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Gestation at birth, mode of birth, infant feeding and childhood hospitalization with infection

Running title: Perinatal factors and childhood infection

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Conflicts of Interest

The author(s) report no conflicts of interest.

Abstract

Introduction: Infections are a leading cause of mortality and morbidity in preschool children. We aimed to assess the impact of the co-occurrence of cesarean section, early birth and formula feeding on hospitalization with infection in early childhood. *Material and methods:* Population-based retrospective record-linkage cohort study of 488 603 singleton livebirths ≥ 32 weeks gestational age in New South Wales, Australia, 2007–2012. Multivariable Cox-regression was used to estimate independent and combined adjusted associations of gestational age, mode of birth (vaginal or cesarean section by labor onset) and formula feeding with time to first and repeat hospitalization with infection for children < 5 years of age. *Results:* 95 346 (19.5%) children were hospitalized with infection, and of these 24.8% (23 615) more than once. Median age at first and repeat hospitalization was 1.1 and 1.7 years, respectively. Earlier gestation, modes of birth other than spontaneous vaginal, and formula feeding were independently associated with an increased risk of first and repeat hospitalization with infection. At 32-36 weeks gestation, co-occurrence of perinatal factors (Cf. spontaneous vaginal birth at 39+ weeks without formula feeding) was associated with a 2-fold and 1.5-fold increased risk of first and repeat hospitalization, respectively. For births at 37-38 weeks, the increased risk was 1.5-fold and 1.25-fold for first and repeat hospitalization, respectively. *Conclusions:* Cesarean section, labor induction, birth < 39 weeks and formula feeding increase the risk of infection-related

hospitalization in childhood, which increases further when these factors co-occur. Reducing early planned birth and supporting breastfeeding are potentially cost-effective approaches to reducing these hospitalizations.

Keywords

Preterm birth; Early-term birth; Cesarean; Induction of labor; Breastfeeding; Infections; Neonatology.

Abbreviations

CS cesarean section

GA gestational age

NSW New South Wales

Key message

The co-occurrence of cesarean section and/or labor induction, birth <39 weeks gestation and formula feeding are associated with an increased risk of infection-related hospitalization in childhood. Reducing early planned birth and supporting breastfeeding may assist to reduce these hospitalizations.

Introduction

Childhood infection is a leading cause of morbidity and mortality worldwide.(1) Population data from high income countries suggest that approximately one quarter of all children are hospitalized at least once with an infection by age five years, and one in ten have multiple hospitalizations.(2, 3) An increased risk of infection among preschool children is associated with socio-demographic (e.g. socioeconomic status, season of birth, parity, maternal age, birth order and sibling number) and perinatal factors (e.g. cesarean section (CS), reduced gestational age (GA), suboptimal intrauterine growth, and infant feeding).(2, 4-8) The proportion of early planned births and births by CS have been increasing worldwide.(9, 10) Birth interventions may have a negative impact on breastfeeding rates, which are also reported to be decreasing. Furthermore, these factors have been associated with compromised immune system in early life (11) and it is important to assess whether the effect is cumulative, persists into childhood and predisposes children to one or many (recurrent) infections. No studies have yet assessed the combined effect of key perinatal factors on the risk of hospitalization with any infection in young children in the general population. Given some of these perinatal factors are modifiable, such data could inform broadly applicable intervention strategies and behavior change.

Two population-based studies from Western Australia found that among children hospitalized with infections, 36% had a repeat hospitalization for any infection before 18 years of age, and 20% had a repeat hospitalization for lower respiratory tract infection before age three.(2, 12) They also found lower birth weight and earlier GA were associated with an increasing number of hospitalizations with infection during childhood.(2) Beyond these studies and factors there is almost no population-based information about the association of perinatal risk factors and repeated hospitalization with infection, and specifically, the time from the first to subsequent hospitalization with infection. Information and understanding of infections in childhood is of increasing importance with recent studies showing infections in early life to impact subsequent child neurodevelopment and adult health later in life by increasing the risk of poorer metabolic and cardiovascular health, as well as psychotic disorders (13, 14, 15).

We investigated the independent and combined associations of mode of birth, GA, and infant feeding with the timing of first and repeat hospitalization with infection in early childhood using population-based linked data.

Material and methods

The study population included all liveborn singletons of ≥ 32 weeks GA born 2007-2012 in New South Wales (NSW), Australia. Births to non-NSW resident mothers (1.4% of births) were excluded as childhood hospitalizations occurring outside of NSW were not available for record linkage.⁽¹⁶⁾ Home births (0.3% of births) were excluded as they lack a hospital delivery record and may have different outcomes. Infants born < 32 weeks GA, those with major congenital conditions, or twins and higher-order multiple births were also excluded as they have very different risk profiles, clinical management for the timing of birth, and outcomes. Each child was followed from birth until the earliest of their fifth birthday, death or the end of the study period (31 March 2014).

We used linked records from the NSW Perinatal Data Collection, the NSW Admitted Patient Data Collection and the NSW Registry of Births, Deaths and Marriages Death Registrations. The Perinatal Data Collection is a population-based statutory collection including all live births and stillbirths of at least 20 weeks gestation or, if GA is unknown, at least 400 grams birth weight. It contains information on maternal characteristics, pregnancy, labor and delivery, and infant outcomes. The Admitted Patient Data Collection includes demographic and service related data for each hospitalization in any public or private hospital in NSW. Diagnoses are coded according to the 10th revision of the International Classification of Diseases, Australian Modification. Death registrations data provided fact of death information. These data were probabilistically linked by the NSW Centre for Health Record Linkage with only de-identified information provided to the researchers.

The perinatal study factors of interest included mode of birth, GA at birth, and infant feeding at discharge from the birth hospitalization. Labor onset and vaginal or CS birth are recorded in the birth record and were combined to create five mode of birth categories: vaginal birth following spontaneous labor, CS following spontaneous labor, vaginal birth following labor induction, CS following labor induction, and pre-labor CS. Planned birth was defined as labor induction or pre-labor CS. GA was determined by the best clinical estimate including early ultrasound and last menstrual period and reported in completed weeks. GA was classified as moderately preterm

(32-33 weeks), late preterm (34-36 weeks), early-term (37-38 weeks), full-term (39-40 weeks) and late-term or post-term (≥ 41 weeks). Infant feeding status at discharge from the birth hospitalization is recorded using one or more of the three following categories: “breastfeeding”, “expressed breast milk” or “infant formula”. These categories were used to create two mutually exclusive groups: any breast milk feeding (breastfeeding or expressed breast milk feeding, with or without infant formula) and only formula feeding (infant formula and no breastfeeding or expressed breast milk feeding).

The study outcome was childhood hospitalization for an infection after discharge from the birth hospitalization to the earliest of the fifth birthday, death, or the end of study period (31 March 2014) at which point data were censored. Primary and first additional diagnoses codes of infection were used to identify any hospitalization with infection.⁽²⁾ These diagnoses codes used were based upon previously published studies; a full list is provided in Supporting Information Table S1.^(2, 17) Any hospitalization with infection occurring within seven days of a previous hospitalization with infection was considered a single event, and inter-hospital transfers were treated as part of the same hospitalization.

Statistical analyses

The number and proportion of children with zero, one, or more than one hospitalization for any infection during the study period were calculated by the perinatal study factors (mode of birth, GA and formula feeding), and covariates. Cox regression with age as the time-scale was used to model the association (hazard ratios) between study factors and age at first hospitalization with infection. Due to the high variability of age at first hospitalization with infection (entry into observation for repeat infection), the analysis of the first repeat infection used Cox regression with time since the first hospitalization as the time-scale.⁽¹⁸⁾ Age at first hospitalization was adjusted for using penalized splines. Multivariable Cox models included adjustment for covariates previously identified in the literature as risk factors (2, 4, 7, 8, 12, 19) and were maternal age, socioeconomic status, Australia-born mother, married or de facto relationship, parity, smoking, hypertension or diabetes during pregnancy, baby’s sex, birthweight z-score (standardized by Australian national GA and sex), infection during the birth admission, neonatal length of stay z-score (standardized by GA and vaginal versus cesarean delivery within the study population), season and year of birth. Socioeconomic status used an area-level measure assigned

according to postcode of residence at the time of birth, and is created using variables for occupation, education or qualifications, and unemployment (see also Supporting Information Table S2). Overall model fit was assessed using the cumulative Hazard function of the Cox-Snell residuals and the proportional hazards assumption was assessed using significance tests and plots of Schoenfeld residuals. Combined associations with infection were calculated for mode of birth, GA at birth (32-36, 37-38, ≥ 39 weeks) and formula feeding.

As the available data did not contain detailed information for the clinical indications or reasons for planned birth (labor induction or pre-labor CS), the main analysis was repeated using a subgroup of low-risk pregnancies to assess the possible impact of residual confounding by indication on the association with mode of birth. A low-risk pregnancy included women aged 20 to 34 years without diabetes or hypertension who delivered a liveborn, singleton infant at ≥ 37 weeks gestation, cephalic presentation, and with a birthweight for GA and sex between the 10th and 90th percentiles. The level of missing information was minimal for all variables (0% to 0.07%) with the exception of formula feeding (0.53%) and relationship status (0.48%). As only 1.2% of children had missing information for any variable a complete case analysis was performed. Analyses were performed in R version 3.3.1 (<https://www.r-project.org/>).

Ethical approval

Approval for the record linkage and use of the data was obtained from the NSW Population and Health Services Research Ethics Committee (#2012-12-430).

Results

The final study population comprised 488 603 children (Figure 1) with a total follow-up time of 1 856 833 child-years and median follow-up of 4.2 years per child. Overall, 95 346 (19.5%) children were hospitalized for an infection, of whom three-quarters (n=71 731, 14.7% of total population) were hospitalized once and a quarter (n=23 615, 4.8%) more than once (Table 1). The proportion of children hospitalized at least once was higher for those born by CS, at lower GA and in those only formula fed (Table 1). Number of hospitalizations by each study covariate

is presented in Supporting Information Table S2. The median age at first hospitalization with infection was 1.1 years (interquartile range 0.5 to 2.1 years).

Mode of birth other than spontaneous vaginal birth, birth <39 weeks GA and formula feeding were each independently associated with an increased risk of child hospitalization with infection, in both crude and adjusted analyses (Table 2). Compared to spontaneous vaginal birth, CS or planned birth was associated with a 1.13 to 1.21-fold increased risk of childhood infection. Risk of hospitalization with infection decreased with increasing GA; with infants born at 32-33 weeks having the highest risk (adjusted hazard ratio 1.86, 95% CI; 1.74 to 2.00) and infants born at 37-38 weeks having a 1.11-fold increased risk of hospitalization (adjusted hazard ratio 1.11, 95% CI; 1.09 to 1.12), compared to infants born at 39-40 weeks (Table 2). Formula fed only (*vs.* breastfed) infants were also more likely to be hospitalized with infection (adjusted hazard ratio 1.14, 95% CI; 1.11 to 1.16). Although model fit was reasonable, there was some evidence of non-proportional hazards for GA and formula feeding. Further analysis stratified by child age revealed evidence of stronger associations with infection in the first 12 months compared to older ages (Supporting Information Table S3). The associations among low-risk pregnancies ($n=227\ 955$, 46.7%) were similar to those in the overall analysis (Table 2).

The co-occurrence of GA, mode of birth and formula only feeding resulted in greater risk of hospitalization for child infection (Figure 2). Compared to vaginal birth following spontaneous labor at ≥ 39 weeks GA with any breast milk feeding, CS or planned birth at <37 weeks with formula feeding was associated with an almost two-fold increased risk of child hospitalization. The increased risk associated with CS or planned birth and formula feeding at 37-38 weeks GA was between 1.4 and 1.5-fold (Figure 2). Even for births at ≥ 39 weeks, planned birth or CS and formula feeding increased the risk of infection-related hospitalization by up to 1.34-fold.

Of the 23 615 children who were hospitalized with infection more than once, the median age at second hospitalization was 1.7 years (interquartile range 1.0 to 2.8 years) with more than half (63.5%) hospitalized within 12 months of their first. Again, mode of birth other than spontaneous vaginal birth, birth <39 weeks GA and formula feeding were independently associated with increased risk of repeat hospitalization for childhood infection (Table 3). Overall model fit was good and there was little evidence the proportional hazards assumption was violated. Among

low-risk pregnancies (n=44 041, 46.2%) the associations for repeat hospitalization were similar but less precise due to reduced sample size (Table 3). Figure 3 presents the combined associations for the perinatal factors and repeat hospitalization for childhood infection, with findings similar to those for the first infection, albeit attenuated.

Discussion

Our study of almost half a million preschool children showed that a fifth were hospitalized at least once for an infection and a quarter of these had greater than one hospitalization. Planned birth or CS, GA <39 weeks and formula only feeding were each independently associated with increased risk of hospitalization with infection. Furthermore, for the first time, we showed the combined effect of the co-occurrence of these perinatal factors; infants born moderately preterm (32-36 weeks GA) by planned birth or CS, and also formula only fed had an almost two-fold increased risk of first hospitalization with infection, and 1.4 to 1.6-fold increased risk of repeat hospitalization, compared to vaginal birth following spontaneous labor at ≥ 39 weeks GA with any breast milk feeding. For infants born early-term (37-38 weeks GA), the combined perinatal factors were associated with a 1.4-1.5-fold increased risk of infection and 1.2-1.3-fold greater risk of repeat hospitalization with infection, compared to vaginal birth following spontaneous labor at ≥ 39 weeks GA with any breast milk feeding.

Infections, including repeat infections among children under five years of age are leading reasons for primary care and acute-care service use, and hospitalization.(1, 3, 20, 21) The independent associations demonstrated in our study are consistent with previous literature (22, 23, 24) reporting that earlier GA, mode of birth (planned birth or CS), and formula feeding are associated with an increased risk of hospitalization with infection in childhood.(2, 4, 5, 8, 22, 23) We also observed stronger associations in infancy for earlier GA and formula only feeding. Similarly a Scottish study (n=502 948) reported stronger associations between formula feeding and hospitalization for overall and clinical sub-groups of infection in the first six months of life.(8)

Less is known regarding overall and time to repeat hospitalization with infection. We found one in four children experienced a subsequent hospitalization with infection, with more than half

occurring within 12 months. Our findings are consistent with the range suggested by previous studies.(2, 12) Additionally, population-based data show that those hospitalized with infection in infancy have three to four times the increased risk of repeat hospitalization with infection later in childhood.(12, 24) Our results add to this and highlight that certain perinatal factors identify children with an increased risk of repeated hospitalization with infection. While, it is well recognized that reduced GA is associated with greater risk of child hospitalization,(19, 25) our study is the first to demonstrate the combined association of GA, mode of birth and formula feeding with time to first repeat hospitalization with infection in childhood.

Findings from the combined associations reveal that early planned birth is associated with an increased risk of hospitalization with infection. Specifically, infants born early term after labor induction or pre-labor CS had a 25-33% increased risk of hospitalization compared to infants born vaginally following spontaneous labor at full-term. The only previous comparable study explored the modifying effects of perinatal factors on child hospitalization for gastroenteritis and reported a 30-40% increased risk of first hospitalization.(4) Two previous US studies found an increased risk of respiratory infections and sepsis associated with reduced GA with elective deliveries compared with expectant management.(22, 23) We provide additional comprehensive information for hospitalization for overall infection, and combined associations by the mode and timing of birth and infant feeding. We also provide the insight that for early planned births, the absence of any breast milk feeding increases the risk of infection from 25-33% to 42-51% compared with spontaneous vaginal birth at full-term.

To our knowledge, no previous study has investigated the association of early planned birth with repeat hospitalization with infection (of any type). For infants born early term following induction or pre-labor CS, there was a 15-20% increased risk of repeat infection compared with spontaneous vaginal birth at full-term. This risk further increased to 20-28% in the absence of any breastfeeding. Approximately a third of women deliver by CS and a similar proportion have labor induction and deliver <39 weeks GA, and additionally, one in ten infants receive formula feeds during the birth hospitalization.(16) The contribution of these potentially modifiable factors to the childhood infection burden is considerable. These findings support clinical trials evaluating practices and policies that discourage planned birth before 39 weeks gestation in the absence of a clear clinical indication and support breastfeeding.(26, 27) However, many of these

studies have focused on short-term birth outcomes, and our findings demonstrate that evaluation of longer term child health and well-being should be assessed.

The mechanisms underlying our epidemiological observations are largely unknown. Our findings provide population-based circumstantial evidence that perinatal factors implicated in dysbiosis of the infant microbiome at birth may increase the risk of infections requiring hospitalization in childhood. The infant microbiome, which is important in early immune development and immune-related outcomes, has been shown to vary by mode of birth, specifically vaginal birth and caesarean section, GA and breastfeeding.(28, 29) The impact of these factors on the infant microbiome and immune system development in early childhood may partly explain the observed associations with later infection risk and mechanistic studies are warranted.

Nevertheless, our findings suggest that vaginal birth at ≥ 39 -40 weeks with breastfeeding may be an effective means to support the appropriate development of the infant microbiome.

Our study used a large population-based cohort which provides complete ascertainment of hospitalizations and reduces the potential impact of selection bias or genetic diversity. We also used variables with demonstrated accuracy and validity.(30) However, administrative data has some unavoidable limitations as only those infections resulting in hospitalization were included and children with less severe infections managed in primary care were not ascertained. Further, data on other potentially relevant factors, such as diet (including duration of breastfeeding), vaccinations, or antibiotic exposure during pregnancy or childhood were not available. Finally the reported associations for planned birth may be subject to confounding by indication. With precise indications for planned birth not available in the data, we examined the associations among a subgroup of low-risk pregnancies and obtained results consistent with the primary analysis.

In conclusion, we have shown using a large population-based record linkage study that the co-occurrence of CS or labor induction, birth before 39 weeks, and formula only feeding increases the risk of first and repeat hospitalization with infection in early childhood. These findings suggest policies that reduce early and planned birth and support breastfeeding may offer a cost-effective population health approach to potentially reduce the burden of pediatric infection.

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Supporting information legends

Table S1. Diagnosis codes used to identify hospital hospitalizations with infection.

Table S2. Study cohort characteristics and number infants hospitalized with infection, NSW 2007-2014.

Footnote: 1. Percent of all children in the row.

2. We used an area-level measure of socioeconomic status assigned according to postcode of residence at the time of birth. This area-level relative measure of socioeconomic status is created using variables for occupation, education or qualifications, and unemployment. Full details are available in the ABS technical document about the construction of the index: Pink, B. Technical paper: Socio-Economic Indexes for Areas (SEIFA). Canberra: Australian Bureau of Statistics, 2011.

Table S3. Hazard ratios for first hospitalization with any infection stratified by age at hospitalization, New South Wales 2007-2014.

Footnote: aHR = adjusted Hazard Ratio, CI = Confidence Interval.

Adjusted for mode of birth, maternal age (by age strata), socioeconomic status, maternal country of birth, marital status, parity (by age strata), smoking in pregnancy, diabetes, hypertension, infant sex, birth weight z-score, length

of stay z-score, infant with an infection in the birth hospitalization (by age strata), season of birth (by age strata), year of birth.

Figure legends

Figure 1. Study flow diagram. NSW, New South Wales; APDC, Admitted Patient Data Collection. *Not mutually exclusive.

Figure 2. Combined associations for age at first hospitalization with infection by mode of birth, gestational age and formula feeding, New South Wales 2007-2014. Adjusted for maternal age, socioeconomic status, maternal country of birth, marital status, parity, smoking in pregnancy, diabetes, hypertension, baby's sex, birth weight z-score, length of stay z-score, infant with an infection in the birth hospitalization, season of birth, year of birth. CI = Confidence Interval.

Figure 3. Combined associations for time to second hospitalization with infection after the first by mode of birth, gestational age and formula feeding, New South Wales 2007-2014. Adjusted for maternal age, socioeconomic status, maternal country of birth, marital status, parity, smoking in pregnancy, diabetes, hypertension, baby's sex, birth weight z-score, length of stay z-score, infant with an infection in the birth hospitalization, season of birth, year of birth. CI = Confidence Interval.

Table 1. Number of infants hospitalized with infection by perinatal factors, New South Wales 2007-2014.

Perinatal factors	Number of infants hospitalized for any infection							
	None		One		Two or more		Total	
	n	% ^a	n	% ^a	n	% ^a	n	%
Total	393 257	80.5	71 731	14.7	23 615	4.8	488 603	100.0

Perinatal factors	Number of infants hospitalized for any infection							
	None		One		Two or more		Total	
	n	% ^a	n	% ^a	n	% ^a	n	%
Mode of birth								
Vaginal, spontaneous labor	191 835	81.4	33 336	14.1	10 537	4.5	235 708	48.2
Vaginal, labor induction	82 160	80.0	15 411	15.0	5093	5.0	102 664	21.0
Cesarean, pre-labor	69 068	78.9	13 663	15.6	4766	5.4	87 497	17.9
Cesarean, spontaneous labor	27 302	79.9	5087	14.9	1790	5.2	34 179	7.0
Cesarean, labor induction	22 892	80.2	4234	14.8	1429	5.0	28 555	5.8
Gestational age at birth (weeks)								
32-33	1859	68.6	537	19.8	312	11.5	2708	0.6
34-36	14 806	74.3	3573	17.9	1539	7.7	19 918	4.1
37-38	93 360	79.1	18 279	15.5	6372	5.4	118 011	24.2
39-40	223 966	81.2	39 394	14.3	12 344	4.5	275 704	56.4
≥41	59 266	82.0	9948	13.8	3048	4.2	72 262	14.8
Formula feeding only								
No	350 298	81.1	61 947	14.3	19 756	4.6	432 001	88.4
Yes	42 959	75.9	9784	17.3	3859	6.8	56 602	11.6

^aPercent of all children in the row.

Table 2. Risk of first hospitalization with childhood infection by perinatal factors, New South Wales 2007-2014.

Perinatal factors	Number	All, crude		All, adjusted ^a		LRP, adjusted ^a	
		N=488 603		N=488 603		N=227 955	
		HR	95% CI	HR	95% CI	HR	95% CI
Total hospitalizations for childhood infection	95 346						
Mode of birth							
Vaginal, spontaneous labor	43 873	1.00	Reference	1.00	Reference	1.00	Reference
Vaginal, labor induction	20 504	1.09	1.07-1.11	1.13	1.11-1.15	1.13	1.10-1.15
Cesarean, pre-labor	18 429	1.17	1.15-1.19	1.17	1.15-1.19	1.13	1.10-1.17
Cesarean, spontaneous labor	6877	1.09	1.06-1.12	1.13	1.11-1.16	1.11	1.07-1.16
Cesarean, labor induction	5663	1.08	1.05-1.11	1.21	1.18-1.25	1.23	1.18-1.29
Gestational age (weeks)							
32-33	849	1.96	1.83-2.09	1.86	1.74-2.00		
34-36	5112	1.47	1.42-1.51	1.41	1.37-1.45		
37-38	24 651	1.14	1.12-1.16	1.11	1.09-1.12	1.10	1.08-1.13
39-40	51 738	1.00	Reference	1.00	Reference	1.00	Reference
≥41	12 996	0.94	0.92-0.96	0.91	0.89-0.93	0.90	0.88-0.93
Formula feeding							
No	81 703	1.00	Reference	1.00	Reference	1.00	Reference
Yes	13 643	1.31	1.29-1.33	1.14	1.11-1.16	1.16	1.13-1.19

^aAdjusted for maternal age, socioeconomic status, maternal country of birth, marital status, parity, smoking in pregnancy, diabetes, hypertension, baby's sex, birth weight z-score, length of stay z-score, infant with an infection in the birth hospitalization, season of birth, year of birth.

Low-risk pregnancy (LRP) was defined as a woman aged 20 to 34 years without diabetes or hypertension with a liveborn, singleton infant born at ≥37 weeks gestation, cephalic presentation, and with a birth weight for GA and sex between the 10th and 90th percentiles.

LRP = Low-risk pregnancies, HR = Hazard Ratio, CI = Confidence Interval.

Table 3. Risk of repeat hospitalization with childhood infection by perinatal factors, New South Wales 2007-2014.

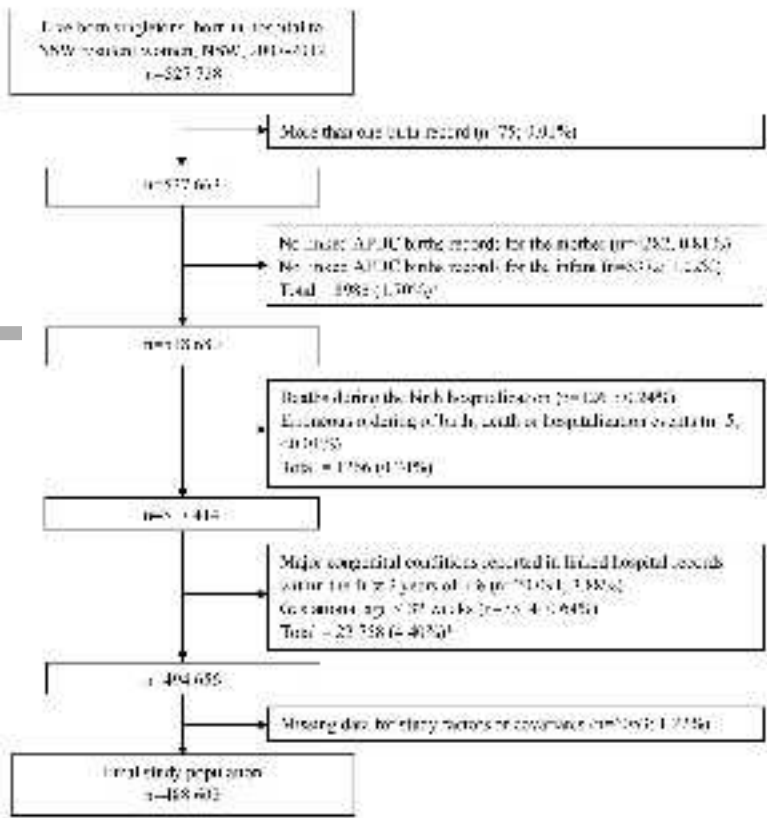
Perinatal factors	Number	All, crude N=95 346		All, adjusted ^a N=95 346		LRP, adjusted ^a N=44 041	
		HR	95% CI	HR	95% CI	HR	95% CI
Total hospitalizations for childhood infection	23 615						
Mode of birth							
Vaginal, spontaneous labor	10 537	1.00	Reference	1.00	Reference	1.00	Reference
Vaginal, labor induction	5093	1.05	1.02-1.09	1.07	1.04-1.11	1.06	1.01-1.11
Cesarean, pre-labor	4766	1.11	1.07-1.15	1.10	1.06-1.14	1.07	1.01-1.14
Cesarean, spontaneous labor	1790	1.11	1.06-1.17	1.11	1.05-1.17	1.07	0.98-1.16
Cesarean, labor induction	1429	1.10	1.04-1.16	1.14	1.07-1.20	1.08	0.98-1.18
Gestational age (weeks)							
32-33	312	1.63	1.46-1.83	1.52	1.36-1.70		
34-36	1539	1.31	1.24-1.38	1.26	1.19-1.33		
37-38	6372	1.09	1.06-1.13	1.07	1.04-1.11	1.07	1.02-1.12
39-40	12 344	1.00	Reference	1.00	Reference	1.00	Reference
≥41	3048	0.97	0.93-1.01	0.96	0.92-1.00	0.94	0.90-1.00
Formula feeding							
No	19 756	1.00	Reference	1.00	Reference	1.00	Reference
Yes	3859	1.15	1.11-1.19	1.08	1.04-1.12	1.06	1.00-1.12

^aAdjusted for maternal age, socioeconomic status, maternal country of birth, marital status, parity, smoking in pregnancy, diabetes, hypertension, baby's sex, birth weight z-score, length of stay z-score, infant with an infection in the birth hospitalization, season of birth, year of birth.

Low-risk pregnancy (LRP) was defined as a woman aged 20 to 34 years without diabetes or hypertension with a liveborn, singleton infant born at ≥37 weeks gestation, cephalic presentation, and with a birth weight for GA and sex between the 10th and 90th percentiles.

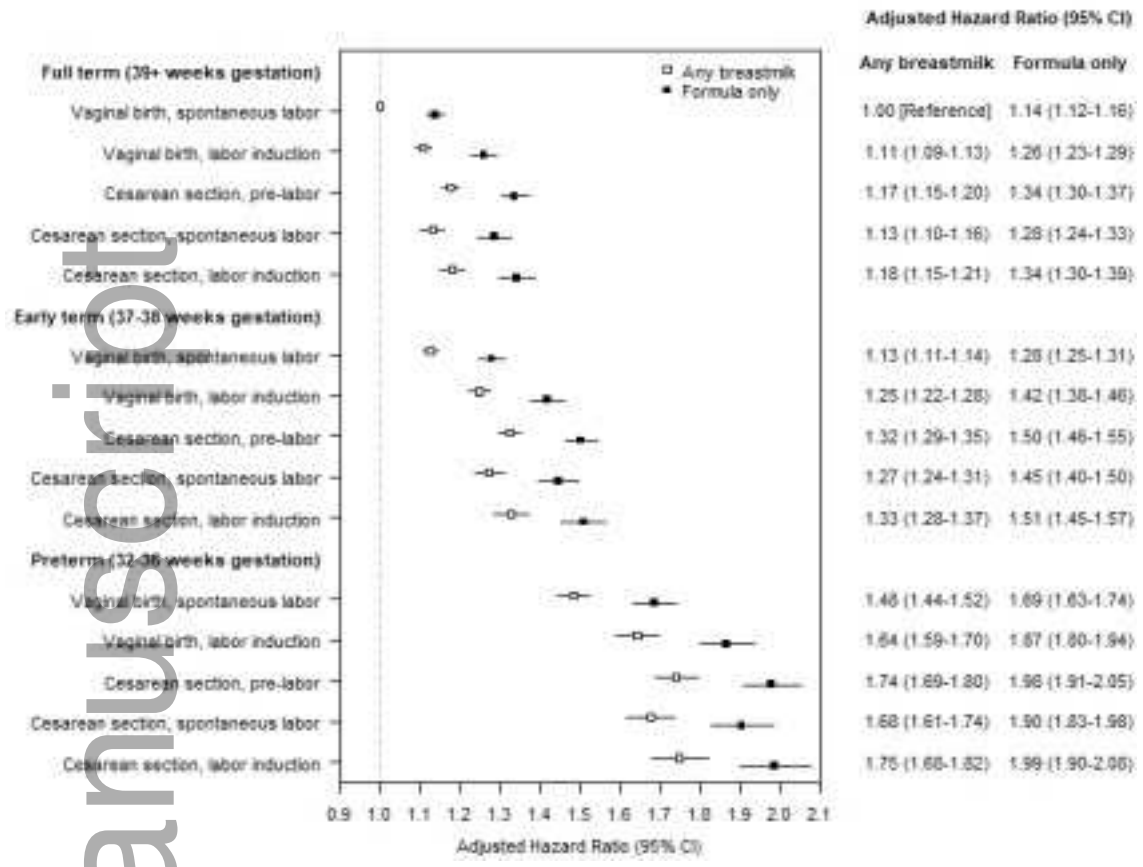
LRP = Low-risk pregnancies, HR = Hazard Ratio, CI = Confidence Interval.

Figure 1. Study flow diagram

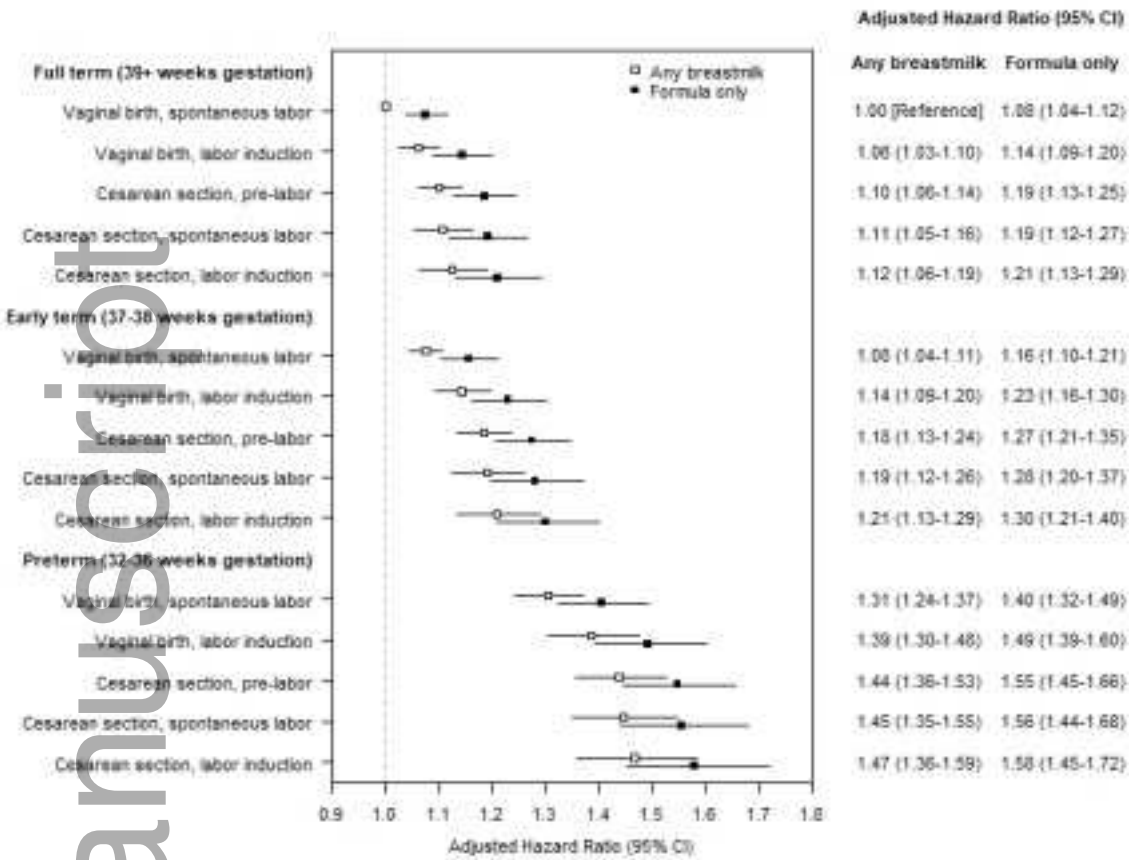


* Not suitable for analysis

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