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Title: Neighborhood Disadvantage and Early Respiratory Outcomes in Very Preterm Infants with Bronchopulmonary Dysplasia.

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Objective: To investigate the impact of neighborhood conditions on respiratory-related hospital admissions in the first year after discharge from the neonatal unit in a population of infants born very preterm with bronchopulmonary dysplasia (BPD).

Study design: Very preterm infants (gestational age (GA) <33 weeks) who had BPD at 36 weeks post-conceptual age and who received follow-up in a French regional medical network were included. Socioeconomic context was estimated using a neighborhood-based socioeconomic deprivation index. Poisson regression analysis was used to identify risk factors associated with rehospitalization.

Results: The study included 423 infants with a mean (SD) GA of 27±2 weeks and birth weight of 941±277 g; 51% of the population lived in disadvantaged areas. The hospital admission rates increased from 8.8% to 24% in infants living in affluent and disadvantaged areas, respectively ($p < 0.01$), and reached 30% in extremely preterm infants from disadvantaged areas. After adjusting for perinatal characteristics, home oxygen therapy and season of birth, the respiratory-related hospitalization rate was almost 3-fold higher in infants living in disadvantaged areas, with an adjusted incidence rate ratio (95% confidence interval) of 2.79 (95% CI, 1.29 – 6.09; $P < .01$).

Conclusions: Disadvantaged neighborhoods adversely impact early respiratory outcomes in infants born very preterm with BPD. The social context should be considered in routine follow-up care of children born preterm. Further studies investigating the underlying mechanisms are warranted for implementing preventive strategies.

Bronchopulmonary dysplasia (BPD) is a chronic lung disease of prematurity that occurs in 40% to 50% of infants with a gestational age (GA) of < 30 weeks [1,2]. The incidence of BPD remains unchanged despite advances in perinatal care over recent decades, which is due in part to improved survival rates in extremely preterm (EPT) infants [3-5]. [1,2]. BPD can be regarded as a consequence of various perinatal and neonatal insults that affect lung development through a number of pathways, including inflammatory and vascular disorders [6-8].

Preterm infants with BPD are at high risk of mortality and respiratory morbidity that remains significant beyond the neonatal period [2,6]. After discharge from the neonatal unit, infants with BPD often require emergency visits and hospital admissions for wheezing exacerbations, pulmonary hypertension, bronchiolitis or lower respiratory tract infections [9-11]. These adverse respiratory events occurring early in life are associated with worse lung dysfunction in adults who have BPD [6,12-14,15,16].

Low socioeconomic status (SES) negatively impacts child health, yet few studies have addressed this issue in children born very preterm [17-19,21]. Socioeconomic status can be assessed at the household level (based on factors including income, insurance status, and educational level) or by using area-based socioeconomic indexes, also called neighborhood disadvantage indexes. These indexes capture individual SES, especially when individual data are lacking, but they may also represent geographic disparities in various factors that contribute to health inequalities, such as access to health care, health behaviors, educational level, chronic stress and social isolation, and adverse environmental exposures (smoking and air pollution) [22]. In the child population as a whole, low SES has been associated with mortality, emergency department visits, and hospital admissions [17-19,20-23]. Recent studies have shown the same trend in children born preterm [17,19]. However, little is known about the impact of the socio-economic context on premature infants with BPD, a population

that often benefits from care organization with close medical follow-up and extended health insurance coverage as offered in some countries, including France.

Using a dataset from a French regional medical follow-up network database, we aimed to determine whether neighborhood disadvantages influenced the risk of respiratory-related hospital admission in the year after discharge from the neonatal unit in a population of very preterm-born infants with BPD.

METHODS:

This observational and population-based study included data from a population of surviving preterm infants with BPD born with a GA of less than 32⁺⁶ weeks between September 2006 and December 2014. Bronchopulmonary dysplasia was defined as the need for oxygen or ventilator support (including high-flow nasal cannula therapy) at 36 weeks postmenstrual age (PMA). Infants with valid family addresses, those who had no severe congenital anomalies, and those who received follow-up care from a regional medical network based in the west of the Provence-Alpes-Côte-d'Azur (PACA) region named the Naître et Devenir-Méditerranée Network (the NaDeM Network) up to one year after discharge from the neonatal unit were eligible for inclusion [17]. Among infants born and living in the region, about 82% received care from the network up to one year of age during the study period. Based on the study design, infants requiring prolonged hospitalization for nasal intermittent ventilation or tracheostomy were also excluded (n = 17).

The NaDeM Network obtained authorization for clinical research from the French data protection authority for clinical research (Commission Nationale de l'Informatique et des Libertés or CNIL, No. 1460797). Infants were included in this medical network after written informed parental consent. All data were prospectively collected in the database and were deidentified. The purpose of the network is to screen for clinical anomalies and to tailor the

healthcare and follow-up of very preterm infants up to the age of 6 years. In the first year, the children attended regular follow-up visits with trained pediatricians every 3 months, and clinical data, including hospitalization with causes, were collected. Infants discharged with supplemental oxygen received regular home nurse visits and were seen every month until oxygen was discontinued. Consistent with national guidelines, infants with BPD aged 6 months or under, or requiring oxygen therapy or inhaled treatment and under 2 years of age at the beginning of the winter season, received respiratory syncytial virus infection immune prophylaxis (palizivumab) free of charge [24]. All infants with BPD had universal healthcare insurance, meaning that all their medical healthcare costs were covered. A paid parental leave program is offered to parents who postpone their work activity and stay at home with their infant for 6-12 months after neonatal hospital discharge.

The socioeconomic status of each infant was assessed using a geographical socioeconomic disadvantage index (SDI) calculated on a small area scale across the entire PACA region [25]. Five key socioeconomic and demographic variables were extracted from 2008 and 2012 census data linked to each local residential municipality (*French National Institute of Statistics and Economic Studies, Institut National de la Statistique et des Etudes Economiques*): median household income, unemployment rate, percentage of people aged ≥ 15 years who failed to graduate from high school, percentage of single-parent families, and percentage of families in rented accommodation. Socioeconomic disadvantage index scores ranged from level 1 (least disadvantaged) to level 5 (most disadvantaged). Within the present study, areas were sorted by SDI score into three disadvantage categories: low (SDI levels 1 and 2, affluent areas), medium (level 3) and high (levels 4 and 5, disadvantaged areas). Residential addresses of parents and their infants were obtained at the time of enrollment in the NaDeM Network, at discharge from the neonatal unit and after any residential changes.

On the basis of these addresses, an SDI category (low, medium or high disadvantage level) was assigned to each infant.

Data collection and statistical analyses

The following neonatal data were collected: sex, gestational age (GA), birth weight (and z-score for birth weight), season of birth, necrotizing enterocolitis, brain injury (\geq grade II intraventricular hemorrhage, posthemorrhagic hydrocephalus, periventricular leukomalacia, and white matter injury), retinopathy of prematurity (ROP \geq stage 2), oxygen therapy on discharge and breastfeeding on discharge. Gestational age was categorized as follows: $\leq 27^{+6}$ weeks (extremely preterm infants), 28 - 29⁺⁶ weeks, and 30 - 32⁺⁶ weeks. Small for GA (SGA) at birth was defined using Fenton growth charts [26]. Extrauterine growth restriction (EUGR) was defined as small for corrected GA at discharge according to Fenton growth charts. Maternal school education level (equivalent to graduation from high school) was also collected. Seasons of birth were defined as follows: winter (January, February, March), spring (April, May, June), summer (July, August, September) and autumn (October, November, December). The urbanicity of West-PACA municipalities was categorized as rural or almost rural (<9999 residents), suburban (towns with 10 000-99 999 residents), and urban (towns with $\geq 100\ 000$ residents).

Respiratory-related hospital admission was defined as at least 1 overnight stay in the hospital during the year following discharge from the neonatal unit for respiratory causes, including upper (rhinopharyngitis and laryngitis) and lower respiratory tract disorders (bronchiolitis, lower respiratory tract infections, wheezing, and asthma), according to International Classification of Disease codes.

Univariate parametric and nonparametric analyses were performed using the chi-square test or Fisher exact test for categorical variables and Student t-test or the Mann-Whitney test for quantitative variables as appropriate. Poisson regression analysis was performed to estimate

the risk ratios of respiratory-related hospital admission up to 1 year after discharge from the neonatal unit. Variables with a *P* value < 0.2 in the univariate analysis were included in the final regression model. Home oxygen therapy was included in the model because it is associated with adverse respiratory outcomes. Regarding the effects of maternal smoking status and because of the high rate of missing values (41%), we performed a multiple imputation method with five repetitions, including SDI level, maternal education level, birth weight z-score, GA and breastfeeding. This method did not change the final result of the regression analysis (data not shown), but the results should be interpreted with caution because of the high percentage of missing data. The results are expressed as the adjusted incidence rate ratio (aIRR) with a 95% confidence interval (95% CI). All tests were 2-sided, and *P* values less than .05 were considered significant. SPSS version 20.0 software (IBM, Armonk, New York) was used for all statistical analyses.

RESULTS

During the study period, 591 very preterm infants with BPD were eligible for inclusion in the NaDeM Network. Infants with no valid residential address or lacking relevant variables (*n* = 11), with congenital anomalies (*n* = 29) and those whose parents refused to provide consent (*n* = 38) were not included. Of the remaining 513 infants, 47 were lost to follow-up, 36 moved outside the NaDeM Network, and 7 died (2 infants with SIDS and 5 infants who died before discharge from the hospital). Ultimately, 423 infants were included in the study. The mean (SD) GA and birth weight of the study population were 27 ± 2 weeks and 940 ± 275 g, respectively. Approximately half of the infants (*n* = 217, 51.3%) lived in disadvantaged areas. By comparison with the excluded population (*n* = 83), the studied infants were more premature at birth (57.2% vs. 39.7%, for GA < 28 weeks, *p* < 0.05), needed home oxygen therapy more frequently (26.9% vs. 4.8%, *p* < 0.001), were more likely to have

EUGR on discharge (54.1% vs. 37.3%, $p < 0.01$) and to live in affluent areas (26.9% vs 15.7%, for low SDI level areas, $p < 0.05$) (Table I; available at www.jpeds.com).

Seventy-six infants (18%) were hospitalized for respiratory causes in the first year after discharge from the neonatal unit, which accounted for 96 hospitalizations. The principal causes of hospitalization were: bronchiolitis (60/96, 62.5%), pneumonia (12/96, 12.5%), asthma (10/96, 10.4%), upper respiratory disease (9/96, 9.4%) and BPD decompensation (5/96, 5%). Seventeen infants (22%) were hospitalized at least 2 times. Respiratory syncytial virus was tested in 41/60 (68%) of bronchiolitis events and 55% of them were positive for RSV. Compared with the nonhospitalized infants, the hospitalized infants were more premature at birth ($p < 0.05$), were born more frequently during the winter season ($p < 0.05$) and lived in urban areas ($p < 0.001$) (Table 2; available at www.jpeds.com). The remaining characteristics, including neonatal morbidity, were comparable with the exception of SDI level. The hospitalized infants lived preferentially in disadvantaged areas (SDI High level) (68.4% vs. 47.5%, $p < 0.001$).

Table 3 shows infant characteristics in terms of SDI level. Hospital admission rates were approximately 3 times higher in infants living in disadvantaged areas, ranging from 8.8% at the SDI Low level to 24% at the SDI High level ($p < 0.01$) and gestational age, sex, home oxygen therapy, and season of birth were comparable. As expected, maternal high school education level and breastfeeding rates declined as the SDI level increased. Hospital admission rates also varied depending on GA and rose as high as 30% in extremely preterm infants living in disadvantaged areas (SDI High level) (Figure).

The adjusted analysis showed a 2- to 3-fold higher incidence rate of respiratory-related hospitalization in infants living in a disadvantaged neighborhood (SDI High Level) than in those living in affluent areas (SDI Low Level), with an aIRR of 2.79 (95% CI, 1.29 – 6.09; $p < 0.01$) (Table 4). Extremely preterm birth and home oxygen therapy were not found to be

significant factors.

DISCUSSION

We found that very preterm-born infants with BPD living in socioeconomically disadvantaged areas were at high risk of hospital admission for respiratory disease in their first year of life. After adjustment for principal neonatal risk factors, including gestational age, home oxygen therapy, and season of birth, these socioeconomically vulnerable infants had a 2 to 3 times higher rate of being admitted to the hospital for respiratory causes during the first year after discharge from the neonatal unit.

The influence of socioeconomic context on respiratory outcomes in preterm infants with BPD has rarely been investigated. Although hospitalization rates have been reported to vary from 39% to 60% in this population, there is limited evidence regarding the role of social health disparities [27-29]. In one observational study with a limited sample size (n=135), public insurance coverage, a surrogate marker of low SES in the United States, was associated with a decreased risk of hospitalization [30]. In contrast, using a geographical socioeconomic disadvantage index, which is a valid method to capture the complex dimension of individual SES, especially when individual data are unavailable, we found adverse effects of living in disadvantaged areas [17]. We did not expect such a large adverse effect in our study on account of universal health coverage, which is supposed to reduce health care inequalities. Indeed, all preterm-born infants with BPD have free-of-charge health insurance in France. However, the fact that hospitalization rates were relatively low (18%) compared with the data in the literature suggests that the provision by health care authorities of universal health insurance coverage and close medical follow-up for infants with BPD with regular home nurse visits attenuated the adverse impact of limited family resources related to health inequalities. All of these findings suggest that familial and geographical socioeconomic

contexts should be regarded as relevant indicators for clinicians to identify infants at risk of early adverse respiratory outcomes.

The mechanisms by which disadvantaged neighborhoods negatively impact child health are unknown. Several factors could be involved, such as social and material factors (limited access to healthcare, overcrowded and unsanitary housing, inadequate parental health-related behavior, social isolation and segregation) and limited health knowledge or education. People living in poverty are often overexposed to stressful life events and to toxic environmental factors including smoking, traffic pollution, and infections [31,32]. Some of these factors may alter biological systems, including the immune system, which can occur early during fetal development as well [33-36]. Preterm infants born to mothers from disadvantaged areas have been reported to have increased systemic inflammatory markers early in life [33]. In both humans and animals, overexposure to maternal gestational air pollution or smoking impairs fetal lung development and affects long-term pulmonary function [35,36]. Consecutive inflammation, oxidative stress and epigenetic modifications may alter both fetal lung development and functions, which in turn enhance vulnerability to long-term respiratory diseases. Further studies are clearly required to investigate the pathophysiological pathways linking disadvantaged neighborhoods and adverse respiratory outcomes in very preterm infants; researchers should combine biomarkers and social and neighborhood indicators and focus on both prenatal and postnatal periods.

We acknowledge certain limitations in this observational population-based study. Numerous reliable variables are lacking in the NaDeM database and thus could not be analyzed, such as duration of mechanical ventilation, indicators of BPD severity, pulmonary hypertension assessment, and second-hand smoking. RSV infection was found in 55% of patients with bronchiolitis tested for RSV, but we had insufficient data to accurately examine the interaction effect of RSV immune prophylaxis on hospitalization for bronchiolitis. Data

regarding the effects of second-hand smoking on respiratory outcomes in preterm infants with BPD are limited and conflicting. A previous study in this cohort found no effects of second-hand smoking on respiratory illness in the first two years, but other authors have reported an association with increased incidence of respiratory symptoms, including recurrent wheezing, nighttime symptoms and activity limitations, without increasing the hospital admission rate [37,38]. However the mediated role of parental smoking between low SES and respiratory disease in children is questioned. Some studies have reported sustained adverse impact of low SES after adjusting for parental smoking [39]. Finally, we were unable to assess racial and ethnic disparities; for ethical concerns, it is not possible to record ethnicity in the French databases. The influence of race/ethnicity on the respiratory outcomes of preterm infants is still questioned [18,40]. However, it has been proposed that racial and ethnic disparities in perinatal and child health outcomes are driven by socioeconomic factors, with race/ethnicity considered a proxy for individual life experience [41,42].

The strength of the present study is that it represents general clinical practice. This is a population-based study using a dataset from a large regional medical network database that includes a variety of professionals from local, private and public medical care and general and university hospitals. We do not believe the excluded population limits the significance of our findings because the neonatal morbidity was moderate and a larger proportion of excluded infants tended to live in disadvantaged areas. Outpatient medical visits, emergency department visits and the use of inhaled treatment are lacking in the database, but the hospital admission information used in this study is considered a more robust severity marker of respiratory disease.

In conclusion, we report that very preterm-born infants with BPD living in socioeconomically disadvantaged areas were at higher risk of hospital admission for respiratory disease in their first year of life. This adverse effect was still observed despite

regular medical follow-up care and universal health insurance coverage, making social health inequality in this vulnerable population a public health concern. The socioeconomic context should be taken into account in routine follow-up care of preterm infants with BPD. Simple preventive strategies beyond universal health insurance coverage should be considered before discharge in this disadvantaged population, which may include avoiding exposure to indoor air pollution (including second-hand smoking), scheduling nurse visits, and using social workers to avoid social isolation and to promote parental nurse education and competence in caring for their baby. Further studies investigating the underlying mechanisms by combining biological and socioeconomic factors are warranted for implementing specific preventive strategies.

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LEGENDS

Figure 1: Respiratory-related hospital admission rate according to gestational age and SDI level.

The hospitalization rate for respiratory disease increased with degree of immaturity and reached 30 % in extremely preterm infants (GA < 28 wks) from disadvantaged areas (SDI High level, black bars); SDI Low level (affluent areas, white bars) and SDI Middle level (grey bars).

Figure 1

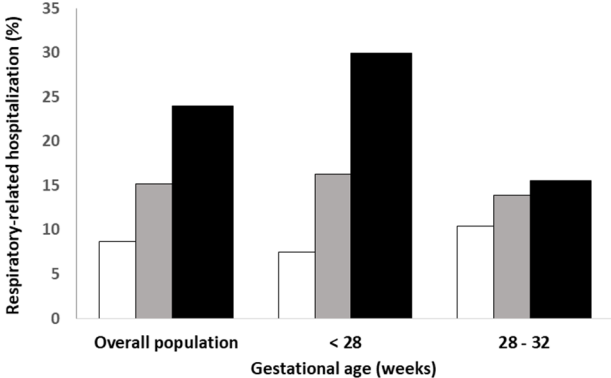


Table 1 Online only: Characteristics of the study and excluded infant populations

	Study population N = 423	Excluded population n = 83	P value
GA (wk), n (%)			0.04
< 28	242 (57.2)	33 (39.7)	
28 - 29	128 (30.3)	33 (39.7)	
30 - 32	53 (12.6)	17 (20.4)	
Birth weight (BW), mean (SD)	940 (275)	997 (220)	0.10
BW z-score, median (min,max)	0.04 (-2.44, 2.72)	0.05 (-1.73, 2.72)	0.21
SGA, n (%)	60 (14.2)	8 (9.6)	0.26
Female gender, n (%)	194 (45.8)	39 (47)	0.85
Multiple pregnancies, n (%)	107 (25.3)	23 (27.7)	0.64
Siblings, n (%)	204 (48.2)	48 (57.8)	0.11
Maternal high school level, n (%)	254 (60)	41 (49.4)	0.07
Cerebral injury, n (%)	65 (15.4)	7 (8.4)	0.09
NEC, n (%)	42 (9.9)	6 (7.2)	0.44
ROP, n (%)	53 (12.6)	5 (6)	0.09
EUGR, n (%)	229 (54.1)	31 (37.3)	<0.01
Home O ₂ therapy, n (%)	114 (26.9)	4 (4.8)	<0.001
Breastfeeding at discharge, n (%)	150 (35.5)	22 (26.5)	0.11
Breastfeeding at 3 mo CA, n (%)	48 (9.9)	6 (7.2)	0.26
Season of birth, n (%)			0.42
Winter	116 (27.4)	22 (26.5)	
Spring	109 (25.7)	19 (22.9)	
Summer	108 (25.5)	18 (21.7)	
Autumn	90 (21.3)	24 (28.9)	
URBANICITY, n (%)			0.37
Rural - almost rural	95 (22.4)	10 (12.1)	
Almost urban	157 (37.1)	33 (39.7)	
Urban	171 (40.4)	40 (48.2)	
SDI Level, n (%)			0.29
Low (Affluent areas)	114 (26.9)	13 (15.7)	
Middle	92 (21.7)	20 (24.1)	
High (Disadvantaged areas)	217 (51.3)	50 (60.2)	

Table 2 Online only : Characteristics of the study population

	Overall population N = 423	Hospitalized infants n = 76	Non-hospitalized infants N = 347	P value
GA < 28 wk, n (%)	242 (57.2)	51 (67.1)	191 (55)	0.05
BW, mean (SD)	940 (275)	935 (258)	941 (278)	0.84
BW z-score, median (min,max)	0.04 (-2.44, 2.72)	0.06 (-1.73, 2.72)	0.01 (-2.44, 2.33)	0.21
SGA, n (%)	60 (14.2)	8 (10.5)	52 (14.9)	0.31
Female gender, n (%)	194 (45.8)	35 (46)	159 (45.8)	0.97
Multiple pregnancies, n (%)	107 (25.3)	18 (23.7)	89 (25.6)	0.72
Siblings, n (%)	204 (48.2)	39 (51.3)	165 (47.5)	0.55
Maternal smoking, n (%)	58/248 (23.4)	9/42 (21.4)	49/206 (23.8)	0.60
Maternal high school level, n (%)	254 (60)	40/76 (52.6)	214/336 (63.7)	0.14
Cerebral injury, n (%)	65 (15.4)	10 (13.1)	55 (15.8)	0.55
NEC, n (%)	42 (9.9)	7 (9.2)	35 (10.1)	0.81
ROP, n (%)	53 (12.6)	11 (14.5)	42 (12.1)	0.57
EUGR, n (%)	229 (54.1)	37 (48.6)	192 (55.3)	0.29
Home O ₂ therapy, n (%)	114 (26.9)	24 (31.6)	90 (25.9)	0.31
Breastfeeding at discharge, n (%)	150 (35.5)	23 (30.2)	127 (36.6)	0.29
Breastfeeding at 3 mo CA, n (%)	48 (9.9)	9 (11.8)	39 (10.4)	0.88
Season of birth, n (%)				0.21
Winter	116 (27.4)	28 (36.8)	88 (25.4)	
Spring	109 (25.7)	16 (21)	93 (26.8)	
Summer	108 (25.5)	16 (21)	92 (26.5)	
Autumn	90 (21.3)	16 (21)	74 (21.3)	
URBANICITY, n (%)				0.10
Rural - almost rural	95 (22.4)	10 (13.2)	85 (24.5)	
Almost urban	157 (37.1)	31 (40.8)	126 (36.3)	
Urban	171 (40.4)	35 (46)	136 (39.2)	
SDI Level, n (%)				0.002
Low (Affluent areas)	114 (26.9)	10 (13.2)	104 (30)	
Middle	92 (21.7)	14 (18.4)	78 (22.5)	
High (Disadvantaged areas)	217 (51.3)	52 (68.4)	165 (47.5)	

BW: birth weight; EUGR: extra-uterine growth restriction; GA: gestational age in weeks (wks); NEC: necrotizing enterocolitis; SDI: socioeconomic disadvantage index; ROP: retinopathy of prematurity; SGA: small for gestational age.

Table 3 : Characteristics of the population according to socioeconomic context

	SDI Low (Affluent areas) (N = 114)	SDI Middle (N = 92)	SDI High (Disadvantaged areas) (N = 217)	P value
GA < 28 wks, n (%)	66 (57.9)	49 (53.3)	127 (58.5)	0.68
BW, mean (SD)	925 (249)	952 (248)	943 (264)	
BW z-score, median (min, max)	-0.04 (-1.77, 1.99)	-0.04 (-2.10, 1.77)	0.03 (-2.44, 2.72)	0.21
Female gender, n (%)	51 (44.7)	44 (47.8)	99 (45.6)	0.9
SGA, n (%)	17 (14.9)	13 (14.1)	30 (13.8)	0.96
Multiple pregnancies, n (%)	32 (28.1)	27 (29)	48 (22.1)	0.3
Siblings, n (%)	54 (47.4)	37 (40.2)	113 (52.1)	0.16
EUGR (Z-score), n (%)	62 (54.4)	51 (55.4)	116 (53.5)	0.95
Cerebral injury, n (%)	20 (17.5)	11 (12)	34 (15.7)	0.53
NEC \geq 2, n (%)	4 (3.5)	9 (9.8)	29 (13.4)	0.02
ROP \geq 2, n (%)	8 (7)	15 (16.3)	30 (13.8)	0.1
Home O2 therapy, n (%)	33 (28.9)	18 (19.6)	63 (29)	0.2
Breastfeeding at discharge, n (%)	57 (50)	33 (35.9)	60 (27.6)	<0.001
Maternal smoking, n (%)	17/68 (25)	14/57 (24.6)	64/123 (21.9)	0.87
Maternal high school level, n (%)	92 (80.7)	65 (70.7)	97 (44.7)	<0.001
Season of birth, n (%)				0.19
Winter	25 (21.9)	24 (26.1)	67 (30.9)	
Spring	36 (31.6)	21 (22.8)	52 (23.9)	
Summer	32 (28.1)	30 (32.6)	46 (21.2)	
Autumn	21 (18.4)	17 (18.5)	52 (23.9)	
Urbanicity, n (%)				0.01
Rural - almost rural	45 (39.5)	35 (38)	15 (6.9)	
Almost urban	43 (37.7)	33 (35.9)	81 (37.3)	
Urban	26 (22.8)	24 (26.1)	121 (55.8)	
Respiratory-related Hosp, n (%)	10 (8.8)	14 (15.2)	52 (24)	<0.01

BW: birth weight; EUGR: extra-uterine growth restriction; GA: gestational age in weeks (wks); NEC: necrotizing enterocolitis; SDI: socioeconomic disadvantage index; ROP: retinopathy of prematurity; SGA: small for gestational age.

Table 4 : Factors associated with respiratory-related admissions to hospital

	Crude IRR (95%CI)	<i>P</i> value	Adjusted IRR (95%CI)	<i>P</i> value
GA < 28 wk	0.72 (0.44 – 1.18)	0.19	0.62 (0.30 – 1.29)	0.21
BW z-score, median (min, max)	1.34 (1.01-1.36)	<0.05	1.06 (0.77 – 1.48)	0.69
EUGR, n (%)	0.67 (0.42 – 1.06)	0.09	0.89 (0.54 – 1.46)	0.66
Home O2 therapy, n (%)	1.19 (0.74 – 1.89)	0.46	1.37 (0.83 – 1.35)	0.21
Breastfeeding at discharge, n (%)	0.70 (0.13 – 1.14)	0.15	0.89 (0.54 – 1.45)	0.64
Maternal high school level, n (%)	0.58 (0.37 – 0.91)	<0.05	0.78 (0.49 – 1.24)	0.29
siblings	1.51 (0.96 – 2.38)	0.07	1.24 (0.81 – 1.90)	0.31
Season of birth, n (%)				
Winter	1 [Reference]		1 [Reference]	
Spring	0.52 (0.28 – 0.94)	0.03	0.58 (0.33 – 1.03)	0.06
Summer	0.55 (0.29 – 1.04)	0.07	0.63 (0.34 – 1.16)	0.14
Autumn	0.51 (0.28 – 0.94)	<0.05	0.51 (0.28 – 0.91)	<0.05
Urbanicity, n (%)				
Rural - almost rural	1 [Reference]		1 [Reference]	
Almost urban	2.56 (1.24 – 5.26)	0.01	1.89 (0.89 – 3.03)	0.09
Urban	2.49 (1.26 – 2.94)	<0.01	1.49 (0.66 – 3.37)	0.33
SDI Level, n (%)				
Low (Affluent areas)	1 [Reference]		1 [Reference]	
Middle	1.67 (0.77 – 3.62)	0.19	1.76 (0.77 – 4.00)	0.17
High (Disadvantaged areas)	3.50 (1.83 – 6.67)	<0.001	2.79 (1.29 – 6.02)	<0.01

EUGR: extra uterine growth restriction; GA: gestational age in weeks (wks); SDI: socioeconomic disadvantage index. **P* <0.05. † *P* = 0.01. ‡*P* < 0.001.