Objective:** Evaluate the perinatal factors associated with wheezing in the first year of life in a prospective cohort of premature babies at a referral maternity hospital in southern Brazil.

**Methods:** This is a prospective cohort of premature babies, less than 37 weeks of gestational age (defined by the Capurro Method or by ultrasound), and non-premature babies. The sample was non-probabilistic and defined by the ability to schedule follow-up appointments at the pulmonology outpatient clinic. The incidence rate for the occurrence of wheezing in the first year was estimated among full-term, premature, and extremely premature babies and adjusted for 1000 babies / year.

**Results:** The number of newborns considered in the final analysis was 138 children (64 premature babies and 74 term babies). Regarding the general characteristics of the mothers, there was a predominance of low education (65.9%), of white ethnicity (79.7%), with an average age of 26 years. During the first year of life, 91 children (65.9%) visited the emergency room and 43 (31.2%) had at least one episode of wheezing. The occurrence of wheezing was 42.6% in male children ( $p = 0.010$ ). There was a higher percentage of wheezing episodes (35.9%) in preterm infants, especially those younger than 33 weeks (45%); however, this result was not statistically significant ( $p 0.260$ ). In the multivariate analysis, only the male gender remained associated with the occurrence of wheezing in the first year of life (HR 2.24; 95% CI 1.19-4.21;  $p 0.012$ ).

**Conclusions:** In this follow-up study, the occurrence of wheezing in preterm infants in the first year of life was high, with twin pregnancy as the main risk factors, the male gender and the use of mechanical ventilation

## Introduction

Prematurity has been associated with the occurrence of respiratory symptoms throughout childhood, such as bronchiolitis and pneumonia (1, 2) In addition, a large number of unscheduled visits to the emergency room and hospital admissions (3) have been associated with respiratory causes, resulting in higher economic and family costs (4). Use of invasive mechanical ventilation, duration of oxygen use, congenital heart disease, neonatal sepsis and absence of breastfeeding have often been associated with wheezing after birth (5–8). In the first two years of life, prematurity represents an important risk factor for hospitalizations for respiratory reasons and admissions to intensive care units (9, 10). However, some other maternal and perinatal factors, such as time of mechanical ventilation of the newborn, maternal education, twinning and neonatal sepsis, have not been fully explored in prospective studies of premature infants in southern Brazil.

The identification of factors related to respiratory morbidity in childhood has direct implications for management and prevention. The International Study of Wheezing in Infants (EISL) initiative sought to retrospectively detect the occurrence of wheezing in the first year of life and estimated a high association between wheezing and viral infection, mainly by the respiratory syncytial virus (RSV) (11). More recently, genetic profiles have been identified with an increased predisposition to early wheezing (12), as well as biomarkers related to the development of bronchopulmonary dysplasia (13) and parameters of neonatal lung function associated with greater respiratory morbidity in the first year of life (14). In addition, exclusive breastfeeding longer than 90 days has been described as a protector for respiratory events in the first years of life (15).

In Brazil, prospective studies on premature infants in the first year of life are scarce with an emphasis on the occurrence of wheezing, respiratory admissions and outpatient follow-up of these patients. Nunes et al. in a hospital-based study, they found almost 39% of preterm infants who were admitted to a neonatal ICU and needed to be readmitted after being discharged during the first year, with two-thirds due to respiratory problems (16). In another national study, more than 50% of premature babies had respiratory morbidity during the first year after discharge, with a high percentage of pneumonia and hospitalization (5).

The present study aimed to evaluate the perinatal factors associated with wheezing in the first year of life in a prospective cohort of premature babies at a referral maternity hospital in southern Brazil. The secondary objective was to assess the respiratory morbidity of preterm infants from different gestational age groups.

## **Methodology**

### **Design and Sampling**

This is a prospective cohort of premature babies, less than 37 weeks of gestational age (defined by the Capurro Method or by ultrasound), and non-premature babies born in the period June to August 2018 in a high-risk tertiary maternity hospital in Joinville, Santa Catarina. Maternity XXX is a reference for high-risk pregnant women attended by SUS in Joinville (population estimated at 600 000 habitants in 2020 according to IBGE). The maternity hospital has xx neonatal ICU beds, a medical residency service in pediatrics and neonatology, and approximately 7200 deliveries per year. The sample was non-probabilistic and defined by the ability to schedule follow-up appointments at the pulmonology outpatient clinic. All premature babies born in the mentioned period of inclusion were selected for inclusion in the study, as well as a non-premature baby born on the same day in the same maternity and selected randomly, by simple drawing. The follow-up time was up to one year through routine outpatient consultations (minimum of 1 consultation). The study was approved by the Ethics Committee of the Regional Hospital Hans Dieter Schmidt, with the number of opinions 2,438,754, on 12/14/2017. Informed consent terms were applied to those responsible for each research subject.

## Collected variables and outcomes.

The maternal variables considered were age, race, education, marital status and family income. The variables related to peripartum were history of maternal smoking during pregnancy, consumption of alcohol or illicit drugs, presence of comorbidities (hypertension, diabetes), presence of pre-eclampsia, hemorrhage, gestational diabetes, use of antenatal corticosteroids, previous prematurity, via delivery, premature rupture of membranes, all due to the mother's self-report. The variables related to birth were sex, weight, height, gestational age, APGAR scale. The variables related to care in the neonatal ICU were considered the presence of hyaline membrane, use of surfactant, diagnosis of early and late sepsis, diagnosis of heart disease, use of enteral diet, age of full diet, age of weight recovered, use and duration of invasive and non-invasive ventilatory support, duration of oxygen use, presence of retinopathy, leukomalacia and ventricular hemorrhage. The variables related to birth and ICU care were based on the medical record. The baby's wheezing report by the mother and diagnosed by a doctor at any time after hospital discharge was the main outcome studied. Other outcomes were considered, such as unscheduled visits to the emergency room, use of oral corticosteroids, hospital admissions and ICU admissions.

## Statistical analysis

Qualitative variables were described by their absolute frequencies and percentage. Quantitative variables were presented by their means and standard deviation or median and interquartile range. For comparison between babies with and without wheezing, the T-student or Mann-Whitney test was used for quantitative variables and the chi square test for qualitative variables. The incidence rate for the occurrence of wheezing in the first year was estimated among full-term, premature, and extremely premature babies and adjusted for 1000 babies / year. The Wald test was used to compare the trend of changes in incidence rates by categories of gestational age. The occurrence of wheezing in the first year between premature and non-premature babies is presented through a Kaplan-Meier survival curve and its difference assessed using the Log Rank test. The variables studied were evaluated in a univariate manner by the Cox Regression method to predict the occurrence of wheezing. All variables with a p-value < 0.10 were considered in the multivariate model. The data obtained were analyzed using the Statistical Package for the Social Sciences, Version 18.0 software (SPSS Inc., Chicago, IL, USA).

## Results

The initial sample consisted of 188 children (83 premature and 105 at term). Fifty newborns did not return for post-discharge follow-up visits (27%). There was no difference between children without follow-up in relation to the final sample. The number of newborns considered in the final analysis was 138 children (64 premature babies and 74 term babies). The average follow-up time was 247 days. The average number of consultations was 2.5. There was a predominance of mothers with low education (65.9%), of white ethnicity (79.7%), with an average age of 26 years. Seventy-nine mothers (59%) had an income below 2 minimum wages and 105 (75%) had a stable union. Only 14 (10.1%) reported smoking

during pregnancy. On average, newborns were 36.5 weeks of gestational age and 2763 grams at birth. During the first year of life, 91 children (65.9%) visited the emergency room and 43 (31.2%) had at least one episode of wheezing. The other demographic and clinical characteristics of the sample are described in Table 1

With regard to maternal variables, twin pregnancy was associated with wheezing episodes in the first year of life (Table 2). The occurrence of wheezing was 42.6% in male children ( $p = 0.010$ ) (Table 3). There was a higher percentage of wheezing episodes (35.9%) in preterm infants, especially those younger than 33 weeks (45%); however, this result was not statistically significant ( $p = 0.260$ ).

The presence of early sepsis was 57.7% in babies who wheezed, with a significant association ( $p = 0.001$ ). The use of invasive mechanical ventilation was also associated with wheezing in 50% of babies being followed up in the first year of life ( $p = 0.019$ ). (Table 4).

Regarding outpatient follow-up, patients with wheezing episodes had more use of oral corticosteroids and bronchodilators ( $p < 0.01$ ). In addition, they had a higher number of visits to the emergency room, hospital admissions for respiratory causes ( $p = 0.01$ ) and hospitalizations in intensive care units ( $p < 0.01$ ). (Table 5).

The incidence of wheezing varied according to the gestational age; in extreme premature infants it presented a rate of 67 cases / child-years per 100 children (95% CI 35–129), for premature infants between 34 to 36 weeks the rate was 44 cases / child-years per 100 children (95% CI 26–75) and among newborns aged 37 to 44 weeks of 41 cases / child-years per 100 children (95% CI 26–64). The ratio of incidence rates to a trend of difference between the gestational age ranges was 0.79 (95% CI 0.52–1.20,  $p = 0.275$ , Fig. 1).

In the univariate analysis, the increase in gestational age showed a tendency to protect against wheezing (OR = 0.94, 95% CI 0.87–1.01;  $p = 0.082$ ). Male newborns, the presence of multiple pregnancies, early sepsis and use of enteral diet after birth were risk factors for wheezing (Table 6). In the multivariate analysis, only the male gender remained associated with the occurrence of wheezing in the first year of life (HR 2.24; 95% CI 1.19–4.21;  $p = 0.012$ ).

## Discussion

In this study, we determined the high incidence of respiratory events in premature patients in the first year of life, in a prospective cohort, compared to full-term babies. Among the risk factors surveyed, the male gender, the presence of early sepsis and the use of enteral diet were associated with episodes of wheezing in the first year. In the multivariate analysis, both male gender and use of enteral diet were independent predictors for the occurrence of wheezing in the sample studied.

In a previous study in Latin America, Mallol demonstrated that recurrent wheezing occurs in 1.6 out of 10 children, with a significant variation in severity and prevalence, with a high association with viral episodes

(3). In a prospective study, Blanken (1) evaluated 3952 children and identified the frequency of day care and hospitalization for bronchiolitis as factors associated with recurrent wheezing. In our study, the age of admission to the day care center was late (median 7 months) and was not related to a greater number of wheezing episodes. Simões, in a retrospective study, identified a positive association between family history of atopy, low gestational age and living with two or more children as risk factors for recurrent wheezing (17). Low gestational age was associated with a higher incidence of wheezing events in our study, with decreasing incidence rates as the gestational age increases.

The use of mechanical ventilation was significantly associated with wheezing episodes in our cohort. The definition of bronchopulmonary dysplasia (BPD) is based on the need for supplemental oxygen at 36 weeks of corrected gestational age and the time of use of invasive mechanical ventilation (13, 18). Other risk factors are associated with the development of BPD, such as maternal smoking, fluid overload, genetic predisposition (19), persistent arterial duct, delayed sepsis, premature rupture of membranes and male sex (9).

The history of early neonatal sepsis was also associated with episodes of wheezing in the segment of these patients. Dessardo described in a previous study a pro-inflammatory fetal environment (FIRS), with respiratory implications in premature infants, including repercussions up to the age group of 10 years (20). Jones highlighted the association between the inflammatory environment among female babies, chorioamnionitis and the development of chronic childhood lung disease (21).

Our study also demonstrated an important impact on admissions to pediatric ICUs for respiratory causes in this group, as well as high use of medications such as oral corticosteroids and bronchodilators.

Our study has some limitations. First, of the total number of children eligible for birth, there was a loss of follow-up in both the premature and control groups (23% and 30%, respectively). In the analysis of this subgroup without follow-up, no significant maternal or perinatal characteristics were found in relation to the group that completed the follow-up. However, high-cost prospective cohort studies are more scarce in developing countries. The adoption of prospective follow-up at a single center also does not allow the main results to be directly extrapolated. Even so, the follow-up time of 1 year, with at least three face-to-face consultations, provided greater data accuracy, reducing potential memory biases of those responsible for the children.

## Conclusions

In this follow-up study, the occurrence of wheezing in preterm infants in the first year of life was high, with twin pregnancy as the main risk factors, the male gender and the use of mechanical ventilation. Outpatient follow-up also showed significant respiratory morbidity, with the use of medications in large proportions and hospitalizations in intensive care units. Special attention to multiple pregnancies, more gentle management of ventilatory support and outpatient follow-up with an emphasis on respiratory care can help to minimize the impact of this condition in early childhood in our country.

# Declarations

## Ethics approval

This research was approved by the Research Ethics Committee of the Hans Dieter Schmidt Regional Hospital, an agency linked to CONEP. The number of the approval opinion was 2.438.754, in 14 december 2017.

## Consent for publication

Consent for data publication was obtained through approval with CONEP.

## Availability of data and materials

Not applicable

## Competing interests

Not applicable

## Author's contribution

The authors contributed to the project design, data collection and analysis, as well as corrections for submissions in scientific journals.

## Acknowledgements

Not applicable

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## Tables

Table 1  
Clinical and demographic characteristics

	<b>N</b>	<b>%</b>
Low maternal education	91	65.9
White Ethnicity	110	79.7
Family Income < 2 minimum wages	79	59.2
Suitable for gestational age	105	76.1
Exclusive breastfeeding > 90 days	71	63.4
Episode of wheezing in the 1st year of life	43	31.2
Visit to the emergency room.	91	65.9
Use of oral corticosteroids.	25	18.1
Use of bronchodilators	40	29
Respiratory cause admission	18	13
PICU admission due to wheezing	7	5
	<b>Median</b>	<b>IQR</b>
Maternal age (years)	26	20–31
Gestational Age (weeks)	36.5	35–39
Birth weight (grams)	2763	2255–3420
Breastfeeding time (days)	112	60–170
Age of first wheezing (days)	240.3	184–299
Age of admission to daycare (months)	7	6–8

Table 2  
Maternal characteristics related to wheezing.

	Sibilância			<i>p</i>
	Presente	Ausente	Total (%)	
Mother age, years; mean (SD)				
Ethnia, n (%)				0,134
White	31(28,2)	79(71,8)	110(100)	
Non-White	12(42,9)	16(57,1)	28(100)	
Education, n (%)				0,523
≤ 8 Years	13(27,7)	34(72,3)	47(100)	
> 8 Years	30(33,0)	61(67,0)	91(100)	
Marital status, n (%)				0,146
Married / Stable Union	29(27,9)	75(72,1)	104(100)	
Non-Married / Stable Union	14(41,2)	20(58,8)	34(100)	
Income, n (%)				0,948
≤ 2 mw	24(30,4)	55(69,6)	79(100)	
> 2 mw	17(30,9)	38(68,1)	55(100)	
Gestational Smoking				0,825
Yes	4(28,6)	10(71,4)	14(100)	
No	39(31,4)	85(68,6)	124(100)	
Hypertension				0,865
Yes	4(33,3)	8(66,7)	12(100)	
No	39(30,9)	87(69,1)	126(100)	
Hypertensive disease specific to pregnancy				0,119
Yes	3(15,8)	16(84,2)	19(100)	
No	40(33,6)	79(66,4)	119(100)	
Multiple Gestation				0,013
Yes	11(55)	9(45)	20(100)	
No	32(27,1)	86(72,9)	118(100)	

	Sibilância			<i>p</i>
	Presente	Ausente	Total (%)	
Previous premature				0,220
Yes	6(46,1)	7(53,8)	13(100)	
No	37(29,6)	88(70,4)	125(100)	

Table 3  
Newborn variables related to wheezing (n = 138)

	Wheezing			<i>p</i>
	Yes n (%)	No n (%)	Total n (%)	
Genre				0,010
Feminine	17(22,1)	60(77,9)	77(100)	
Masculine	26(42,6)	35(57,4)	61(100)	
Weight, grams; median (IQR)	2650 (1885/3430)	3020 (2335/3420)		0,148
Premature, < 37 weeks				0,260
Yes	23(35,9)	41(64,1)	64(100)	
No	20(27,0)	54(73,0)	74(100)	
Gestational Age				0,304
24 a 33 weeks	9(45,0)	11(55,0)	20(100)	
34 a 36 weeks	14(31,8)	30(68,2)	44(100)	
37 a 42 weeks	54(73,0)	20(27,0)	74(100)	
Delivery Way				0,906
Vaginal	24(31,6)	52(68,4)	76(100)	
Caesarean	19(30,6)	43(69,3)	62(100)	

Table 4  
Neonatal management variables related to wheezing.

	Wheezing			<i>p</i>
	Yes	No	Total (%)	
Early Sepsis				0,001
Yes	15(57,7)	11(42,3)	26(100)	
No	28(25,0)	84(75,0)	112(100)	
Enteral Diet				0,003
Yes	18(51,4)	17(48,6)	35(100)	
No	25(24,3)	78(75,7)	103(100)	
NIV use (n = 136)				0,095
Yes	13(43,3)	17(56,7)	30(100)	
No	29(27,4)	77(72,6)		
MV use (n = 136)				0,019
Yes	13(50,0)	13(50,0)	26(100)	
No	29(26,4)	81(73,6)	110(100)	
VM time, days; median (IQR)	4(3/12)	7(3/14)		0,738
NIV time, days; median (IQR)	4(1/11)	2(2/4)		0,550

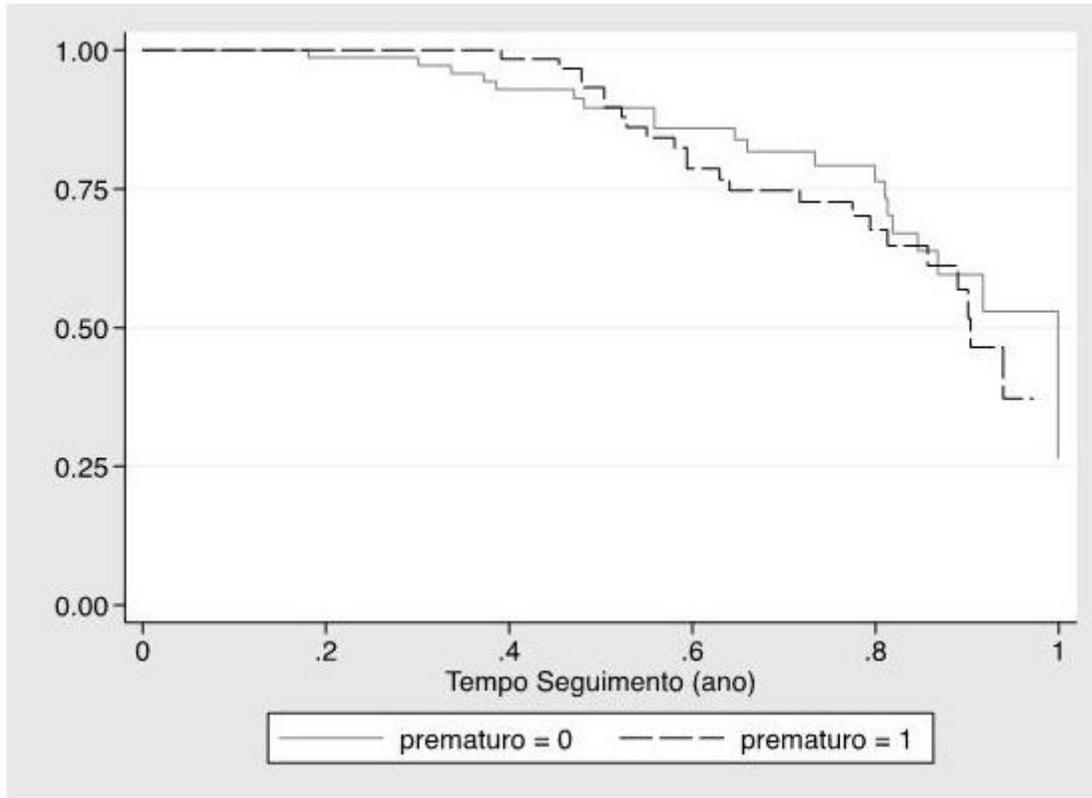
Table 5  
Outpatient follow-up variables related to wheezing.

	Wheezing			<i>p</i>
	Yes	No	Total (%)	
Daycare admission				0,140
Yes	6(50)	6(50)	12(100)	
No	37(29,4)	89(70,6)	126(100)	
Exclusive breastfeeding				0,372
Yes	33(29,5)	79(70,5)	112(100)	
No	10(38,5)	16(61,5)	26(100)	
Breastfeeding > 90 days, n (%) (n = 112)				0,409
Yes	19(26,8)	52(73,2)	71(100)	
No	14(26,8)	27(65,8)	41(100)	
Use of Oral Corticosteroids				< 0,001
Yes	22(88)	3(12)	25(100)	
No	21(18,6)	92(81,4)	113(100)	
Use of Bronchodilator				< 0,001
Yes	35(87,5)	5(12,5)	40(100)	
No	8(8,2)	90(91,8)	98(100)	
Post-discharge PICU admission				0,001
Yes	6(85,7)	1(14,3)	7(100)	
No	37(28,2)	94(71,8)	131(100)	
First Aid Service				< 0,001
Yes	41(45)	50(55)	91(100)	
No	2(4,3)	45(95,7)	47(100)	
Respiratory Cause admission				< 0,001
Yes	16(88,9)	2(11,1)	18(100)	
No	27(22,5)	93(77,5)	120(100)	

Table 6  
Predictors for Wheezing Occurrence (Univariate and Multivariate Analysis)

Variável	HR	95% CI	Valor p	HR	95% CI	Valor p
Mother's age (per year of increase)	0,99	0,94 - 1,03	0,558			
Mother Education (> = 8 years x < 8 years)	0,84	0,43 - 1,63	0,617			
Birth weight (per unit of increase)	1,00	1,00 - 1,00	0,131			
Gestational age (per unit of increase)	0,93	0,87-1.01	0,082	1,01	0,90 - 1,13	0,882
Newborn Sex (men x women)	2,11	1,13 - 3,94	0,019	2,11	1,12 - 3,98	0,021
Multiple Gestation (yes x no)	2,06	1,03-4,14	0,041	1,93	0,68 - 5,48	0,218
Premature Previous (yes X no)	1,31	0,54 - 3,15	0,549			
Ruprema (yes x no)	1,37	0,65 - 2,86	0,401			
Early sepsis (yes x no)	2,37	1,26 - 4,46	0,008	1,26	0,29 - 5,42	0,754
Daycare (yes x no)	1,24	0,52 - 3,00	0,627			
Ethnicity (white vs. non-white)	0,58	0,30 - 1,14	0,115			
Income (> 2mw x < 2mw)	1,03	0,55 - 1,93	0,927			
Smoking (yes x no)	0,76	0,27 - 2,18	0,617			
DHEG (yes x no)	0,42	0,13 - 1,36	0,147			
Gestational diabetes (yes x no)	0,86	0,12 - 6,29	0,884			
Antenatal corticosteroids (yes x no)	1,10	0,56 - 2,16	0,771			
Childbirth type (cesarean x vaginal)	0,76	0,42 - 1,40	0,385			
Hyaline Membrane (yes x no)	0,88	0,35 - 2,25	0,794			
MV use	1,82	0,94 - 3,52	0,075	0,37	0,09 - 1,59	0,183
Enteral diet (yes x no)	2,33	1,26 - 4,31	0,007	3,51	1,11-11,12	0,033
Exclusive breastfeeding (yes x no)	0,61	0,30 - 1,24	0,170			

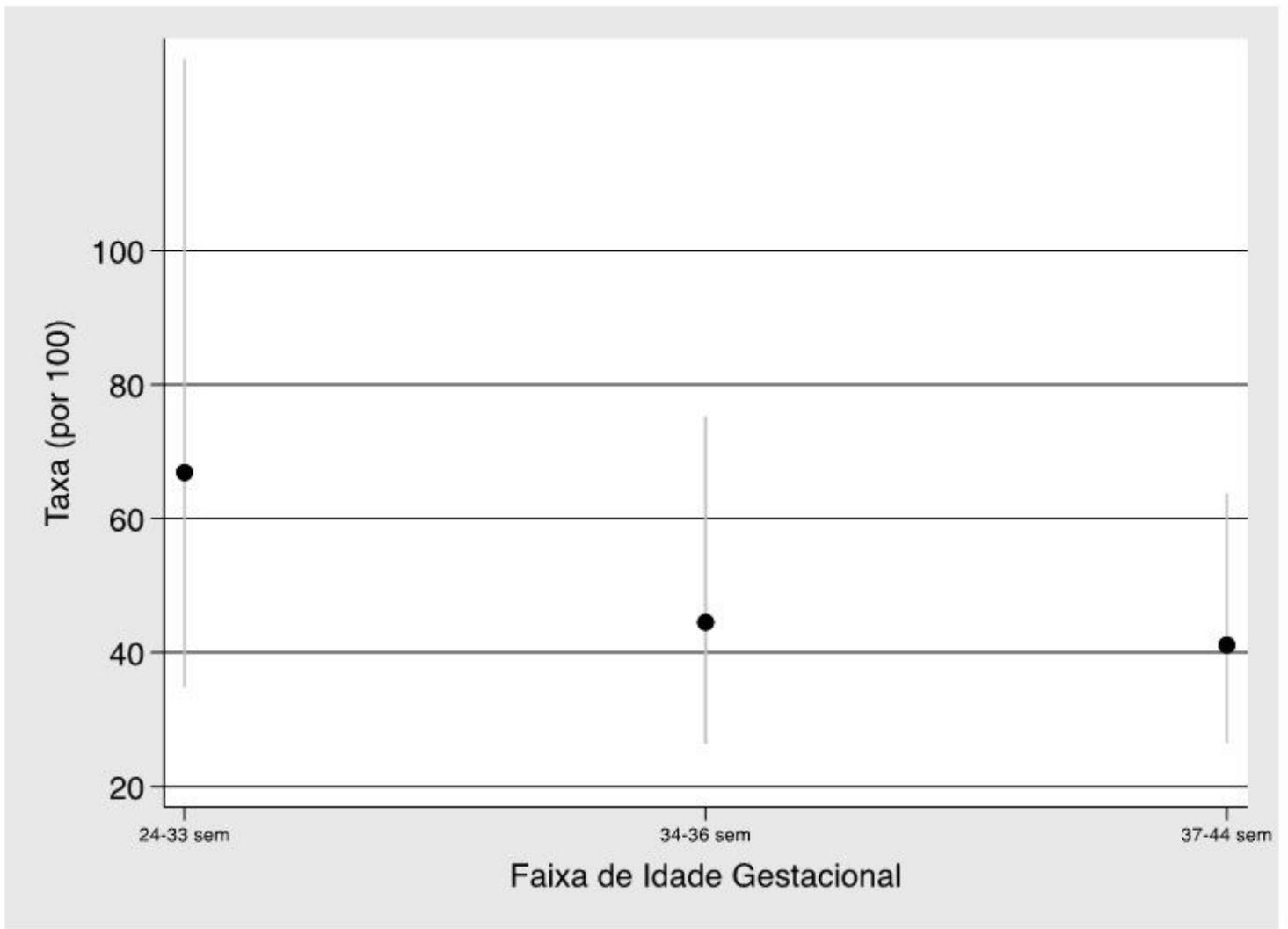
# Figures



**Figure 1**

Wheezing Occurrence Curve Between Premature and Non-Premature (Kaplan-Meier).

Log Rank Test,  $p=0,464$ .



**Figure 2**

Wheezing Incidence Rate by Gestational Age Range (per 100 babies)

RR=0,79 (95% CI 0,52-1,20; p=0,275), Wald Test.