Neonatal ventilatory support and respiratory diseases in children up to six years of age: the 2004 Pelotas (Brazil) Birth Cohort study

Suporte ventilatório ao nascer e associação com doenças respiratórias aos seis anos: Coorte de Nascimentos de Pelotas, Rio Grande do Sul, Brasil, 2004

Soporte ventilatorio en el período neonatal y enfermedades respiratorias en los seis primeros años de vida: Cohorte de Nacimientos de Pelotas, Rio Grande do Sul, Brasil, 2004

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Abstract

The study's objective was to evaluate the association between neonatal ventilatory support and the subsequent occurrence of respiratory diseases in children up to six years of age. This was a population-based birth cohort study. The main exposure was ventilatory support at birth, defined as the use of nasal continuous positive airway pressure (NCPAP) and/or mechanical ventilation (MV) for more than three hours from the time of hospitalization at birth until the first 28 days of life. Outcomes were: chest wheezing in the twelve months prior to the follow-up interview, medical diagnosis of asthma any time in the child´s life, and occurrence of pneumonia up to six years of age. Crude and adjusted analyses for potential confounding variables were performed using Poisson regression. 3,624 children were analyzed. NCPAP plus MV or MV alone was associated with higher frequency of medical diagnosis of asthma, even after adjusting for maternal and child characteristics (PR = 2.24; 95%CI: 1.27-3.99). The results highlight medium-term respiratory complications associated with neonatal ventilatory support.

Interactive Ventilatory Support; Pneumonia; Asthma; Child Health

Resumo

O objetivo do estudo foi avaliar a associação entre suporte ventilatório no período neonatal e doenças respiratórias até os seis anos de idade. Estudo de coorte de nascimentos de base populacional. A exposição principal foi o suporte ventilatório ao nascimento, definido como o uso de pressão contínua positiva nasal (CPAPn) e/ou ventilação mecânica (VM) por mais de três horas, desde o momento da hospitalização ao nascimento até os 28 dias. Os desfechos foram chiado no peito nos últimos 12 meses, diagnóstico médico de asma alguma vez na vida e episódio de pneumonia ocorrido até os seis anos de idade. Foram realizadas análises brutas e ajustadas para potenciais variáveis de confusão, usando regressão de Poisson. Foram analisadas 3.624 crianças. O uso de CPAPn e VM ou unicamente VM esteve associado com maior frequência de diagnóstico médico de asma, mesmo após ajuste para características maternas e das crianças (RP = 2,24; IC95%: 1,27-3,99). Os resultados do presente estudo alertam para as complicações respiratórias, em médio prazo, decorrentes do suporte ventilatório realizado no período neonatal.

Suporte Ventilatório Interativo; Pneumonia; Asma; Saúde da Criança

Introduction

While infant mortality has decreased in the world, due mainly to a constant decline in post-neonatal mortality, neonatal mortality has become the most important component of infant mortality [1]. In Brazil, prematurity is the leading cause of neonatal death and 70% of the deaths on the first day of life [2,3]. Studies in recent decades have shown an improvement in survival rates of preterm newborns [4,5,6]. The Brazilian Network for Neonatal Research reported improved survival in extremely preterm newborns and those with very low birth weight (< 1,500g) in the year 2012, compared to the results in 2008. As an example, the survival of newborns in the 400-499g weight range, nearly non-existent in 2008, increased to 7.4% in 2012, and the survival of newborns with birth weight in the 1,250-1,499g range was 94.3% in 2012 [7].

In addition to its contribution to mortality, prematurity is responsible for the high morbidity in survivors, due to acute and long-term complications, with important physical and intellectual sequelae [8,9,10]. From the respiratory point of view, due to their immature lungs, premature newborns frequently present respiratory distress syndrome, apnea, and infection, requiring prolonged oxygen therapy and/or ventilatory support.

The combination of ventilatory support and prolonged oxygen use in the neonatal period, especially in premature newborns with gestational age less than 30 weeks, is related to the appearance of bronchopulmonary dysplasia [11,12]. Various studies have also found that premature newborns that received mechanical ventilation (MV) during the neonatal period showed greater risk of developing respiratory diseases like asthma and pneumonia in early childhood when compared to those that did not receive MV [13,14,15,16,17]. Neonatal MV was also associated with altered pulmonary function (spirometry) at 8-9 years [18], as well as increased odds of asthma during childhood and adulthood [19,20,21].

Although the literature includes studies in countries like the United Kingdom and United States on the mid and long-term consequences of neonatal ventilatory support, there are still few findings on these problems in children from middle and low-income countries. The main objective of the current study was to assess the association between neonatal ventilatory support and respiratory diseases at six years of age in children from the 2004 Pelotas (Rio Grande do Sul State, Brazil) Birth Cohort study.

Methods

Data source

In 2004, a birth cohort study was launched in Pelotas with an estimated population of 340,000. The majority of the residents lived in the urban area (93%), and the city had five maternity hospitals and two neonatal intensive care units (ICU). There were 4,263 live births during the year in mothers that resided in the city, 4,231 of which were included in the study (0.8% losses). Less than 1% of the deliveries occurred outside the hospital.

The newborns were examined at the maternity hospital immediately after birth. The mothers answered a questionnaire after the delivery, with socioeconomic information on the family, prenatal care, and use of healthcare services. Children in the cohort were followed up for a mean (standard deviation) at 3.0 (0.1), 11.9 (0.2), 23.9 (0.4), 49.5 (1.7), and 82.2 (4.0) months of life. The numbers of children identified at these ages (including children that had died and were identified as belonging to the cohort) were 3,985, 3,907, 3,869, 3,799, and 3,722, respectively, with response rates ranging from 90 to 96%. Figure 1 shows the flow chart for the 2004 cohort, highlighting the deaths, refusals, and losses over the course of the study. All follow-up visits were conducted at the homes, except for the last visit, which was held at a clinic especially organized for this purpose. Detailed information on the methodology of the 2004 Pelotas Birth Cohort study has been published elsewhere [22].

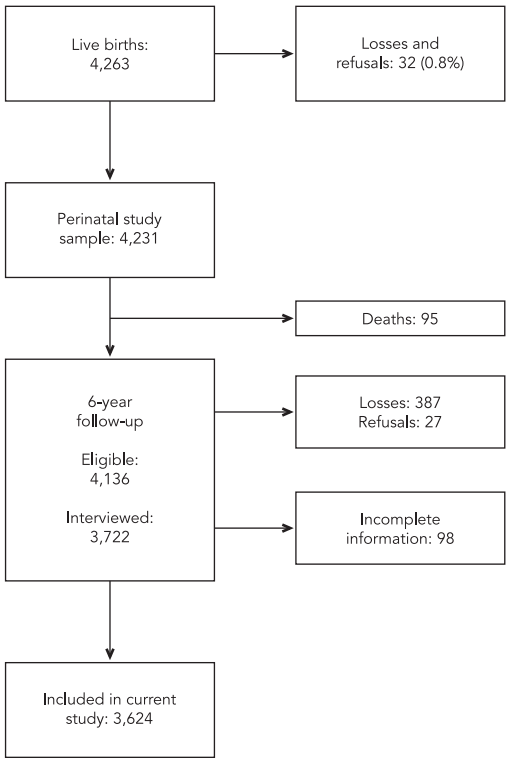
Outcomes

The study outcomes were chest wheezing in the previous twelve months (between five and six years of age), lifetime history of medical diagnosis of asthma, and episode of pneumonia between hospital discharge after birth and six years of age.

The variable "chest wheezing in the last twelve months" was defined according to the ISAAC questionnaire (*International Study of Allergy and Asthma in Childhood*) [23,24], collected at the six-year follow-up with the following question: "*did <child's name> have chest wheezing in the last twelve months*?" For medical diagnosis of asthma, the mother or person accompanying the child at the six-year follow-up was asked: "*did a doctor ever say that <child's name> had asthma*?" Pneumonia as the outcome variable was assessed at each follow-up, with the following question: "*has <child's name> ever had* pontada *or pneumonia?"* For this outcome, the term "pontada"

Figure 1

Flow chart for 2004 Pelotas (Brazil) Birth Cohort study.



(a local lay term) was considered synonymous with "pneumonia".

Principal exposure

The principal exposure variable was neonatal ventilatory support, as recorded on the hospital patient chart. Ventilatory support was defined as the use of nasal continuous positive airway pressure (NCPAP) and/or MV for more than three hours from the moment of hospitalization at birth up to 28 days of life. This variable was categorized as "use of NCPAP alone", "NCPAP plus MV or MV alone", and "no ventilatory support".

Potential confounding variables

- **Maternal variables**

a) Socioeconomic and demographic characteristics

Family income in the month prior to the child's birth was recorded in *Reais* and standardized in multiples of the prevailing minimum wage. Maternal schooling (complete years of formal education), marital status, parity, and maternal skin color (classified according to the interviewer's observation) were recorded at the time of delivery.

b) Characteristics of the index pregnancy

Mothers were asked when the last prenatal visit had occurred. Smoking during the pregnancy was based on the woman's own report, and smoking was defined as at least one cigarette per day dur-

ing any trimester of the pregnancy. Mothers were asked if they had had a urinary tract infection during the pregnancy. Prenatal steroid use was also investigated. Type of delivery was classified as vaginal (induced or not) or cesarean.

- **Infant's variables**

a) Information collected at birth

Gestational age of the newborns was assessed by date of last menstruation recorded on the mother's prenatal card or reported by her (in this order of priority); when the date was unknown or inconsistent, it was assessed by ultrasound prior to 20 weeks of gestation; and when the mother did not have an ultrasound report, the Dubowitz method was used, performed in the majority of the newborns.

Birth weight was measured with an electronic pediatric scale, accurate to 10g. Information was recorded on twin births, sex, and five-minute Apgar score, performed by the pediatrician or other health professional attending the newborn.

Statistical analysis

The descriptive analyses included calculation of frequency distributions for outcomes and categorical exposures. Dichotomous outcomes were related to categorical exposure variables using contingency tables, and prevalence ratios with respective 95% confidence intervals (95%CI) were estimated. Statistical tests were based on the chi-square test.

The multivariate analyses used Poisson regression with robust variance, with results expressed as prevalence ratios (PR) and their respective 95%CI. The multivariate analysis only included potential confounding factors for the association between neonatal ventilatory support and each of the three target outcomes. Confounding variables were defined as those that presented an association with the principal exposure and the outcome (for example, chest wheezing) with p-value < 0.20 and without participating in the causal chain between the exposure and outcome. We analyzed which exposure variables might act as confounding factors for each of the target associations. All the analyses used Stata 12.1 (Stata Corp., College Station, USA).

Ethical issues

The protocols for all the follow-up visits in the 2004 Pelotas Birth Cohort study were approved by the Ethics Research Committee at the School of Medicine, Federal University of Pelotas. The protocol for the current study was also approved by the Ethics Research Committees at the School of Medicine and the respective committees at the São Francisco de Paula University Hospital (Catholic University of Pelotas) and the Academic Hospital (Federal University of Pelotas).

Results

Of the 4,231 children participating in the 2004 Pelotas Birth Cohort study, 254 (6%) were admitted at birth to neonatal ICU, and of these, 121 (47.6 %) required ventilatory support at birth. Of the 254 children admitted to the neonatal ICU, 37 (14.6%) died during the neonatal period, 8 (3.1%) in the post-neonatal period, and 4 (1.6%) between one and six years of age. Of the children not admitted to the neonatal ICU at birth, 10 (0.3%) died during the neonatal period, 22 (0.6%) in the post-neonatal period, and 14 (0.3%) between one and six years of age. The current study analyzed 3,624 children (85.7% of the original cohort) with information available on the study outcomes.

After excluding the 95 children that died during the first 6 years of follow-up of the 2004 Pelotas Birth Cohort, the 3,624 children included in the current study were compared to the 512 children for whom the study outcomes were not available (387 losses, 27 refusals, and 98 children with incomplete information). Loss of information for the study outcomes was more frequent in children of mothers with more previous children (Table 1).

Of the 3,624 children included in the study, 3,553 (98%) did not receive ventilatory support at birth, 32 (0.9%) received only NCPAP, and 39 (1.1%) received NCPAP and MV or MV alone. In all, 22.4% (n = 812) had presented chest wheezing in the previous 12 months (between 5 and 6 years of age), 18.8% (n = 680) had already received a medical diagnosis of asthma, and 20.8% (n = 752) had a history of pneumonia between hospital discharge after birth and six years of age. Figure 2 depicts the association between use of neonatal ventilatory support and frequency of the target outcomes up to six years of age. Children that required NCPAP and MV or MV alone presented the highest frequencies of pneumonia following hospital charge after birth, chest wheezing between five and six years of age, and medical diagnosis of asthma (41%, 43.6%, and 48.7%, respectively).

Table 2 shows the distribution of the outcomes pneumonia, chest wheezing, and asthma according to maternal characteristics. Children of poorer families and of mothers with less schooling and black or brown skin color, mul-

Table 1

Characteristics of children with information available (n = 3,624) and without information (n = 512) on study outcomes. 2004 Pelotas (Brazil) Birth Cohort study *.

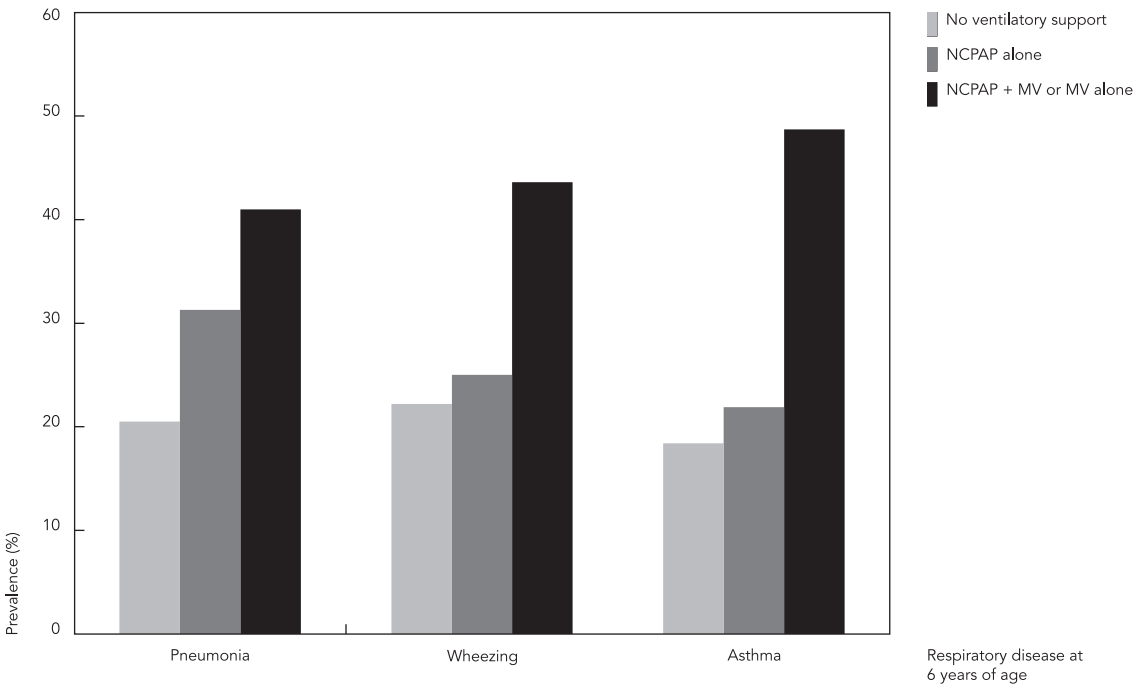
Variables	Information available n (%)	Without information available n (%)	p-value
Maternal schooling (years)			0.210
0-4	541 (15.1)	94 (18.6)	
5-8	1,495 (41.7)	198 (39.1)	
9-11	1,192 (33.2)	161 (31.8)	
≥ 12	361 (10.1)	53 (10.5)	
Maternal skin color			0.551
White	2,664 (73.5)	370 (72.3)	
Black/Mixed	960 (26.5)	142 (27.7)	
Maternal age (years)			0.176
< 20	684 (18.9)	93 (18.2)	
20-34	2,442 (67.4)	363 (70.9)	
≥ 35	496 (13.7)	56 (10.9)	
Parity			0.047
0	1,442 (39.8)	188 (36.7)	
1	966 (26.7)	124 (24.2)	
≥ 2	1,215 (33.5)	200 (39.1)	
Urinary tract infection during index pregnancy			0.590
No	2,276 (63.0)	315 (61.8)	
Yes	1,337 (37.0)	195 (38.2)	
Smoked during index pregnancy			0.213
No	2,650 (73.1)	361 (70.5)	
Yes	974 (26.9)	151 (29.5)	
Prenatal steroid use			0.070
No	3,545 (98.7)	507 (99.6)	
Yes	48 (1.3)	2 (0.4)	
Type of delivery			0.185
Vaginal	1,968 (54.3)	294 (57.4)	
Cesarean	1,656 (45.7)	218 (42.6)	
Sex			0.491
Male	1,885 (52.0)	258 (50.4)	
Female	1,739 (48.0)	254 (49.6)	
Gestational age (weeks)			0.706
< 34	156 (4.3)	26 (5.1)	
34-36	340 (9.4)	46 (9.0)	
≥ 37	3,124 (86.3)	439 (85.9)	
Low birth weight			0.453
No	3,299 (91.1)	461 (90.0)	
Yes	324 (8.9)	51 (10.0)	
Singleton pregnancy			0.192
No	73 (2.0)	6 (1.2)	
Yes	3,551 (98.0)	506 (98.8)	
Ventilatory support			0.958
None	3,553 (98.0)	502 (98.0)	
NCPAP alone	32 (0.9)	5 (1.0)	
NCPAP + MV or MV alone	39 (1.1)	5 (1.0)	

MV: mechanical ventilation; NCPAP: nasal continuous positive airway pressure.

* The comparison excluded the 95 children that died in the first 6 years of follow-up of the 2004 Pelotas (Brazil) Birth Cohort Study.

Figure 2

Association between ventilatory support at birth ("no support"; "NCPAP"; and "NCPAP + MV or MV alone") and respiratory disease at 6 years of age. 2004 Pelotas (Brazil) Birth Cohort study.



MV: mechanical ventilation; NCPAP: nasal continuous positive airway pressure.

tiparous mothers, and those with a history of urinary tract infection during the index pregnancy had higher prevalence rates of pneumonia and asthma. Children of mothers less than 20 years of age had higher prevalence rates of pneumonia and chest wheezing. Children of mothers that smoked during the index pregnancy showed higher frequency of pneumonia, chest wheezing, and medical diagnosis of asthma. No differences were observed in pneumonia, chest wheezing, or asthma based on type of delivery or prenatal steroid use. As for the children's characteristics (Table 3), boys showed higher prevalence rates for chest wheezing and asthma when compared to girls. Pneumonia and asthma were the most frequent diseases in preterm or low birth weight children.

Table 4 shows the crude and adjusted association between neonatal ventilatory support and each of the study outcomes. In the crude analysis, newborns exposure to ventilatory support at birth (NCPAP with MV or MV alone) showed a twofold prevalence of pneumonia and chest wheezing and a nearly threefold prevalence of medical diagnosis of asthma, when compared to those who had not used neonatal ventilatory support. After adjusting for potential confounding variables, the association between ventilatory support and medical diagnosis of asthma remained virtually unchanged in relation to the crude model, and the associations between ventilatory support and pneumonia and wheezing lost significance.

Discussion

The current study was conducted in a cohort of 4,231 newborns, of which 6% were admitted to a neonatal ICU at birth, and of these, nearly half required some form of ventilatory support during their hospital stay. The use of ventilatory support (NCPAP and MV or MV alone) was associated with higher prevalence of medical diagnosis of asthma assessed at six years de life, even after adjusting for a series of maternal and child variables.

Prevalence of preterm births has increased in many countries, even in high-income nations [25]. A report published in 2012 by the World Health Organization (WHO) estimated that more

Table 2

Frequency of each study outcome according to maternal characteristics. 2004 Pelotas (Brazil) Birth Cohort study (N = 3,624).

Variables	Pneumonia * n (%)	Wheezing ** n (%)	Asthma *** n (%)
Family income (times minimum wage)	p < 0.001	p = 0.065	p < 0.001
≤ 1.0	173 (23.7)	186 (25.5)	176 (24.1)
1.1-3.0	384 (22.9)	382 (22.8)	326 (19.5)
3.1-6.0	126 (15.2)	162 (19.6)	125 (15.1)
6.1-10.0	30 (14.5)	41 (19.8)	31 (15.0)
> 10	36 (20.5)	38 (21.6)	19 (10.8)
Maternal schooling (years)	p = 0.003	p = 0.053	p < 0.001
0-4	138 (25.5)	130 (24.0)	141 (26.1)
5-8	322 (21.5)	358 (24.0)	304 (20.3)
9-11	230 (19.3)	238 (20.0)	177 (4.9)
≥ 12	58 (16.1)	74 (20.5)	51 (14.1)
Maternal skin color	p = 0.001	p = 0.209	p = 0.003
White	518 (19.4)	583 (21.9)	470 (17.6)
Black/mixed	234 (24.4)	229 (23.9)	211 (22.0)
Marital status	p = 0.021	p = 0.100	p = 0.434
Without husband or partner	139 (23.3)	143 (25.0)	114 (20.0)
With husband or partner	613 (20.1)	669 (21.9)	567 (18.6)
Maternal age (years)	p = 0.026	p < 0.001	p = 0.152
< 20	153 (22.4)	184 (26.9)	136 (19.9)
20 to 34	518 (21.2)	545 (22.3)	467 (19.1)
≥ 35	81 (16.3)	81 (16.3)	78 (15.7)
Parity	p = 0.006	p = 0.489	p = 0.006
0	277 (19.2)	331 (23.0)	242 (16.8)
1	186 (19.3)	203 (21.0)	176 (18.2)
≥ 2	289 (23.8)	277 (22.8)	262 (21.6)
Urinary tract infection during index pregnancy	p = 0.001	p = 0.321	p = 0.010
No	436 (19.2)	497 (21.8)	396 (17.4)
Yes	316 (23.6)	311 (23.3)	279 (20.9)
Smoking during index pregnancy	p = 0.034	p < 0.001	p < 0.001
No	527 (19.9)	554 (20.9)	442 (16.7)
Yes	225 (23.1)	258 (26.5)	239 (24.5)
Trimester of first prenatal visit	p = 0.113	p = 0.112	p = 0.036
1st	528 (20.0)	576 (21.8)	468 (17.8)
2nd	195 (23.0)	208 (24.5)	184 (21.7)
3rd	15 (16.7)	15 (16.7)	18 (20.0)
Prenatal steroid use	p = 0.068	p = 0.256	p = 0.260
No	727 (20.5)	790 (22.3)	660 (18.6)
Yes	15 (31.3)	14 (29.2)	12 (25.0)
Type of delivery	p = 0.659	p = 0.261	p = 0.121
Vaginal	403 (20.5)	455 (23.1)	388 (19.7)
Cesarean	349 (21.1)	357 (21.6)	293 (17.7)

p-value = χ^2 test.

* Pneumonia any time between post-natal hospital discharge and 6 years of age;

** Chest wheezing in the previous 12 months (5-6 years of age);

*** Medical diagnosis of asthma any time up to 6 years of age.

than 10% of all births in the world are premature. The report also identified Brazil as the tenth leading country in the world in absolute number of preterm births [1]. This high prevalence of prematurity has important social and economic repercussions in both the short and long term. Neonatology faces numerous challenges in the acute treatment of diseases in premature new-

Table 3

Frequency of each study outcome according to the children's characteristics. 2004 Pelotas (Brazil) Birth Cohort study (N = 3,624).

Variables	Pneumonia * n (%)	Wheezing ** n (%)	Asthma *** n (%)
Sex	p = 0.281	p = 0.049	p = 0.018
Male	378 (20.1)	447 (23.7)	382 (20.3)
Female	374 (21.5)	365 (21.0)	299 (17.2)
Gestational age (weeks)	p = 0.005	p = 0.362	p = 0.005
< 34	41 (26.3)	42 (26.9)	43 (27.6)
34-36	89 (26.2)	78 (22.9)	73 (21.5)
≥ 37	620 (19.9)	691 (22.1)	564 (18.1)
Low birth weight	p = 0.011	p = 0.112	p = 0.001
No	667 (20.2)	728 (22.1)	598 (18.1)
Yes	85 (26.2)	84 (25.9)	83 (25.6)
Singleton pregnancy	p = 0.004	p = 0.129	p = 0.932
No	727 (20.5)	801 (22.6)	667 (18.8)
Yes	25 (34.3)	11 (15.1)	14 (19.2)
5-minute Apgar < 7	p = 0.606	p = 0.619	p = 0.365
No	731 (20.6)	791 (22.3)	664 (18.7)
Yes	14 (23.3)	15 (25.0)	14 (23.3)
Admitted to neonatal ICU	p = 0.039	p = 0.131	p = 0.019
No	757 (19.1)	760 (22.1)	630 (18.3)
Yes	62 (24.4)	50 (26.9)	47 (25.1)

ICU: intensive care unit; p-value = χ^2 test.

* Pneumonia between post-natal hospital discharge and 6 years of age;

** Chest wheezing in the previous 12 months (5-6 years of age);

*** Medical diagnosis of asthma any time up to 6 years of age.

borns and in the prevention of long-term sequelae. Ideally, prematurity would be prevented at any cost, but few measures have been associated with significant population-based reductions in preterm births [26].

The anatomical and physiological formation of the lungs during the prenatal and postnatal periods depends on a complex network of factors that regulate the airways' vascular development and differentiation [27,28,29,30]. This process of bronchoalveolar and vascular maturation of the lungs can be altered at any moment, leading to chronic complications that begin in the neonatal period (neonatal chronic pulmonary disease) or later in the life cycle. Some known factors in the development of these problems are prematurity, use of supplementary oxygen, ventilatory support, infection, late implementation of enteral nutrition, and patent ductus arteriosus [12,31].

The use of MV in the neonatal period can cause alterations in the airways, especially through barotrauma and volutrauma, atelectrauma, and biotrauma. MV also induces the release of pro and anti-inflammatory mediators (IL-1, IL-6, IL-10, and TNF-α), injuring the pulmonary epithelial and endothelial cells, which can lead to alveolar edema and morphological alteration of the bronchoalveolar structure. These lesions produced in an early period of life can be irreversible, even after pulmonary maturation and airway remodeling in later stages [30,31,32].

Previous studies showed an association between use of neonatal ventilatory support and mid and long-term respiratory consequences. Kotecha et al. [18] studied 13,961 newborns from the ALSPAC birth cohort (*Avon Longitudinal Study of Parents and Children*) in the United Kingdom. The authors reported that MV was associated with altered pulmonary function at 8-9 years of age. Vrijlandt et al. [33] studied 690 children in the Netherlands that were born premature in 1983, evaluating them subsequently, in 2002. They found that children born with gestational age less than 32 weeks and/or birth weight less than 1,500g and that received ventilatory support for more than 28 days showed fivefold odds

Table 4

Crude and adjusted effects of the association between neonatal ventilatory support and each of the study outcomes. 2004 Pelotas (Brazil) Birth Cohort study.

Modality of ventilatory support *	Pneumonia ** PR (95%CI)	Wheezing *** PR (95%CI)	Asthma # PR (95%CI)
Crude analysis (p-value)	0.002	0.001	0.003
Never used ventilatory support	1.0 (reference)	1.0 (reference)	1.0 (reference)
NCPAP alone	1.52 (0.82-2.85)	1.13 (0.56-2.26)	1.19 (0.56-2.50)
NCPAP + MV or MV alone	2.01 (1.22-3.29)	1.97 (1.22-3.18)	2.64 (1.68-4.17)
Adjusted analysis (p-value)	0.461 ##	0.078 ###	0.017 §
Never used ventilatory support	1.0 (reference)	1.0 (reference)	1.0 (reference)
NCPAP alone	1.21 (0.57-2.57)	1.05 (0.50-2.22)	0.97 (0.44-2.17)
NCPAP + MV or MV alone	1.64 (0.74-3.65)	1.87 (1.14-3.07)	2.24 (1.27-3.99)

95%CI: 95% confidence interval; ICU: intensive care unit; MV: mechanical ventilation; NCPAP: nasal continuous positive airway pressure; PR = prevalence ratio; p-value = Wald test.

* Reference = never used ventilatory support);

** Pneumonia any time between post-natal hospital discharge and 6 years of age;

*** Chest wheezing in the previous 12 months (5-6 years of age);

Medical diagnosis of asthma any time up to 6 years of age;

Adjusted for urinary tract infection, prenatal steroid use, gestational age, low birth weight, and singleton versus twin prenancy;

Adjusted for low birth weight, singleton versus twin pregnancy, and admission to neonatal ICU;

§ Adjusted for urinary tract infection, type of delivery, gestational age, low birth weight, and admission to neonatal ICU.

of dyspnea at 19 years of age when compared to children that received ventilatory support for less than 28 days. Konefal et al. [34], in a prospective study with 50 newborns that received neonatal NCPAP, found a higher incidence of laryngitis in the first six years and a higher incidence of bronchitis and pneumonia in the first two years of life, but without altered pulmonary function, when compared to newborns that had not received NCPAP. In the current study, the use of NCPAP alone in the neonatal period was not associated with increased prevalence of pneumonia, wheezing, or diagnosis of asthma in any of the models analyzed. Grischkan et al. [35], in a birth cohort in the United States with 241 premature newborns, found that those exposed to MV in the neonatal period showed higher odds of asthma between eight and eleven years of age, when compared to those who had not required this type of ventilatory support. Along the same line as the Grischkan et al. study, the children in the 2004 Pelotas Birth Cohort showed higher prevalence of asthma among children that required neonatal MV. However, the effect sizes in the current study were not as high. This could be due to a greater sampling variation in the Grischkan et al. study, secondary to a small sample size, as evidenced by this study's wide 95%CI. Meanwhile, the current study included information on all the newborns, whether preterm or not, with more conservative measures of association than those reported in studies that only included high-risk children.

The current study's main strengths are that it was a population-based longitudinal study with a high follow-up rate and data collected prospectively, minimizing recall bias and allowing the identification of temporal relations in the associations, which had received little previous research attention in middle or low-income countries. The study's main limitation relates to the lack of information on the fraction of inspired oxygen (FiO_2), besides the lack of data on duration and parameters for the ventilatory support administered to the children. Such information would allow studying dose-response relations, strengthening the causal mechanism in the associations. Another limitation is the way the study outcomes were collected. Data collection on the outcome "chest wheezing" used a questionnaire completed by the parents, potentially introducing information bias. Parents may have referred to other noises as "wheezing", such as those caused by nasal obstruction. Since our study did not ask about lung auscultation by a physician or prescription of bronchodilators, it could be affected by overestimating the true number of children

with wheezing. This outcome (which includes a 12-month recall) could also be affected by recall bias, if the child presented some "wheezing" with little or no clinical repercussions and the parents had forgotten the problem, which would underestimate the frequency of wheezing in the children. Another methodological problem could be present in the outcome "*pontada* or pneumonia" reported by the mother, since there was no information to allow only physician-diagnosed pneumonias in the outcome. This problem could be a source of information bias in our study and contribute to overestimation of the true frequency of pneumonia in children in the cohort. Finally, another limitation is the presence of approximately 14% losses over the course of six years in the study. Although the children lost to follow-up were similar in nearly all their characteristics to the children with information available on the target outcomes, selection bias cannot be ruled out.

The current study's findings highlight the respiratory complications in the medium run from neonatal ventilatory support. Bronchial hyperreactivity/asthma is a chronic illness, and depending on the severity it can lead to important restrictions on patients' lives and high costs for the family and society [36,37]. The increase in prematurity in Brazil, leading to a greater need for specialized care, indicates the need for adequate services for newborns and the implementation of neonatal protocols that minimize the risks of complications and sequelae from treatments in the long term.

Resumen

El objetivo del estudio fue evaluar la asociación entre el soporte ventilatorio durante el período neonatal y las enfermedades respiratorias durante los seis primeros años de vida. Se trata de un estudio de cohorte de nacimiento con base poblacional. La exposición principal, soporte ventilatorio al nacimiento, fue definida como el uso de presión positiva nasal (CPAPn) y/o ventilación mecánica (VM) durante más de tres horas, desde la hospitalización al nacimiento, hasta los 28 días de vida. Los resultados analizados fueron: broncoespasmo en los últimos doce meses, diagnóstico médico de asma -realizado alguna vez en la vida- y episodio de neumonía ocurrido hasta los seis años de edad. Se realizaron análisis brutos y ajustados para potenciales variables de confusión, usando la regresión de Poisson. Fueron estudiados 3.624 niños. El uso de soporte ventilatorio estuvo asociado con una mayor frecuencia de diagnóstico médico de asma, incluso tras ajustar las características maternas y de los niños (RP = 2,24; IC95%: 1,27-3,99). Los resultados alertan sobre las complicaciones respiratorias a medio plazo tras el soporte ventilatorio realizado en el período neonatal.

Soporte Ventilatorio Interativo; Pneumonía; Asma; Salud del Niño

Contributors

F. S. Chiuchetta, T. N. Munhoz, I. S. Santos, A. M. B. Menezes, and A. Matijasevich participated in the study's conceptualization and design, data interpretation, writing of all versions of the article, and critical revision. E. Albernaz collaborated in the data interpretation, writing of all versions of the article, and critical revision. F. C. Barros contributed to the study design, data interpretation, writing of all versions of the article, and critical revision.

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