This is the accepted manuscript of the article, which has been published in Paediatric and Perinatal Epidemiology. 2020, 34(2), 139-149. https://doi.org/10.1111/ppe.12631

Hospital admissions for lower respiratory tract infections after early-, late- and post-term birth

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This large national register study evaluated the risk of admission for lower respiratory tract infections among term subgroups of children. Early-term birth associated with a higher risk of admission for all lower respiratory tract infections, while late- and post-term birth decreased the risk of bronchiolitis/bronchitis.

Synopsis

Study question

The aim was to assess whether the incidence and risk factors of admission for lower respiratory tract infections by seven years of age differ after early-, full-, late- and post-term birth.

What's already known

Early-term birth has been associated with later respiratory morbidity such as asthma, and post-term birth may decrease this risk.

What This Study Adds

Early-term birth was associated with an increased risk of hospital admission for all lower respiratory tract infections, while late-term and post-term birth decreased the risk of admission for bronchiolitis/bronchitis compared with full-term birth.

Smoking during pregnancy, birth by elective caesarean delivery, ventilator therapy and neonatal antibiotic therapy were independent risk factors of lower respiratory tract infections.

Abstract

Background: Recent data suggest that early-term births are associated with later respiratory morbidity, and post-term births may decrease this risk.

Objectives: To assess the association of early-term (37^{+0}–38^{+6} weeks), late-term (41^{+0}–41^{+6} weeks) and post-term (≥42 weeks) birth with hospital admissions for lower respiratory tract infections (LRTI) compared with infants born full-term (39^{+0}–40^{+6} weeks) and to establish early predictors of LRTI.

Methods: The register study included 948,695 infants born in Finland in 1991-2008. Data were analysed in four term subgroups. Hospital admissions for bronchiolitis/bronchitis and pneumonia were collected up to 7 years of age. Adjusted Cox proportional hazards models were used to assess risk factors of LRTI admissions.

Results: The rates of hospital admission in the early-, full-, late- and post-term groups were 6.7%, 5.5%, 5.1% and 4.8% for bronchiolitis/bronchitis, and 2.8%, 2.4%, 2.3% and 2.3% for pneumonia. Early-term birth was associated with an increased risk of admission for bronchiolitis/bronchitis (hazard ratio HR 1.21, 95% confidence interval CI 1.18, 1.23) and pneumonia (HR 1.16, 95% CI 1.12, 1.20), while late-term (HR 0.93, 95% CI 0.91, 0.95) and post-term births (HR 0.89, 95% CI 0.85, 0.93) were associated with a decreased risk of bronchiolitis/bronchitis admission compared with the full-term group. Maternal age ≤ 20 years, smoking during pregnancy, male sex, caesarean delivery, small for gestational age, 1-min Apgar score <4, ventilator support and neonatal antibiotic therapy were associated with an increased risk of LRTI admission, while being first-born, born in a level-II hospital and in the Northern region was associated with decreased risk.

Conclusion: Early-term birth was associated with a higher risk of all LRTI admissions while late-term and post-term births were associated with lower risk of bronchiolitis/bronchitis admission.

Modifiable risk factors of LRTIs were smoking during pregnancy, birth by elective caesarean delivery, neonatal ventilator support and antibiotic therapy.

Keywords: bronchiolitis; early-term; hospital admission; lower respiratory tract infection;

pneumonia; post-term

Word count: 2569

Background

Health risks of moderately and late preterm infants have been well studied in recent years.[1] There is increasing evidence that the outcomes are different when subgroups of children born after 37 weeks' gestational age (GA), i.e. early-term (37^{+0}–38^{+6} weeks), full-term (39^{+0}–40^{+6} weeks), late-term (41^{+0}–41^{+6}weeks) and post-term (≥42 weeks) birth categories are compared.[2]

Neonatal morbidity risks have been higher in infants born early-term, especially in those born by elective caesarean delivery.[3,4] Post-term birth has also been associated with an increased risk of adverse neonatal outcomes compared with full-term birth.[5,6] A few recent studies have suggested that early-term birth is associated with later respiratory morbidity such as asthma,[4,7,8] whereas post-term birth may decrease the risk of asthma.[9-11] Less information is available on the long-term respiratory infectious morbidity of children born early-term and post-term. Lower respiratory tract infections (LRTIs) are the leading cause of hospitalisation in preschool children and result in a remarkable burden on health services.[12]

In a previous study,[13] showed an increased risk of hospital admission for bronchiolitis/bronchitis and pneumonia in preschool children born moderately or late preterm compared with those born at term. In the present study on term subgroups of children derived from the same population we aimed to determine the impact of early-term, late-term and post-term birth on hospital admission for LRTIs up to the age of seven years. Additionally, our aim was to explore maternal and perinatal factors associated with the risk of admission for LRTIs in these GA groups, also focusing on the post-term group.

Methods

The study population was derived from the cohort of all live-born children (N=1,039,263) in Finland in 1991–2008, reported previously in detail.[13] Data on a subgroup of infants born at ≥37 weeks of GA (N= 978,224) were derived from the Medical Birth Register (MBR), the Register of Congenital Malformations, and the Cause of Death Register. Twins or higher-order multiple gestations (N=16,508), infants with missing data on GA (N=5520), those with major congenital anomalies (N=12,123), and those who died before one year of age (N=898) were excluded. The final cohort included 948,695 (97.0% of all) infants who were analysed in the early-term (n=168,239; 17.7%), full-term (n=543,815; 57.3%), late-term (n=189,325; 20.0%) and post-term (n=47,316; 5.0%) groups.

Perinatal and neonatal data were obtained from the MBR. The GA data were based on early-pregnancy ultrasonography, which was performed nationally during the study period. The correction to GA was made if the ultrasound-based estimation showed a discrepancy of more than 5–7 days compared with GA based on the last menstrual period. Caesarean deliveries were classified as elective (scheduled upon and undertaken before labour) or emergency (undertaken according to maternal or fetal indications during labour) procedures. Small for gestational age infants were defined as those with a birth weight more than 2.0 standard deviation (SD) below the mean weight for gestational age and large for gestational age infants as those with a birth weight more than 2.0 SD above the mean weight for gestational age according to sex-specific fetal growth curves.[14] Ventilator support included all endotracheal mechanically assisted ventilation. Finland was divided into five geographical regions according to level-III hospital catchment regions.

Morbidity data collected from the HDR included all inpatient and all outpatient (since 1998) visits to all public hospitals in Finland. The study subjects were considered to have had LRTI, as an outcome measure, if the following diagnoses had been recorded in the HDR by the end of 2009 (ICD-9 in 1991–1995 and ICD-10 in 1996–2009): acute bronchiolitis/bronchitis (466, J20–J21) and pneumonia (480–486, J12–18). According to Finnish Current Care Guidelines, bronchiolitis is defined as the first virus-induced wheezing episode in infants under the age of 12 months. Acute wheezing bronchitis is defined as any wheezing in children aged 12 to 36 months during an acute respiratory viral infection or repeated wheezing in children aged six to 12 months.[15] The definition of pneumonia includes viral or bacterial infection of the pulmonary alveoli or interstitial diagnosed by chest radiography or on the basis of clinical findings, such as the presence of fever and acute respiratory symptoms.[15] All hospital admissions and discharges with these diagnoses as the main or secondary diagnoses were collected. Diagnoses were also collected separately for three age categories: 0–11, 12–35 and 36–84 months. The infants were followed-up to seven years of age or up to 2009. Data from different registers were linked via anonymised codes.

Ethics approval

The Ethics Committee of Tampere University Hospital region approved the study. The registering organisations (the Finnish Institute for Health and Welfare and Statistics Finland) gave permission to use sensitive health data for research.

Statistical analysis

Only variables that have been reliably recorded with a low amount of missing data with good validity in the registers covering the whole study period were included in the analysis.[16-18]

Risk factors of hospital admissions for LRTIs were sought by using multivariable adjusted Cox proportional hazard regression models, both in the whole study population and in the post-term group. A directed acyclic graph (DAG) was created to establish a rationale for selection of covariates associated with LRTIs (**e Figure 1**). All clinically relevant maternal- (age, smoking during pregnancy, primiparity), delivery- (place of birth, region of birth and mode of delivery) and newborn-related (sex, gestational weight, Apgar score, resuscitation at birth, ventilator or antibiotic therapy during the first week of life) variables were selected and modelled as explanatory variables. Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI). The proportional hazard assumptions in Cox hazard regression models were tested based on Schoenfeld residuals. Because of the study design, the follow-up time in children born after the year 2002 was less than seven years. Cumulative hazards were calculated for bronchiolitis/bronchitis and pneumonia both at the age of three and seven years. Statistical analyses were performed by using IBM SPSS Statistics version 25.0 software (IBM SPSS, Chicago, Illinois).

Results

Characteristics of the infants and their mothers are presented in **Table 1**. Birth by elective caesarean delivery was most common in the early-term group, while emergency caesarean delivery was most common in the post-term group. Early- and post-term infants were most often admitted to a neonatal unit, whereas post-term infants were most often treated with postnatal antibiotic therapy.

Altogether, 53,128 (5.6%) children were admitted to hospital by seven years of age for bronchiolitis/bronchitis, and 22,954 (2.4%) for pneumonia. The rates of hospital admission for

LRTIs were highest in the early-term group. Post-term children were admitted at an older age, but the majority of all admissions for LRTIs were before the age of 36 months in all groups (**Table 2**). Cumulative hazards for both bronchiolitis/bronchitis and pneumonia were highest in the early-term group (**Figure 1 and 2**).

In the risk factor analysis regarding hospital admissions for LRTIs early-term birth was associated with an increased risk of admission for all LRTIs (**Table 3**). Decreased risks of admission for bronchiolitis/bronchitis were seen in the late- and post-term groups, but not as regards pneumonia admission. Maternal age ≤ 25 years, maternal smoking, male sex, both elective and emergency caesarean delivery, small for gestational age, having 1-min Apgar score <4, ventilator support and neonatal antibiotic therapy were associated with an increased risk of admission for LRTIs. Being first-born, being born in a level-II hospital and in the Northern region decreased the risk of admission for all LRTIs, and higher maternal age was associated with decreased admission for bronchiolitis/bronchitis (**Table 3**).

In the post-term subgroup, maternal smoking, birth in other than the Northern region, ventilator support and neonatal antibiotic therapy associated with an increase in all admissions for LRTIs, and maternal age ≤ 20 years and male sex remained as risk factors of admission for bronchiolitis/bronchitis, but no association was found between birth by caesarean and LRTIs (**Table 4**).

Comment

Principal findings

In this large national cohort of births in Finland early-term birth emerged as a risk factor of hospital admission for all LRTIs up to seven years of age, while increasing GA, and late- and post-term birth, were associated with a decreased risk of admission for bronchiolitis/bronchitis. According to multivariable analyses, the other most relevant risk factors of admission for LRTIs were maternal smoking during pregnancy, caesarean delivery, male sex, neonatal ventilator support and early antibiotic therapy. Several maternal and perinatal factors were associated with the risk of LRTIs, even after exclusion of multiple gestations, preterm infants and those with congenital anomalies.

Strengths of the study

Strengths of this study are the reliable national population-based well-established and validated register data and the large number of infants.[16-18] In Finland there are only public children's hospitals, and therefore in this age group all hospital admissions for LRTIs can be derived reliably from the registers.

Limitations of the data

This study has some limitations. As in all register studies, recording practices may differ among staff, sites and regions, and over time periods. The diagnosis of LRTI is difficult and controversial, especially in younger children, as result of variable presentations and the lack of definitive diagnostic tests. It is challenging to differentiate between diagnoses of bronchiolitis and wheezing bronchitis, and therefore these have often been analysed together. Hence, we included all hospital admissions for bronchiolitis/bronchitis and pneumonia in our analysis to facilitate comparison with other studies.

Because of the study design, children born in the latest years of the study period had shorter follow-up times than those born in earlier years. The mean age was 10–12 months in connection with bronchiolitis/bronchitis and 25–27 months with pneumonia. Approximately 90% of admission for bronchiolitis/bronchitis and 65% of those for pneumonia occurred before the age of three years and most infants were followed up for longer than that. Data on parental asthma, postnatal smoke exposure and duration of breastfeeding were lacking.

Interpretation

The findings on the association between early-term birth and the risk of hospital admission for LRTIs support previous findings.[7,8,19-21] In a cohort study, where children born via induced early-term delivery were compared with those with full- or late-term delivery, early-term birth predicted an increased risk of admission for bronchiolitis but not for pneumonia before the age of five. This risk persisted after excluding infants who received neonatal intensive care and/or respiratory care in the neonatal period.[19] Another population-based cohort study revealed an association between early-term birth and long-term respiratory morbidity (i.e. asthma, bronchiolitis, pneumonia) up to the age of 18 years, while late-term birth predicted a decreased risk and no significant association was seen with post-term birth.[20] In a large Australian register study, increased relative risks of admission for LRTIs by 18 years of age were found in children born at 37–38 weeks, whereas birth at 41 weeks or later was associated with modestly reduced rates of admission.[21] Similarly, we also found lower rates of admission for LRTIs in children born late- and post-term. This association could be partly explained by continuous intrauterine maturation of the airways. The last weeks of gestation represent a critical period of lung growth and development with both short- and long-term health consequences.[4, 22] Neonatal ventilator support was associated with an increased risk of LRTIs, also in the post-term subgroup. It seems that regardless of the etiology of lung disease, ventilator support in the neonatal period may be associated with long-term respiratory consequences.

Supported by previous studies,[23,24] an association was detected between maternal smoking and LRTIs in the offspring. Maternal smoking during pregnancy affects fetal lung development, inducing long lasting structural changes, and in addition it may predispose to preterm delivery.[24] Likewise, male sex appeared to increase the risk of hospital admission for both bronchiolitis/bronchitis[23] and pneumonia in the whole study population.

Previous studies have revealed an association between caesarean delivery and later infectious respiratory morbidity.[3,25-27] Studying respiratory outcomes after early-term birth is confounded by higher rates of caesarean delivery in this GA group.[3] Our results suggest that both early-term birth and caesarean delivery are independent risk factors of admission for LRTIs. Interestingly, we found no association between caesarean delivery and LRTIs in the post-term subgroup. The elective caesarean delivery rate was highest in the early-term group, and emergency caesarean delivery was most frequent in the post-term group. Infants born by caesarean delivery, especially by elective caesarean delivery, are exposed differently to maternal hormones, labour-induced stress and microbiota compared with those born by vaginal delivery, and these differences may alter immune modulation and could predispose the infant to an adverse respiratory outcome.[3,26,28] The indication of caesarean delivery could also be a reflection of other risk factors influencing the outcome. Data on underlying reason for the obstetric intervention were not available in the present register study. In Finland national guidelines have recommended clinical assessment at 41-42 weeks of gestation and possible induction of labour at or after 42^{+0} weeks of gestation. The post-term birth rate has remained at approximately 4.1-5.3% over the past 20 years.[29]

Our finding on the association between early antibiotic therapy and later LRTIs suggests long-lasting effects of neonatal antibiotic exposure. Antibiotics affect the infant's gastrointestinal microbiota and maturation of the immune system and may disrupt the development of immunological tolerance.[30] Some reports have linked early antibiotic exposure to asthma, [31,32] but the link to LRTIs is not yet well established. Some confounding factors may play a role, including the fact that antibiotic therapy is more common in infants who are admitted to a neonatal ward. Perinatal infection itself may also modify immune programming.[31]

In line with a previous study, [33] first-born children had a decreased risk of LRTIs. Accordingly, having siblings at home have previously increased the risk of LRTIs.[27] First-born children might be better protected from respiratory infections transmitted by siblings. On the other hand, it has been suggested that first-born children may have a reduced anti-inflammatory profile in their T-cells at birth and thus an enhanced risk of subsequent immune-related diseases.[34] Supporting previous findings, small birth weight for gestational age [21] and low 1-min Apgar scores were associated with bronchiolitis/bronchitis, [23] as well as pneumonia.

Young maternal age was associated with an increased risk of hospital admission for LRTIs among the offspring, and higher maternal age seemed to decrease the risk of bronchiolitis/bronchitis. Higher maternal age has been related to adverse neonatal risks, but maternal age at birth may also reflect other health and social processes.[35] Young maternal age and low maternal socioeconomic status (SES) have been associated with an increased risk of hospital admission for bronchiolitis.[22] Data on maternal SES were not available in the present study, but maternal smoking can be regarded as a surrogate marker of SES, because smoking during pregnancy correlates strongly with lower maternal SES in Finland.[36]

The association between births in other than level-III hospitals and the decreased risk of admission for LRTIs could be explained by the fact that level-III hospitals are located in larger cities with the highest population densities. Accordingly, a decreased risk of admission was seen in the Northern region, i.e. the region with the lowest population density.

Conclusions

Early-term birth was associated with an increased risk of hospital admission for LRTIs by seven years of age, while late-term and post-term birth decreased the risk of admission for bronchiolitis/bronchitis compared with full-term birth. Much is still unknown about the risk factors of childhood LRTIs, but our results suggest that early-life exposures seem to have an important role. Means to affect underlying risk factors such as maternal smoking during pregnancy, timing of birth by elective caesarean delivery, ventilator support and neonatal antibiotic therapy should be considered.

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Funding

Funding for the work (Dr. Haataja) was received from Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital (grant number 9R051) and Tampere Tuberculosis Foundation. The funding sources had no role in the study.

Table 1. Perinatal and neonatal characteristics of the mothers and the infants born at ≥ 37 weeks of gestation in 1991–2008 and followed-up to seven years of age (N=948,695).

	Early-term 37^{+0}–38^{+6} weeks (n=168,239)		Full-term 39^{+0}–40^{+6} weeks (n=543,815)		Late-term 41^{+0}–41^{+6} weeks (n=189,325)		Post-term ≥ 42 weeks (n=47,316)	
Mothers								
Maternal age (years), n (%)								
≤ 20	7699	(4.6)	25,717	(4.7)	9894	(5.2)	2613	(5.5)
21-25	31,990	(19.0)	110,696	(20.4)	40,443	(21.4)	10,330	(21.8)
26-30	57,339	(34.1)	194,139	(35.7)	67,818	(35.8)	16,677	(35.2)
31-35	46,197	(27.5)	145,747	(26.8)	49,814	(26.3)	12,294	(26.0)
≥ 36	25,014	(14.9)	67,516	(12.4)	21,367	(11.3)	5402	(11.4)
Smoking, n (%)								
No	137,559	(81.8)	452,051	(83.1)	156,913	(82.9)	38,632	(81.6)
Yes	26,428	(15.7)	79,292	(14.6)	28,409	(15.0)	7752	(16.4)
Missing	4252	(2.5)	12,472	(2.3)	189,325	(2.1)	932	(2.0)
First delivery, n (%)	66,331	(39.4)	212,858	(39.1)	81,652	(43.1)	25,057	(53.0)
Previous deliveries, Median (IQR)	1	(0-2)	1	(0-2)	1	(0-1)	1	(0-1)
Place of birth, n (%)								
University hospital (level-III)	54,915	(32.6)	166,672	(30.6)	55,913	(29.5)	15,590	(30.9)
Central hospital (level-II)	75,254	(44.7)	250,753	(46.1)	89,391	(47.2)	22,123	(46.8)
Other[a]	38,050	(22.6)	126,317	(23.2)	43,999	(23.2)	9593	(20.3)
Missing	20	(0.0)	73	(0.0)	22	(0.0)	10	(0.0)
Region of birth, n (% of infants in region)								
Southern	55,238	(32.8)	184,664	(34.0)	67,586	(35.7)	18,930	(40.0)
Eastern	24,778	(14.7)	82,662	(15.2)	27,924	(14.7)	6393	(13.5)
Western	32,311	(19.2)	106,683	(19.4)	36,690	(19.4)	8723	(18.4)
Southwest	29,969	(17.8)	83,757	(15.4)	28,271	(14.9)	5484	(11.6)
Northern	25,764	(15.3)	85,504	(15.7)	28,686	(15.2)	7768	(16.4)
Missing	179	(0.1)	545	(0.1)	168	(0.1)	18	(0.0)
Mode of delivery, n (%)								
Vaginal	131,724	(78.3)	471,990	(86.8)	169,123	(89.3)	38,873	(82.2)

Elective caesarean	22,395	(13.3)	39,448	(7.3)	3176	(1.7)	1092	(2.3)
Emergency caesarean	13,996	(8.3)	31,922	(5.9)	16,886	(8.9)	7316	(15.5)
Missing	124	(0.1)	455	(0.1)	140	(0.1)	35	(0.1)
Newborns								
Boys, n (%)	89,311	(53.1)	274,205	(50,4)	94,235	(49.8)	24,211	(51.2)
Birthweight, g, Median (IQR)	3275	(2970-3590)	3600	(3310-3900)	3775	(3490-4080)	3850	(3560-4150)
Birthweight-for-gestational age, n (%)								
Small for gestational age	4597	(2.7)	7592	(1.4)	1948	(1.0)	302	(0.6)
Appropriate for gestational age	155,954	(92.7)	521,382	(95.9)	182,853	(96.6)	45,520	(96.2)
Large for gestational age	7697	(4.6)	14,841	(2.7)	4524	(2.4)	1494	(3.2)
Apgar 1 min, Median (IQR)	9	(9-9)	9	(9-9)	9	(8-9)	9	(8-9)
0-3	1325	(0.8)	3543	(0.7)	1691	(0.9)	618	(1.3)
4-10	166,664	(99.1)	539,561	(99.2)	187,402	(99.0)	46,656	(98.6)
Missing	250	(0.1)	711	(0.1)	232	(0.1)	42	(0.1)
Resuscitation at birth, n (%)	563	(0.3)	1362	(0.3)	716	(0.4)	318	(0.7)
Admission to neonatal unit, n (%)	162,210	(9.6)	26,6362	(4.8)	10,059	(5.3)	3231	(5.9)
Ventilator support, n (%)	750	(0.4)	1148	(0.2)	574	(0.3)	228	(0.5)
Antibiotic therapy in the first week of life, n (%)	4514	(2.7)	11,403	(2.1)	5623	(3.0)	1949	(4.1)

Statistically significant differences were assessed by Pearson's chi-square test or the Kruskal-Wallis test.

[a] Regional hospital, private hospital, health center, home birth.

IQR, interquartile range

Table 2. Hospital admissions for lower respiratory tract infections up to the age of seven years among early-term, full-term, late-term and post-term children. 1991–2008 (n=948,695).

	Early-term 37^{+0}–38^{+6} weeks (n=168,239)		Full-term 39^{+0}–40^{+6} weeks (n=543,815)		Late-term 41^{+0}–41^{+6} weeks (n=189,325)		Post-term ≥ 42 weeks (n=47,316)	
Acute bronchiolitis/bronchitis (466, J20-J21), n (%)	11,349	(6.7)	29,919	(5.5)	9602	(5.1)	2258	(4.8)
Age at diagnosis, Median (IQR), in months	10	(4-21)	11	(4-22)	12	(4-23)	12	(4-24)
0-11 months, n (%)	6173	(54.4)	15,112	(50.5)	4727	(49.2)	1115	(49.4)
12-35 months, n (%)	4085	(36.0)	11,477	(38.4)	3767	(39.2)	848	(37.6)
36-84 months, n (%)	1091	(9.6)	3330	(11.1)	1108	(11.5)	295	(13.1)
Number of visits, Median (IQR)	2	(1-2)	2	(1-2)	2	(1-2)	2	(1-2)
Pneumonia (480-486, J12-18), n (%)	4660	(2.8)	12,859	(2.4)	4369	(2.3)	1066	(2.3)
Age at diagnosis, Median (IQR), in months	25	(15-43)	25	(15-43)	26	(15-44)	27	(16-45)
0-11 months, n (%)	766	(16.4)	1953	(15.2)	619	(14.2)	148	(13.9)
12-35 months, n (%)	2291	(49.2)	6562	(51.0)	2230	(51.0)	517	(48.5)
36-84 months, n (%)	1603	(34.4)	4344	(33.8)	1520	(34.8)	401	(37.6)
Number of visits, Median (IQR)	1	(1-2)	1	(1-2)	1	(1-2)	1	(1-2)

IQR, interquartile range

Table 3. Cox proportional hazard regression models regarding hospital admissions for bronchiolitis/bronchitis (n=53,128) and pneumonia (n=22,954) by the age of seven years in the whole study population in 1991–2008 (N=948,695).

		Bronchiolitis/bronchitis n=53,128/N=948,695		Pneumonia n=22,954/N=948,695	
Explanatory variables	N	n	Adjusted HR (95% CI)	n	Adjusted HR (95% CI)
Gestational age group					
Full-term	543,815	29,919	1.00 (Reference)	12,859	1.00 (Reference)
Early-term	168,239	11,349	1.21 (1.18,1.23)	4660	1.16 (1.12,1.20)
Late-term	189,325	9602	0.93 (0.91,0.95)	4369	0.98 (0.95,1.01)
Post-term	47,316	2258	0.89 (0.85,0.93)	1066	0.96 (0.90,1.02)
Mother's age (years)					
≤ 20	45,923	3088	1.41 (1.35,1.47)	1183	1.13 (1.06,1.20)
21-25	193,459	11,387	1.14 (1.11,1.67)	4720	1.05 (1.01,1.09)
26-30	335,962	183,99	1.00 (Reference)	8007	1.00 (Reference)
31-35	254,052	13,723	0.92 (0.90,0.94)	6165	1.00 (0.96,1.03)
≥ 36	119,299	6531	0.89 (0.86,0.92)	2879	0.98 (0.94,1.02)
Smoking					
No	785,155	41,301	1.00 (Reference)	18,672	1.00 (Reference)
Yes	141,881	10,588	1.39 (1.36,1.42)	3689	1.08 (1.05,1.12)
First delivery					
No	562,797	35,589	1.00 (Reference)	14,037	1.00 (Reference)
Yes	385,898	17,539	0.63 (0.62,0.64)	8917	0.88 (0.86,0.91)
Place of birth					
University hospital (level-III)	293,090	17,143	1.00 (Reference)	7381	1.00 (Reference)
Central hospital (level-II)	437,521	24,722	0.95 (0.93,0.97)	10,263	0.91 (0.89,0.94)
Other[a]	217,959	11,261	0.84 (0.82,0.86)	5306	0.97 (0.93,1.00)
Region of birth					
Northern	147,722	7252	1.00 (Reference)	2640	1.00 (Reference)
Southern	326,418	18,682	1.29 (1.25,1.32)	7850	1.38 (1.32,1.45)
Eastern	141,757	7587	1.11 (1.07,1.14)	3750	1.52 (1.45,1.60)
Western	184,407	11,069	1.26 (1.22,1.30)	4834	1.50 (1.43,1.57)
Southwest	147,481	8527	1.23 (1.19,1.27)	3864	1.48 (1.40,1.55)
Mode of delivery					
Vaginal	811,710	45,010	1.00 (Reference)	19,416	1.00 (Reference)

Elective caesarean	66,111	4124	1.10 (1.07,1.14)	1712	1.06 (1.00,1.11)
Emergency caesarean	70,120	3962	1.10 (1.06,1.14)	1804	1.08 (1.02,1.13)
Sex					
Girl	466,733	20,248	1.00 (Reference)	10,598	1.00 (Reference)
Boy	481,962	32,880	1.58 (1.55,1.61)	12,356	1.12 (1.10,1.15)
Birthweight-for-gestational age					
Appropriate for gestational age	905,700	50,473	1.00 (Reference)	21,878	1.00 (Reference)
Small for gestational age	14,439	920	1.10 (1.03,1.18)	400	1.11 (1.01,1.23)
Large for gestational age	28,556	1735	1.02 (0.97,1.07)	676	0.94 (0.87,1.02)
1-min Apgar score					
≥4	940,283	52,566	1.00 (Reference)	22,698	1.00 (Reference)
0-3	7177	496	1.02 (1.03,1.25)	233	1.20 (1.04,1.37)
Resuscitation at birth					
No	945,736	52,922	1.00 (Reference)	22,848	1.00 (Reference)
Yes	2959	206	0.95 (0.82,1.11)	106	1.12 (0.90,1.39)
Ventilator support					
No	945,995	52,886	1.00 (Reference)	22,840	1.00 (Reference)
Yes	2700	242	1.27 (1.10,1.47)	114	1.38 (1.12,1.71)
Antibiotic therapy					
No	925,206	51,345	1.00 (Reference)	22,226	1.00 (Reference)
Yes	23,489	1783	1.36 (1.29,1.43)	728	1.22 (1.13,1.32)

Multivariable adjusted results are given as hazard ratios (HRs) and 95% confidence intervals (CIs). Adjusted for maternal- (age, smoking during pregnancy, primiparity), delivery- (place of birth, region of birth and mode of delivery) and newborn-related (sex, gestational weight, Apgar score, resuscitation at birth, ventilator or antibiotic therapy during the first week of life) variables.

Results for missing values are not shown.

[a] Regional hospital, private hospital, health center, home birth.

Table 4. Cox proportional hazard regression models regarding hospital admissions for bronchiolitis/bronchitis (n=2258) and pneumonia (n=1066) by the age of seven years among post-term children in 1991–2008 (N=47,316).

		Bronchiolitis/bronchitis n=2258/N=47,316		Pneumonia n=1066/N=47,316	
Explanatory variables	N	n	Adjusted HR (95% CI)	n	Adjusted HR (95% CI)
Mother's age (years)					
≤ 20	2613	166	1.58 (1.32,1.88)	68	1.27 (0.97,1.66)
21-25	10,330	512	1.12 (1.00,1.26)	237	1.11 (0.94,1.31)
26-30	16,677	776	1.00 (Reference)	348	1.00 (Reference)
31-35	12,294	537	0.87 (0.78,0.98)	287	1.10 (0.94,1.29)
≥ 36	5402	267	0.94 (0.82,1.08)	126	1.08 (0.88,1.33)
Smoking					
No	38,632	1737	1.00 (Reference)	837	1.00 (Reference)
Yes	7752	485	1.36 (1.23,1.51)	210	1.23 (1.07,1.45)
First delivery					
No	22,259	1242	1.00 (Reference)	524	1.00 (Reference)
Yes	25,057	1016	0.63 (0.57,0.69)	542	0.87 (0.77,1.00)
Place of birth					
University hospital (level-III)	15,590	777	1.00 (Reference)	369	1.00 (Reference)
Central hospital (level-II)	22,123	1023	0.90 (0.82,0.99)	478	0.90 (0.78,1.03)
Other[a]	9593	458	0.90 (0.80,1.02)	219	0.99 (0.83,1.17)
Region of birth					
Northern	7768	322	1.00 (Reference)	128	1.00 (Reference)
Southern	18,930	959	1.31 (1.15,1.49)	422	1.40 (1.14,1.71)
Eastern	6393	261	1.00 (0.85,1.16)	171	1.69 (1.34,2.12)
Western	8723	450	1.26 (1.09,1.45)	206	1.47 (1.18,1.83)
Southwest	5484	256	1.13 (0.96,1.33)	139	1.56 (1.23,1.99)
Mode of delivery					
Vaginal	38,873	1885	1.00 (Reference)	876	1.00 (Reference)
Elective caesarean	1092	50	1.00 (0.76,1.33)	23	0.95 (0.63,1.44)
Emergency caesarean	7316	322	0.99 (0.87,1.12)	167	1.01 (0.85,1.20)
Sex					
Girl	23,105	881	1.00 (Reference)	532	1.00 (Reference)
Boy	24,211	1337	1.51 (1.39,1.64)	534	0.95 (0.85,1.08)

Birthweight-for-gestational age					
Appropriate for gestational age	45,520	2180	1.00 (Reference)	1020	1.00 (Reference)
Small for gestational age	302	12	0.79 (0.45,1.40)	10	1.40 (0.75,2.62)
Large for gestational age	1494	66	0.89 (0.69,1.14)	36	1.06 (0.76,1.48)
1-min Apgar score					
≥4	46,656	2221	1.00 (Reference)	1047	1.00 (Reference)
0-3	618	32	0.95 (0.65,1.38)	16	0.88 (0.51,1.50)
Resuscitation at birth					
No	46,998	2236	1.00 (Reference)	1053	1.00 (Reference)
Yes	318	22	1.13 (0.70,1.84)	13	1.32 (0.70,2.51)
Ventilator support					
No	47,088	2237	1.00 (Reference)	1053	1.00 (Reference)
Yes	228	21	1.67 (1.01,2.76)	13	2.00 (1.04,3.85)
Antibiotic therapy					
No	45,367	2140	1.00 (Reference)	1004	1.00 (Reference)
Yes	1949	118	1.28 (1.05,1.57)	62	1.33 (1.00,1.75)

Multivariable adjusted results are given as hazard ratios (HRs) and 95% confidence intervals (CIs). Adjusted for maternal- (age, smoking during pregnancy, primiparity), delivery- (place of birth, region of birth and mode of delivery) and newborn-related (sex, gestational weight, Apgar score, resuscitation at birth, ventilator or antibiotic therapy during the first week of life) variables.

Results for missing values are not shown

[a] Regional hospital, private hospital, health center, home birth.

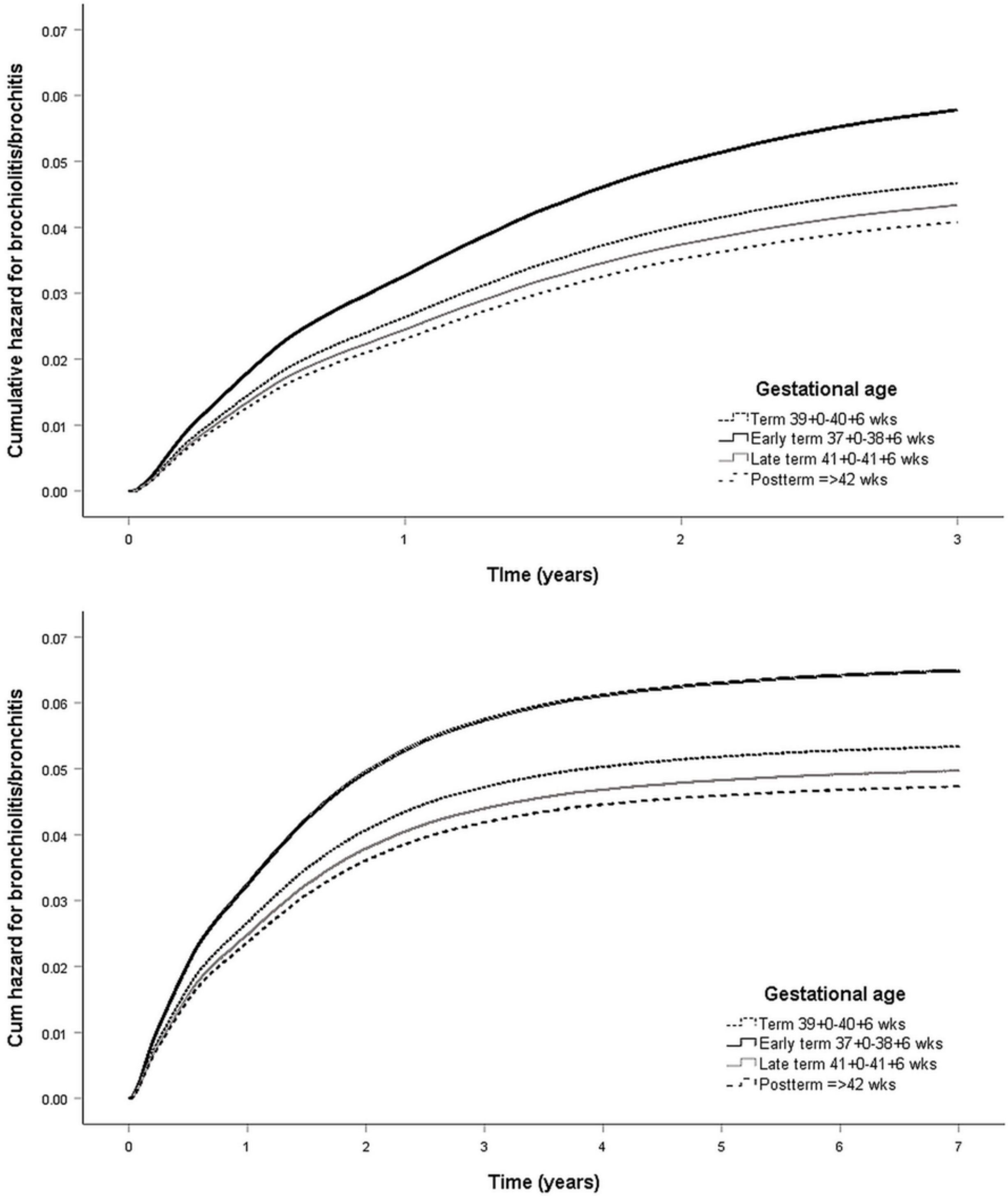
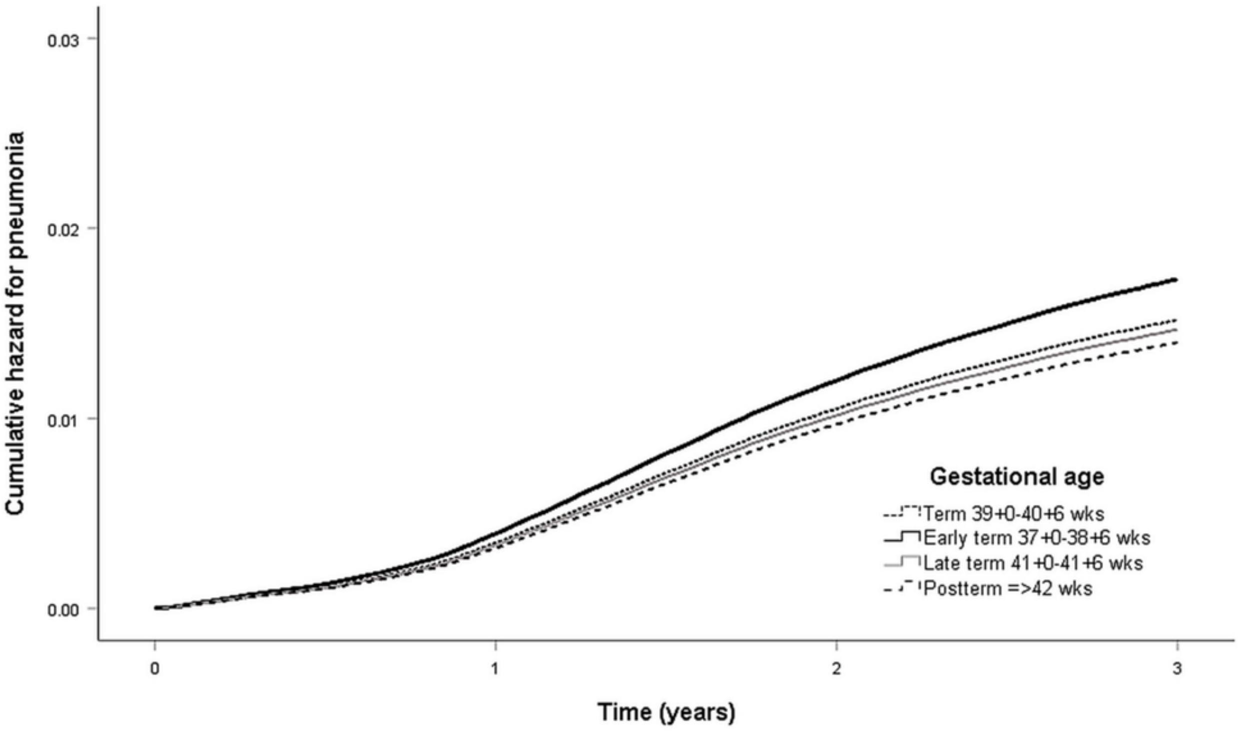


Figure 1. Cumulative hazard for bronchiolitis/bronchitis between the GA groups, follow-up time three and seven years (derived from the multivariable adjusted Cox model).



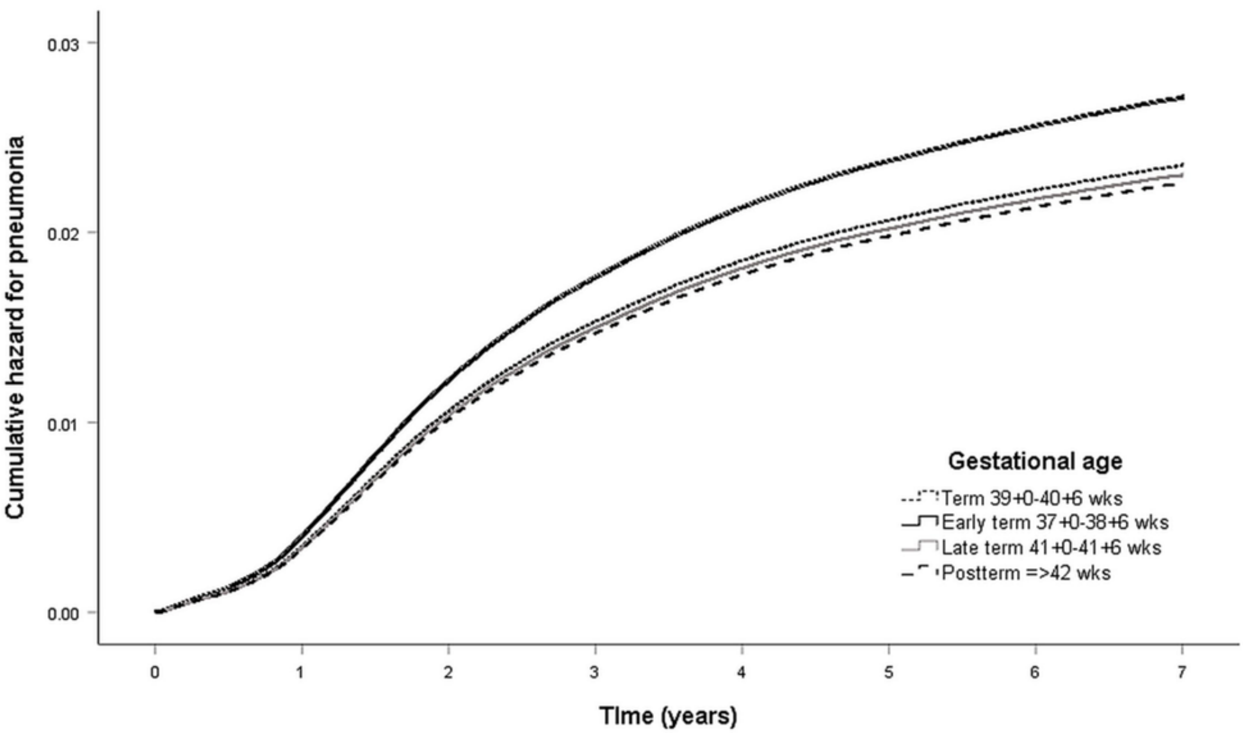


Figure 2. Cumulative hazard for pneumonia between the GA groups, follow-up time three and seven years (derived from the multivariable adjusted Cox model).

eFigure 1. Directed acyclic graph model showing a rationale for selection of covariates associated with LRTIs.