

Asthma and atopic dermatitis in children born moderately and late preterm

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Abstract This national register study aimed to evaluate the need of asthma medication reimbursement and hospitalization due to asthma and atopic dermatitis up to 7 years of age in moderately preterm (MP) (32–33 weeks) and late preterm (LP) (34–36 weeks) children compared to very preterm (VP) (<32 weeks) and term (≥37 weeks) children. Altogether, 1,018,302 children born in Finland between 1991 and 2008 were assessed. The MP and LP groups received asthma medication reimbursement more frequently than term controls (8.0 and 5.7 vs. 3.8 %), but less frequently than VP children

(15.4 %). Hospitalization due to asthma was more common among MP (10.6 %) and LP (7.3 %) children than term children (4.8 %) but less common than in VP children (20.1 %). Hospitalization due to atopic dermatitis was more frequent among term (5.2 %) compared to MP (4.2 %) and LP (4.7 %) children. Male sex, maternal smoking, maternal diabetes, and ventilator therapy predicted asthma medication in the MP and/or LP children.

Conclusion: MP and LP children seem to need medication and hospitalization for asthma more often than term controls

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but less frequently than VP children followed by 7 years of age. Hospitalization due to atopic dermatitis becomes more common with increasing gestational age.

What is Known:

- *MP and LP infants have an increased risk for early respiratory morbidity and to asthma.*
- *Less is known on the occurrence of atopic dermatitis in this patient group.*

What is New:

- *Medication and hospital care due to asthma were more frequent in school-aged MP and LP than in term infants. Male sex, maternal smoking, maternal diabetes and ventilator therapy predicted asthma.*
- *Hospitalization due to atopic dermatitis became more common with increasing gestational age.*

Keywords Asthma · Atopic dermatitis · Moderately preterm · Late preterm · Preterm

Abbreviations

AGA	Appropriate for gestational age
AHR	Airway hyper-responsiveness
GA	Gestational age
LGA	Large for gestational age
LP	Late preterm
MP	Moderately preterm
MBR	Medical birth register
PROM	Premature rupture of membranes
SD	Standard deviation
SGA	Small for gestational age
VP	Very preterm

Introduction

Moderately and late preterm (MP and LP) children born at 32–36 weeks of gestational age (GA) currently constitute over 80 % of all preterm births [31]. These infants have an increased risk of early respiratory morbidities such as respiratory distress syndrome and transient tachypnea of the newborn compared to term infants [8].

Asthma and atopic dermatitis are common problems in childhood. Fetal and perinatal exposures are thought to have a role in the development of these diseases [4, 23]. An association between extremely preterm birth and chronic respiratory morbidity, including asthma, has been established [5]. Asthma and airway hyper-responsiveness (AHR) subsequent to extremely premature birth seem to differ from typical childhood asthma, showing more association with neonatal respiratory problems and oxygen therapy than with current inflammation [15]. Few studies have evaluated the development of

asthma in MP and LP children compared to children born VP and term [5, 6, 16, 36]. Atopic dermatitis is the most common inflammatory condition in children [4]. Prematurity has been linked to a decreased long-term risk of atopic sensitization [32] and atopic dermatitis [4], but the findings are inconsistent [22].

We aimed to (1) evaluate the association between moderately and late preterm births and the risk of asthma and severe atopic dermatitis and (2) to compare the peri- and neonatal risk factors for asthma and atopic dermatitis by school age among VP, MP, LP, and term groups. We assumed that the risk factors of childhood asthma might differ according to the degree of prematurity.

Materials and methods

The national register-based population was acquired from the Medical Birth Register (MBR). Data on deaths were obtained from the Cause of Death Register and data on major structural anomalies and chromosomal defects [9] from the Register of Congenital Malformation. The data collection has been explained in detail in our previous publication [17]. Altogether, 1,039,263 infants were born alive in Finland between 1991 and 2008. Infants who died before 1 year of age ($n=2576$, 0.25 %), had major congenital anomalies ($n=13,007$, 1.25 %), or had missing data on GA ($n=5,520$, 0.5 %) were excluded. The remaining 1,018,302 (98.0 %) cases were analyzed in VP ($<32^{+0}$ weeks, $n=6347$, 0.6 %), MP (32^{+0} – 33^{+6} weeks, $n=6799$, 0.7 %), LP (34^{+0} – 36^{+6} weeks, $n=39,932$, 3.9 %), and term (≥ 37 weeks, $n=965,224$, 94.8 %) groups. Infants were followed up to 7 years of age or to 2009. Data on all specialized health care outpatient (since 1998) and inpatient visits in public hospitals were collected from the Hospital Discharge Register. A child was considered to have the disease if the following diagnosis was recorded in the register by the end of 2009 (International Classification of Disease 9th Revision ICD-9 in the years 1991–1995 and 10th Revision ICD-10 in the years 1996–2008): asthma (493 and J45, J46), atopic dermatitis (691.8, L20.0), or dermatitis due to ingested food (693.1, L27.2). It was not possible to differentiate between primary and secondary diagnoses. Data on children entitled to asthma medication reimbursement were collected from Finland's Social Insurance Institution database. To be eligible for the reimbursement, a patient must provide a doctor's certificate confirming that asthma has been diagnosed according to the National Finnish Current Care Guidelines [2]. We defined an asthma case as a child who had an asthma medication reimbursement recorded. Register data were linked with a unique anonymized identification code.

Only variables with good validity in the registers were included in the analysis [11, 34]. As possible confounders for the associations between GA groups and asthma and atopic

dermatitis, we included maternal- and delivery-related factors (age, smoking, first delivery, diabetes, assisted reproduction technology, antenatal steroid, number of fetuses, premature rupture of membranes (PROM), level of hospital, and mode of delivery) and newborn-related factors (sex, gestational weight, admission to neonatal unit, ventilator, and antibiotic therapy).

The GA was based on early pregnancy ultrasound, which was nationally used during the study period. A correction of GA was made if the ultrasound-based estimation had a discrepancy of more than 5–7 days compared to last menstrual period [11]. Maternal smoking included smoking during pregnancy and diabetes included mother's gestational diabetes and type 1 and 2 diabetes. Small for GA (SGA) infants were defined as those with a birth weight more than 2.0 standard deviation (SD) below the average for GA and large for GA (LGA) infants as those with a birth weight more than 2.0 SD over the mean weight for GA [28]. PROM was defined as onset of labor more than 24 h after rupture.

Statistical analysis

The background parameters of the study population and differences between the GA groups were tested in categorical variables by Pearson's chi-square test or Fisher's exact test and in continuous variables by Mann-Whitney test. Risk factors for asthma medication reimbursement and hospital visits due to atopic dermatitis in each GA group were sought by Cox logistic regression analysis using multivariate enter models in which all variables were entered simultaneously into the model for each GA category (Tables 3 and 4). The association between GA groups and asthma medication reimbursement or hospital visits due to atopic dermatitis was studied by adjusting the multivariate model by GA categories, using term group as reference. Results were expressed as hazard ratios (HR) and 95 % confidence intervals (95 % CI). Statistical analyses were performed on IBM SPSS Statistics version 20.0.0 (SPSS, Chicago, IL). *p* values <0.05 were considered statistically significant.

Results

The characteristics of infants and their mothers are presented in Table 1. Of all 1,018,302 children followed up to the age of 7 years, 39,991 (3.9 %) received reimbursement for asthma medication and 51,532 (5.1 %) needed hospital care due to asthma and 52,191 (5.1 %) due to atopic dermatitis. The frequencies of asthma medication reimbursement and hospital visits due to asthma increased with decreasing GA (Table 2). All preterm groups received the first reimbursement at younger ages compared to term children. The nonlinear decreasing trend in the incidence of hospital visits due to asthma with

increasing GA and the steepest decline at 30–32 weeks' gestation are shown in Fig. 1. In the multivariate risk factor analyses, male sex and ventilator therapy increased the risk of asthma medication reimbursement among all preterm groups and maternal smoking increased this risk among MP, LP, and term children (Table 3). Maternal diabetes predicted asthma medication in the MP group. Independent HRs for asthma medication reimbursement compared to the term group were in the VP group 3.18 (95 % CI 2.91–3.46), in the MP group 1.77 (95 % CI 1.61–1.94), and in the LP group 1.40 (95 % CI 1.33–1.47).

Hospital visits due to atopic dermatitis became more common with increasing GA (Table 2, Fig. 1). Among children with asthma medication reimbursement (*n*=39,991), the frequencies of hospital visits due to atopic dermatitis in the VP, MP, LP, and term groups were 70 (7.2 %), 59 (10.9 %), 303 (13.4 %), and 6318 (17.4 %), respectively (*p*<0.001). The risk factor analyses for hospital visits due to atopic dermatitis showed a less strong association with peri- and neonatal factors (Table 4). Male sex predicted an increased risk of hospital visits among MP, LP, and term children. Independent HRs for hospital visits due to atopic dermatitis compared to the term group were in the VP group 0.64 (95 % CI 0.56–0.74), in the MP group 0.67 (95 % CI 0.59–0.76), and in the LP group 0.84 (95 % CI 0.79–0.88).

Discussion

MP and LP children received reimbursement for asthma medication and needed hospital care due to asthma more often than term controls but less frequently than VP children by 7 years of age. Hospital visits due to asthma became less common and those due to atopic dermatitis more frequent with increasing GA. As expected, the risk factors for asthma were somewhat different across the GA groups.

Others have also reported the association between MP and LP birth and asthma in childhood [5, 6, 16, 36]. A retrospective cohort study found persistent asthma and use of inhaled corticosteroids more often in LP infants by 18 months compared to those born at term [12]. The incidence of asthma and wheeze was increased at 3 and 5 years of age in MP or LP compared with term children, as was the risk of needing asthma treatment with increasing prematurity [6]. By contrast, no association was found between LP birth and the risk of developing asthma in a population of approximately 500 LP infants aged 2–83 months [1].

Data on the prevalence of atopic dermatitis in premature children compared with term children are conflicting partly due to differences in study design. A prospective follow-up study found no difference in the prevalence of atopic dermatitis between preterm and term children in the first 2 years of life [22]. In accord with our results, others have observed an

Table 1 Characteristics of infants and their mothers; years 1991–2008 ($N = 1,018,302$; infants who died under 1 year of age and infants with major congenital malformations excluded)

	Very preterm <32 weeks ($n = 6347$)	Moderately preterm 32 ⁺⁰ –33 ⁺⁶ weeks ($n = 6799$)	Late preterm 34 ⁺⁰ –36 ⁺⁶ weeks ($n = 39,932$)	Term ≥37 weeks ($n = 965,224$)	p^1 MP vs. VP	p^2 LP vs. VP	p^3 MP vs. T	p^4 LP vs. T
Mother								
Age, mean (SD)	30.2	29.8	29.7	29.2	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Smoking, n (%)	1192 (18.8)	1186 (17.4)	6605 (16.5)	144,097 (14.9)	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
First delivery, n (%)	3329 (52.4)	3792 (55.8)	20,041 (50.2)	392,588 (40.7)	$p < 0.001$	$p = 0.001$	$p < 0.001$	$p < 0.001$
Previous deliveries, Md (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	1 (0–2)	$p < 0.001$	$p = 0.092$	$p < 0.001$	$p < 0.001$
Diabetes ^a , n (%)	92 (1.4)	148 (2.2)	969 (2.4)	8468 (0.9)	$p = 0.002$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Assisted reproductive technology, n (%)	609 (9.6)	768 (11.3)	2764 (6.9)	16,264 (1.7)	$p = 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Number of fetuses at birth, n (%)					$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
1	4525 (71.3)	4593 (67.6)	31,065 (77.8)	948,715 (98.3)				
2	1621 (25.5)	1955 (28.8)	8549 (21.4)	16,490 (1.7)				
3–4	201 (3.2)	251 (3.7)	318 (0.8)	19 (0.0)				
PROM, n (%)	344 (5.4)	351 (5.2)	1282 (3.2)	3518 (0.4)	$p = 0.513$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Birth hospital, n (%)					$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
University hospital (level III)	4957 (78.1)	3995 (58.8)	17,156 (43.0)	299,477 (31.0)				
Central hospital (level II)	1343 (21.2)	2727 (40.1)	17,553 (44.0)	444,961 (46.1)				
Other ^b	42 (0.7)	77 (1.1)	5220 (13.1)	220,659 (22.9)				
Mode of delivery, n (%)					$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Vaginal	2537 (40.0)	3212 (47.2)	26,687 (66.8)	820,961 (85.1)				
Cesarean section	3798 (59.8)	3584 (52.7)	13,212 (33.1)	143,493 (14.9)				
Newborn								
Boys, n (%)	3441 (54.2)	3730 (54.9)	21,660 (54.2)	490,223 (50.8)	$p = 0.457$	$p = 0.967$	$p < 0.001$	$p < 0.001$
Birth weight, g, Md (IQR)	1290 (995–1570)	1970 (1730–2200)	2670 (2360–2985)	3590 (3276–3910)	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Gestational weight, n (%)					$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
SGA	1021 (16.1)	883 (13.0)	3245 (8.1)	16,664 (1.7)				
AGA	4974 (78.4)	5639 (82.9)	34,685 (86.9)	919,989 (95.3)				
LGA	284 (4.5)	277 (4.1)	2002 (5.0)	28,571 (3.0)				
Apgar 1 min, Md (IQR)	7 (5–8)	8 (7–9)	9 (8–9)	9 (9–9)	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Apgar 1 min 0–3, n (%)	1014 (16.0)	326 (4.8)	891 (2.2)	7495 (0.8)	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Apgar 1 min 4–10, n (%)	5223 (82.3)	6397 (94.1)	38,907 (97.4)	956,467 (99.1)	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Resuscitation at birth, n (%)	1909 (30.1)	626 (9.2)	795 (2.0)	3076 (0.3)	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Admission to neonatal unit, n (%)	5703 (89.9)	5975 (87.9)	19,158 (48.0)	58,370 (6.0)	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Ventilator therapy, n (%)	3665 (57.7)	1416 (20.8)	1667 (4.2)	2797 (0.3)	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Phototherapy, n (%)	4203 (66.2)	3822 (56.2)	14,153 (35.4)	36,673 (3.8)	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Antibiotic therapy, n (%)	4511 (71.1)	2961 (43.6)	5038 (12.6)	23,852 (2.5)	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Died by 7 years of age, n (%)	31 (0.5)	7 (0.1)	40 (0.1)	648 (0.1)	$p < 0.001$	$p < 0.001$	$p = 0.235$	$p = 0.013$

Statistical differences were tested by Pearson chi-square test or Fisher's exact or by Mann-Whitney test:

p^1 = moderately preterm vs. very preterm, p^2 = late preterm vs. very preterm, p^3 = moderately preterm vs. term, p^4 = late preterm vs. term

AGA appropriate for gestational age, IQR interquartile range, LGA large for gestational age, LP late preterm, Md median, MP moderately preterm, PROM premature rupture of membranes, SD standard deviation, SGA small for gestational age, T term, VP very preterm

^a Register data available for 1991–2003

^b Regional hospital, private hospital, health center, home birth

Table 2 Reimbursement for asthma medication and hospitalizations due to asthma and atopic dermatitis

	Very preterm <32 weeks (n = 6437)	Moderately preterm 32 ⁺⁰ –33 ⁺⁶ weeks (n = 6799)	Late preterm 34 ⁺⁰ –36 ⁺⁶ weeks (n = 39,932)	Term ≥37 weeks (n = 965,224)	p^1 MP vs. VP	p^2 LP vs. VP	p^3 MP vs. T	p^4 LP vs. T
Reimbursement for asthma medication, n (%)	979 (15.4)	543 (8.0)	2259 (5.7)	36,210 (3.8)	<0.001	<0.001	<0.001	<0.001
Age at 1st reimbursement for asthma medication, MD (IQR)	1.97 (1.04–3.42)	2.22 (1.22–3.97)	2.53 (1.46–4.11)	2.88 (1.73–4.48)	<0.001	<0.001	<0.001	<0.001
Hospital visits due to asthma, n (%)	1277 (20.1)	718 (10.6)	2901 (7.3)	46,636 (4.8)	<0.001	<0.001	<0.001	<0.001
Number of visits, Md (IQR)	4 (2–8)	4 (2–7)	4 (2–7)	3 (2–7)	0.403	0.090	0.020	<0.001
Hospital visits due to atopic dermatitis, n (%)	249 (3.9)	283 (4.2)	1864 (4.7)	49,795 (5.2)	0.484	0.008	<0.001	<0.001
Number of visits, Md (IQR)	2 (1–3)	2 (1–4)	2 (1–4)	2 (1–5)	0.035	0.002	0.024	<0.001
Age at 1st visit, v, Md (IQR)	1.37 (0.86–3.45)	1.35 (0.69–2.44)	1.13 (0.60–2.36)	1.08 (0.57–2.40)	0.029	<0.001	0.006	0.240

Newborns alive at the age of 1 year old without major congenital anomalies, followed up to age of 7 years. Years 1991–2008 ($N=1,018,302$)

Statistical differences were tested by Pearson chi-square test or Fisher's exact or by Mann-Whitney test

p^1 = moderately preterm vs. very preterm, p^2 = late preterm vs. very preterm, p^3 = moderately preterm vs. term, p^4 = late preterm vs. term
IQR interquartile range, LP late preterm, MD median, MP moderately preterm, T term, VP very preterm

increased risk of atopic dermatitis with increasing GA [4, 26, 36].

Supporting previous work [13], we found an association between maternal smoking during pregnancy and asthma medication reimbursement of the child. Maternal daily smoking during pregnancy is relatively well covered in the Finnish MBR, though the data is based on self-reporting [19]. According to meta-analysis, exposure to prenatal smoking has increased the risk of wheezing in <6-year-old and the risk of wheezing or asthma in ≥6-year-old children [33]. Tobacco smoke exposure has an effect on fetal lung development. It may predispose the mother to preterm delivery [37] and, thus, increase the risk of early pulmonary problems of the infant. Postnatal exposure to smoking could not be established in our study. Avoidance of smoking during pregnancy seems to be one means to improve the respiratory outcome of the offspring.

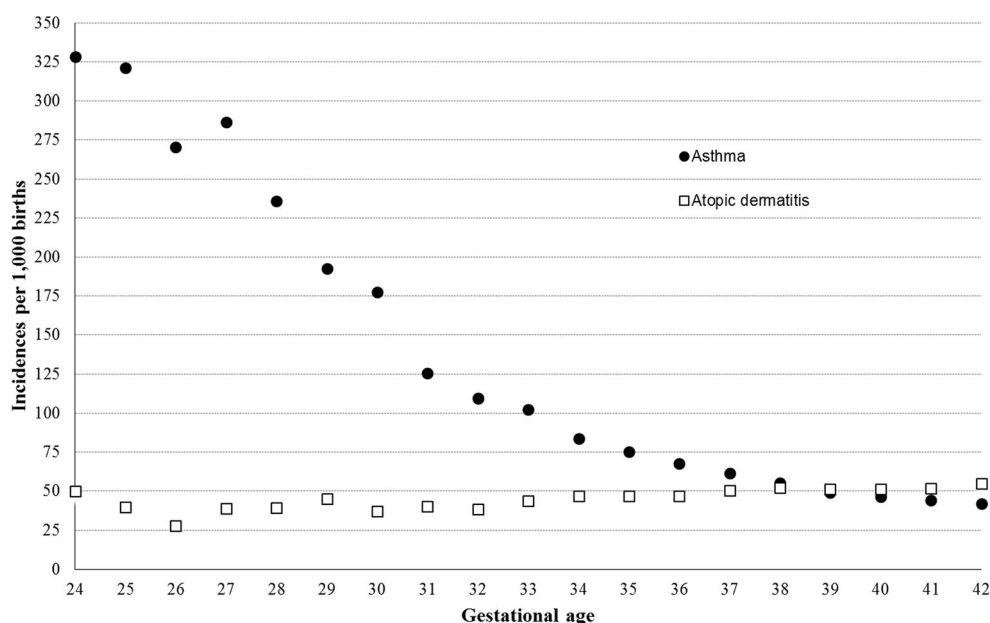
In our study, cesarean delivery appeared to be associated with an increased risk of asthma medication only in the term group. Contrary to previous results, cesarean section also predicted atopic dermatitis in the term group [3]. Lack of influence of the maternal vaginal and intestinal flora on the infant's gastrointestinal microbiota in cesarean sections may have a role in the development of asthma, atopy, and allergy [4, 18, 23]. Preterm infants are more frequently delivered by cesarean section than term infants. In meta-analyses, both cesarean delivery and prematurity have been associated with an increased risk of asthma [3, 5, 35].

Mechanical ventilation has been associated with an increased asthma risk after adjustment for GA [20]. Infants born very preterm may have insufficiently developed airways which make them more prone to recurrent wheezing in early childhood [14]. Accordingly, our results on the increased asthma risk associated with ventilator therapy in MP and LP infants suggest that even slight prematurity may predispose an infant to harmful effects of mechanical ventilation. Minimizing the duration and invasiveness of ventilator therapy might be beneficial for all preterm infants with respect to later asthma risk.

We found maternal diabetes to signify a risk of needing asthma medication among MP children. Fetal exposure to hyperglycemia affects lung growth and alveolization [21], may increase the risk of neonatal respiratory problems [25], and thus to the subsequent development of asthma. Maternal diabetes has predisposed the mother to premature delivery [7], causing a greater risk for surfactant deficiency at birth. Furthermore, high blood glucose levels may inhibit surfactant synthesis and secretion, most markedly in late gestation [25]. The asthma risk in the offspring may be diminished by achieving a good glucose balance in diabetic pregnancies.

Antenatal steroid treatment predicted asthma risk among LP and term infants. Prenatal corticosteroid therapy has also previously been associated with childhood asthma, the

Fig. 1 Incidences of hospital visits due to asthma and atopic dermatitis per 1,000 births by 7 years of age in relation to gestational age at birth, birth years 1991–2008 ($N=1,018,302$)



association being strongest between 3 and 5 years of age [29]. The effects of corticosteroids on the hypothalamus-pituitary axis and the immune function [30] as well as the effects on kidneys, and subsequent hypertension may have a role in the development of asthma [29].

In our study, firstborn children had a lower risk of asthma medication. They might be better protected from infectious epidemics possibly inducing wheeze. Supporting previous results [24], our MP and LP twins seemed to be less prone to develop asthma and atopic dermatitis than singletons. This finding needs to be confirmed in further studies.

Birth in a level II hospital was associated with a decreased risk of needing asthma medication in all GA groups, probably because high-risk infants, who need invasive treatments, are more commonly born in level III hospitals. Supporting our results, male sex has increased the risk of asthma [36] and atopic dermatitis [26] in infancy and childhood.

Our findings suggest that some peri- and neonatal risk factors for asthma are the same in all GA groups (e.g., maternal smoking, male sex) and some differ in full-term and preterm groups (e.g., ventilator therapy). This supports the conception of different asthma etiologies in premature and term infants [15]. Our finding that asthma was more common in preterm children while atopic dermatitis was more frequent in term children suggests that assisted ventilation could induce non-allergic asthma.

We found preterm children to need hospital care due to atopic dermatitis less frequently than term children, both in the whole study population and among children with asthma medication reimbursement. Antenatal exposures or earlier exposure to extrauterine environment may modulate the disease risk through influencing the

Th1/Th2 balance [23]. The decreased risk of atopic dermatitis in VP children might also be related to their functionally impaired skin barrier resulting in early transcutaneous exposure to antigens and the development of tolerance or their reduced diversity of intestinal microflora [4].

The limitation in register-derived data is the possible variation in recording practices. In our study, children born after the year 2002 were followed up to 1 to 6 years of age. This might decrease the incidence of asthma during the latest study years. However, the median age at first reimbursement for asthma medication was 2.0–2.9 years. Thus, most infants were followed up longer than that. The primary health care data were not available in this study, but the asthma medication reimbursements cover all asthma diagnoses, including those made in primary health care. The information on ethnicity was not included, but the Finnish population is fairly homogenous. No data were obtained on parental asthma or atopy, maternal education, or breastfeeding. It was not possible to differentiate non-atopic asthma from atopic asthma. Furthermore, the purchase of the asthma medication was not analyzed here.

The strength of this study is an excellent health information system in Finland based on national registers of high quality and good coverage [10, 11, 34]. The present study population was substantial. In Finland, asthma diagnosis given by a pediatrician, preceded by the need of inhaled corticosteroid treatment for 6 months, is required to qualify for medication reimbursement [2]. Social Insurance Institution database is as a valid source of prevalence data and able to

Table 3 Risk factor analysis for receiving reimbursement for asthma medication ($n = 39,991$) in the years 1991–2008 by the age of 7 years using time from birth to the first reimbursement following time separately for four gestation week categories ($N = 1,018,302$)

	Very preterm <32 weeks ($n = 979/N = 6347$)		Moderately preterm 32 ⁺⁰ –33 ⁺⁶ weeks ($n = 543/N = 6799$)		Late preterm 34 ⁺⁰ –36 ⁺⁶ weeks ($n = 2259/N = 39,932$)		Term ≥ 37 weeks ($n = 36210/N = 965,224$)	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Mothers' age	<i>0.99</i>	<i>(0.98–1.00)</i>	1.00	<i>(0.98–1.02)</i>	<i>0.98</i>	<i>(0.97–0.99)</i>	<i>0.98</i>	<i>(0.98–0.98)</i>
Smoking								
No	1.00		1.00		1.00		1.00	
Yes	<i>1.15</i>	<i>(0.98–1.34)</i>	<i>1.32</i>	<i>(1.08–1.63)</i>	<i>1.21</i>	<i>(1.09–1.35)</i>	<i>1.14</i>	<i>(1.11–1.18)</i>
First delivery								
No	1.00		1.00		1.00		1.00	
Yes	<i>0.70</i>	<i>(0.61–0.80)</i>	<i>0.79</i>	<i>(0.66–0.94)</i>	<i>0.77</i>	<i>(0.71–0.85)</i>	<i>0.82</i>	<i>(0.80–0.84)</i>
Diabetes ^a								
No	1.00		1.00		1.00		1.00	
Yes	<i>0.96</i>	<i>(0.58–1.69)</i>	<i>1.62</i>	<i>(1.02–2.58)</i>	<i>0.78</i>	<i>(0.63–1.11)</i>	<i>1.09</i>	<i>(0.99–1.21)</i>
Assisted reproduction technology								
No	1.00		1.00		1.00		1.00	
Yes	<i>1.01</i>	<i>(0.78–1.29)</i>	<i>0.77</i>	<i>(0.54–1.11)</i>	<i>1.20</i>	<i>(1.00–1.43)</i>	<i>1.21</i>	<i>(1.12–1.31)</i>
Antenatal steroid ^b								
No	1.00		1.00		1.00		1.00	
Yes	<i>0.69</i>	<i>(0.49–0.95)</i>	<i>1.01</i>	<i>(0.62–1.64)</i>	<i>1.46</i>	<i>(1.46–2.09)</i>	<i>1.72</i>	<i>(1.27–2.33)</i>
Number of fetuses								
1	1.00		1.00		1.00		1.00	
2	<i>0.93</i>	<i>(0.79–1.09)</i>	<i>0.81</i>	<i>(0.65–1.00)</i>	<i>0.85</i>	<i>(0.76–0.96)</i>	<i>1.01</i>	<i>(0.94–1.10)</i>
3 or 4	<i>0.86</i>	<i>(0.57–1.28)</i>	<i>0.56</i>	<i>(0.30–1.05)</i>	<i>0.74</i>	<i>(0.44–1.22)</i>	<i>1.02</i>	<i>(0.14–7.22)</i>
PROM								
No	1.00		1.00		1.00		1.00	
Yes	<i>0.67</i>	<i>(0.45–0.98)</i>	<i>0.67</i>	<i>(0.38–1.15)</i>	<i>0.74</i>	<i>(0.54–1.03)</i>	<i>0.75</i>	<i>(0.59–0.96)</i>
Birth hospital								
University (level III)	1.00		1.00		1.00		1.00	
Central (level II)	<i>0.72</i>	<i>(0.61–0.85)</i>	<i>0.79</i>	<i>(0.66–0.94)</i>	<i>0.88</i>	<i>(0.80–0.96)</i>	<i>0.85</i>	<i>(0.83–0.88)</i>
Other ^c	<i>0.64</i>	<i>(0.26–1.57)</i>	<i>1.33</i>	<i>(0.70–2.53)</i>	<i>0.94</i>	<i>(0.82–1.07)</i>	<i>0.96</i>	<i>(0.93–0.99)</i>
Mode of delivery								
Vaginal	1.00		1.00		1.00		1.00	
Cesarean section	<i>1.04</i>	<i>(0.91–1.20)</i>	<i>1.06</i>	<i>(0.88–1.27)</i>	<i>1.10</i>	<i>(1.01–1.20)</i>	<i>1.17</i>	<i>(1.14–1.21)</i>
Sex								
Boy	<i>1.60</i>	<i>(1.41–1.83)</i>	<i>1.74</i>	<i>(1.46–2.09)</i>	<i>1.65</i>	<i>(1.51–1.80)</i>	<i>1.73</i>	<i>(1.70–1.77)</i>
Girl	1.00		1.00		1.00		1.00	
Gestational weight								
SGA	<i>1.11</i>	<i>(0.93–1.32)</i>	<i>1.11</i>	<i>(0.86–1.42)</i>	<i>1.02</i>	<i>(0.87–1.19)</i>	<i>1.06</i>	<i>(0.98–1.14)</i>
AGA	1.00		1.00		1.00		1.00	
LGA	<i>0.63</i>	<i>(0.44–0.90)</i>	<i>0.90</i>	<i>(0.59–1.37)</i>	<i>0.88</i>	<i>(0.73–1.08)</i>	<i>1.02</i>	<i>(0.96–1.09)</i>
Admission to neonatal unit								
No	1.00		1.00		1.00		1.00	
Yes	<i>0.79</i>	<i>(0.64–0.99)</i>	<i>0.84</i>	<i>(0.65–1.09)</i>	<i>1.13</i>	<i>(1.03–1.24)</i>	<i>1.15</i>	<i>(1.10–1.21)</i>
Ventilator therapy								
No	1.00		1.00		1.00		1.00	
Yes	<i>1.43</i>	<i>(1.22–1.67)</i>	<i>1.26</i>	<i>(1.01–1.57)</i>	<i>1.42</i>	<i>(1.18–1.71)</i>	<i>1.12</i>	<i>(0.94–1.33)</i>
Antibiotic therapy								
No	1.00		1.00		1.00		1.00	
Yes	<i>0.83</i>	<i>(0.70–0.98)</i>	<i>1.09</i>	<i>(0.89–1.33)</i>	<i>1.12</i>	<i>(0.97–1.28)</i>	<i>1.07</i>	<i>(0.99–1.16)</i>

Cox regression multivariate enter models were used; all variables were entered simultaneously into the model for each gestational week categories, results being given as hazard ratios (HR) and 95 % confidence intervals (CI)

Statistically significant ($p < 0.050$) hazard ratios with 95% confidence intervals are italicized. Categories of missing values not shown

AGA appropriate for gestational age, LGA large for gestational age, PROM premature rupture of membranes, SGA small for gestational age

^a Register data available for 1991–2003

^b Register data available from 2004, years 2004–2008 analyzed

^c Regional hospital, private hospital, health center, home birth

Table 4 Risk factor analysis for hospital visits due to atopic dermatitis ($n = 52,191$) in the years 1991–2008 by the age of 7 years using time from birth to the first hospital visit following time separately for four gestation week categories ($N = 1,018,302$)

	Very preterm <32 weeks ($n = 249/N = 6347$)		Moderately preterm 32 ⁺⁰ –33 ⁺⁶ weeks ($n = 283/N = 6799$)		Late preterm 34 ⁺⁰ –36 ⁺⁶ weeks ($n = 1864/N = 39,932$)		Term ≥ 37 weeks ($n = 49,795/N = 965,224$)	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Mothers' age	0.99	(0.96–1.01)	1.02	(1.00–1.04)	1.00	(0.99–1.01)	1.00	(1.00–1.00)
Smoking								
No	1.00		1.00		1.00		1.00	
Yes	0.95	(0.68–1.33)	0.80	(0.57–1.13)	0.93	(0.82–1.06)	0.83	(0.81–0.85)
First delivery								
No	1.00		1.00		1.00		1.00	
Yes	0.86	(0.65–1.12)	0.92	(0.72–1.19)	0.89	(0.81–0.98)	0.97	(0.95–0.99)
Diabetes ^a								
No	1.00		1.00		1.00		1.00	
Yes	2.25	(1.09–4.63)	0.62	(0.23–1.69)	1.30	(0.98–1.72)	1.42	(1.31–1.54)
Assisted reproduction technology								
No	1.00		1.00		1.00		1.00	
Yes	1.37	(0.90–2.07)	1.03	(0.68–1.57)	1.24	(1.03–1.50)	1.23	(1.15–1.31)
Number of fetuses								
1	1.00		1.00		1.00		1.00	
2	1.20	(0.89–1.63)	0.96	(0.73–1.28)	0.85	(0.75–0.96)	0.79	(0.73–0.85)
3 or 4	1.91	(1.08–3.40)	0.52	(0.22–1.22)	0.65	(0.36–1.16)	*	
PROM								
No	1.00		1.00		1.00		1.00	
Yes	1.33	(0.77–2.31)	0.66	(0.34–1.29)	1.21	(0.93–1.56)	1.24	(1.08–1.43)
Birth hospital								
University (level III)	1.00		1.00		1.00		1.00	
Central (level II)	1.00	(0.74–1.37)	1.11	(0.87–1.40)	1.12	(1.02–1.23)	1.07	(1.05–1.09)
Other ^b	*		0.73	(0.18–3.04)	0.95	(0.81–1.11)	0.89	(0.87–0.91)
Mode of delivery								
Vaginal	1.00		1.00		1.00		1.00	
Cesarean section	1.22	(0.97–1.62)	1.03	(0.81–1.32)	1.08	(0.97–1.19)	1.10	(1.08–1.13)
Sex								
Boy	1.26	(0.97–1.62)	1.35	(1.06–1.72)	1.29	(1.17–1.41)	1.25	(1.23–1.28)
Girl	1.00		1.00		1.00		1.00	
Weight for GA								
SGA	1.01	(0.71–1.45)	0.86	(0.59–1.25)	1.02	(0.86–1.21)	0.93	(0.87–1.00)
AGA	1.00		1.00		1.00		1.00	
LGA	1.87	(1.14–3.05)	1.03	(0.57–1.85)	1.21	(1.00–1.46)	1.01	(0.96–1.06)
Admission to neonatal unit								
No	1.00		1.00		1.00		1.00	
Yes	0.69	(0.45–1.08)	1.34	(0.88–2.04)	1.11	(1.00–1.23)	1.16	(1.12–1.21)
Ventilator therapy								
No	1.00		1.00		1.00		1.00	
Yes	0.80	(0.60–1.06)	1.09	(0.81–1.50)	0.89	(0.70–1.13)	0.84	(0.72–0.99)
Antibiotic therapy								
No	1.00		1.00		1.00		1.00	
Yes	1.61	(1.13–2.30)	1.08	(0.82–1.41)	1.13	(0.98–1.32)	1.19	(1.12–1.26)

Cox regression multivariate enter models were used; all variables were entered simultaneously into the model for each gestational week categories, results being given as hazard ratios (HR) and 95 % confidence intervals (CI)

Statistically significant ($p < 0.050$) hazard ratios with 95 % confidence intervals are italicized. Categories of missing values not shown

AGA appropriate for gestational age, LGA large for gestational age, PROM premature rupture of membranes, SGA small for gestational age

*Cannot be computed due to a small sample size

^a Register data available for 1991–2003

^b Regional hospital, private hospital, health center, home birth

accurately identify asthma cases in the general population [27]. Due to the lack of private children's hospitals in Finland, all hospital visits due to asthma and atopic dermatitis are derived reliably from the registers. Children hospitalized due to atopic dermatitis are those with a more severe disease needing specialized care consultation or treatment. Risk factors for severe disease may be different than those of mild and moderate diseases.

Conclusion

MP and LP children appear to receive asthma medication reimbursement and to be hospitalized due to asthma more often than term controls but less frequently than VP children by 7 years of age. There is a nonlinear decreasing trend in hospital visits due to asthma with increasing GA. Instead, the incidence of hospital visits due to atopic dermatitis rises with increasing GA. Moderately and late preterm births might constitute prominent risk factors for the development of asthma and for increased health service use due to asthma in early childhood. Counseling against smoking during pregnancy and minimizing the harmful effects of neonatal mechanical ventilation may be means to decrease the risk of asthma in MP and LP children.

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Author's Contribution Dr. Paula Haataja drafted the initial manuscript, participated in the analytic planning, and approved the final manuscript as submitted.

Drs. Päivi Korhonen, Riitta Ojala, Mikko Hirvonen, Marita Paasilta, and Mika Gissler participated in the analytic planning, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Msc. Tiina Luukkaala conducted the statistical analyses, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Dr. Outi Tammela designed and supervised the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Compliance with Ethical Standards

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors. The study protocol was approved by the regional Ethics Committee. Permissions to use sensitive health data for research were given by the registering organizations (the National Institute for Health and Welfare, Social Insurance Institution and Statistics Finland).

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