Tampere University

PAULA HAATAJA

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A Nationwide register study

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ACADEMIC DISSERTATION
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To my family

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Paula Haataja

ABSTRACT

Asthma and atopic dermatitis are common diseases in childhood and lower respiratory tract infections (LRTIs) are the leading cause of hospitalization in preschool children. Very preterm birth (<32 weeks of gestational age, GA) has been associated with an increased risk of asthma and respiratory infection-related hospital admissions in childhood, whereas the risk of atopic dermatitis in cases of very preterm birth has been found to be decreased compared with children born at term. Long term respiratory morbidity and the risk of atopic dermatitis among children born moderately (MP; 32^{+0}-33^{+0} weeks) and late preterm (LP; 34^{+0}-36^{+0} weeks) and among sub-groups of term-born children, 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), are less well studied. It is suggested that, in addition to GA at birth, some early-life exposures may also play a role in the pathogenesis of these diseases.

The aim of this study was to compare the incidence and risk of long-term respiratory morbidity and severe atopic dermatitis in MP and LP children with those in very preterm and term children by school age. The study also aimed to evaluate the association of early-term, late-term and post-term birth with later risk of asthma, atopic dermatitis and LRTIs. Maternal-, delivery- and newborn-related factors associated with increased long-term respiratory morbidity and atopic dermatitis in relation to GA at birth were explored.

This national register study included all children born in Finland between 1991 and 2008 based on data derived from the Medical Birth Register (n=1,039,263). After excluding infants with missing data on GA, those with any major congenital anomalies, and those who died before the age of one year, the remaining cohort of 1,018,256 (98.0% of all children born) were analyzed as follows: very preterm (n=6,329), MP (n=6,796), LP (n=39,928) and term (n=965,203). In addition, children born after 37 weeks (n=965,203) were divided into four subgroups: early-term (n=181,667), full-term (n=546,845), late-term (n=189,373) and post-term (n=47,318). The incidence and risk factors for asthma, atopic dermatitis and LRTIs by seven years of age were evaluated by linking the health register data. Maternal and neonatal factors associated with the risk of asthma, atopic dermatitis and LRTIs were assessed using multivariable analysis.

The results of this study showed that MP and LP born children received asthma medication reimbursement and were admitted to hospital for asthma and LRTIs more often than term controls but less frequently than very preterm children. Early-term birth was also a predictor of asthma, while late- and post-term births appeared to be associated with a decreased risk of asthma compared with full-term birth. There was a decreasing trend in hospital visits due to asthma and LRTIs with increasing GA. Instead, the incidence of hospital visits due to atopic dermatitis rose with increasing GA and post-term birth associated with an increased risk of atopic dermatitis. Risk factors for respiratory morbidity in fully adjusted models included maternal smoking during pregnancy, birth by cesarean section, male sex, admission to a neonatal unit and ventilator therapy, and neonatal antibiotic therapy was also associated with the risk of LRTIs. The most relevant risk factors for atopic dermatitis were male sex, being first-born, birth in a level II hospital and birth by cesarean section.

In conclusion, these results suggest that in addition to very preterm birth, MP, LP and early-term births are also associated with an increased risk of asthma and LRTIs in early childhood whereas post-term birth appears to reduce this risk. Interestingly, preterm birth seemed to decrease the risk of atopic dermatitis and post-term birth associated with an increased risk of atopic dermatitis. Means to affect underlying modifiable risk factors, such as smoking during pregnancy, timing of birth by elective cesarean section, neonatal ventilator therapy and antibiotic therapy should be considered in clinical practice.

TIIVISTELMÄ

Astma ja atooppinen ihottuma ovat yleisiä lapsuusiän sairauksia ja alahengitystieinfektiot ovat alle kouluikäisten lasten yleisimpiä sairaalahoidon syitä. Hyvin ennenaikaiseen syntymään (<32 raskausviikolla) liittyy lisääntynyt lapsuusiän astmariski ja sairaalahoidon tarve hengitystieinfektioiden vuoksi täysiaikaisena syntyneisiin verrattuna. Toisaalta tässä ryhmässä on raportoitu atooppisen ihottuman riskin olevan vähäisempi. Pitkäaikaisesta hengitystiesairastuvuudesta ja atooppisen ihottuman esiintymistä on vähemmän tutkimustietoa kohtalaisen (32^{+0}-33^{+6} raskausviikoilla) ja hieman (34^{+0}-36^{+6} raskausviikolla) ennenaikaisesti syntyneiden lasten ryhmistä sekä täysiaikaisena syntyneiden lasten alaryhmistä eriteltynä: varhainen täysiaikainen (37^{+0}-38^{+6} raskausviikkoa), 'täysi' täysiaikainen (39^{+0}-40^{+6} raskausviikkoa), hieman yliaikainen (41^{+0}-41^{+6}) ja yliaikainen (≥42 raskausviikkoa). Syntymäraskausviikkojen lisäksi myös varhaisen elämän vaiheen altistuksilla näyttäsi olevan merkitystä näiden sairauksien synnyssä.

Tämän väitöskirjan tavoitteena oli verrata kohtalaisen ja hieman ennenaikaisena syntyneiden lasten pitkäaikaista hengitystiesairastuvauutta ja vaikean atooppisen ihottuman ilmaantuvuutta ja mahdollisia riskitekijöitä suhteessa hyvin ennenaikaisena ja täysiaikaisena (>37 raskausviikkoa) syntyneisiin lapsiin. Lisäksi tutkimuksessa selvitettiin täysiaikaisina syntyneillä raskausviikkoryhmittäin eriteltynä yhteyttä myöhempään astman, atooppisen ihottuman ja alahengitystieinfektioiden sairastumisriskiin. Tutkimuksessa arvioitiin äidin raskaudenaikaisia ja synnytykseen sekä vastasyntyneisyyskauteen liittyviä riskitekijöitä pitkäaikaisen hengitystiesairastuvuuden ja atooppisen ihottuman selittäjinä.

Tähän kansalliseen rekisteritutkimukseen otettiin mukaan kaikki Suomessa syntymärekisterin tietojen mukaan vuosina 1991-2008 syntyneet lapset (n=1,039,263). Tutkimuksesta suljettiin pois lapset, joilta puuttui tieto raskaudenkestosta, joilla oli merkittävä synnynnäinen epämuodostuma ja ne, jotka kuolivat ennen yhden vuoden ikää. Lopullinen tutkimuskohortti (n=1,018,256, joka 98% kaikista) analysoitiin neljässä raskausviikkojen mukaisessa ryhmässä: hyvin ennenaikaiset (n=6,329), kohtalaisen ennenaikaiset (n=6,796), hieman ennenaikaiset (n=39,928) ja täysiaikaiset (n=965,203). Lisäksi täysiaikaisena syntyneet lapset jaettiin vielä neljään ala-ryhmään: varhainen täysiaikainen (n=181,667), 'täysi' täysiaikainen

(n=546,928), hieman yliaikainen (n=189,373) ja yliaikainen (n=47,318). Rekisteritietoja yhdistämällä selvitettiin astman, atooppisen ihottuman ja alahengitystieinfektioiden ilmaantuvuutta ja riskitekijöitä eri raskausviikkoryhmissä seitsemään ikävuoteen mennessä. Monimuuttuja-analyysillä selvitettiin raskaudenaikaisia, synnytykseen ja vastasyntyneisyyskauteen liittyviä riskitekijöitä.

Tutkimuksen tulokset osoittivat, että kohtalaisen ja hieman ennenaikaisena syntyneillä lapsilla oli enemmän astmalääkekorvattavuuksia ja sairaalakäyntejä astman ja alahengitystieinfektioiden vuoksi kuin täysiaikaisena syntyneillä, mutta vähemmän kuin hyvin ennenaikaisesti syntyneillä. Myös varhaiseen täysiaikaiseen syntymään liittyi lisääntynyt astmariski, mutta hieman yliaikainen ja yliaikainen syntymä näyttivät suojaavan astmalta verrattuna 'täyteen' täysiaikaiseen syntymään. Astmaan ja alahengitystieinfektioihin liittyvien sairaalakäyntien ilmaantuvuus väheni raskausviikkojen lisääntyessä. Sitä vastoin, atooppisen ihottuman vuoksi sairaalakäynnit lisääntyivät syntymäraskausviikkojen kasvaessa ja yliaikainen syntymä yhdistyi lisääntyneeseen riskiin. Vakioidussa monimuuttuja-analyysissä hengitystiesairastuvuutta lisääviä riskitekijöitä olivat äidin raskaudenaikainen tupakointi, syntymä keisarileikkauksella, pojan sukupuoli, hoitojakso vastasyntyneiden osastolla ja hengityskonehoito. Lisäksi vastasyntyneisyyskauden antibioottihoito yhdistyi alahengitystieinfektiosairastavuuteen. Merkittävimpiä atooppista ihottumaa ennustavia tekijöitä olivat pojan sukupuoli, esikoisuus, syntymä keskus- tai aluesairaalassa ja syntymä keisarileikkauksella.

Johtopäätöksenä voidaan todeta, että hyvin ennenaikaisesti syntyneiden lasten lisäksi myös kohtalaiseen ja hieman ennenaikaiseen syntymään kuten myös varhaiseen täysiaikaiseen syntymään liittyy lisääntynyt sairastuvuus astmaan ja alahengitystieinfektioihin varhaislapsuudessa, mutta yliaikainen syntymä näyttäisi vähentävän tätä sairastuvuutta. Atooppisen ihottuman sairastuvuutta ennenaikaisuus näyttäsi vähentävän, mutta yliaikaisuus vastaavasti lisäävän tätä. Keinoja vaikuttaa sairastumisriskiä vähentäviin tekijöihin, kuten raskaudenaikainen tupakointi, elektiivisen keisarileikkauksen ajankohta, vastasyntyneisyyskauden hengityskonehoito ja antibioottien käyttö, tulisi harkita käytännön työssä.

CONTENTS

ABBREVIATIONS

AGA	appropriate for gestational age
ACOG	American College of Obstetricians and Gynecologists
CI	confidence interval
GA	gestational age
GINA	Global Initiative for Asthma
HDR	Hospital Discharge Register (Care Register for Health Care)
HR	hazard ratio
ICD	International Classification of Diseases
IQR	interquartile range
KELA	Social Insurance Institution of Finland
LGA	large for gestational age
LP	late preterm
LRTI	lower respiratory tract infection
MBR	Medical Birth Register
MP	moderately preterm
OR	odds ratio
PAR	population attributable risk
RSV	respiratory syncytial virus
SD	standard deviation
SES	socioeconomic status
SGA	small for gestational age
THL	National Institute for Health and Welfare
Th	T-helper cell
WHO	World Health Organization

ORIGINAL PUBLICATIONS

This study is based on the following original publications, which are referred to in the text by Roman numerals I-IV.

I Haataja P, Korhonen P, Ojala R, Hirvonen M, Paassilta M, Gissler M, Luukkaala T, Tammela O. Asthma and atopic dermatitis in children born moderately and late preterm. Eur J Pediatr. 2016 Jun;175(6):799-808.

II Haataja P, Korhonen P, Ojala R, Hirvonen M, Korppi M, Gissler M, Luukkaala T, Tammela O. Hospital admissions for lower respiratory tract infections in children born moderately/late preterm. Pediatr Pulmonol. 2018 Feb;53(2):209-217.

III Korhonen P, Haataja P, Ojala R, Hirvonen M, Korppi M, Paassilta M, Uotila J, Gissler M, Luukkaala T, Tammela O. Asthma and atopic dermatitis after early-, late-, and post-term birth. Pediatr Pulmonol. 2018 Mar;53(3):269-277.

IV Haataja P, Korhonen P, Ojala R, Hirvonen M, Korppi M, Gissler M, Luukkaala T, Tammela O. Hospital admissions for lower respiratory tract infections after early-, late- and post-term birth. Submitted.

1 INTRODUCTION

Asthma and atopic dermatitis are common diseases in childhood, affecting approximately 10% of children in Western countries (Asher et al. 2006; Roduit et. al 2017), and lower respiratory tract infections (LRTIs) are the leading cause of hospitalization in preschool children (Nair et al. 2013). Children born preterm appear to carry an increased risk of asthma and respiratory infection-related hospital admissions in childhood (Been et al. 2014; Boyle et al. 2012; Miller et al. 2016), whereas the risk of atopic dermatitis has been found to be reduced (Trønnes et al. 2013; Barbarot et al. 2013) compared with children born at a later gestational age (GA).

Moderately and late preterm (MP and LP) children born at 32^{+0}-36^{+6} weeks of GA currently constitute more than 80 % of all preterm births (Shapiro-Mendoza 2012). These infants are at a greater risk of early neonatal morbidities and are more likely to be readmitted to hospital after the neonatal period (Boyle et al. 2015; Kuzniewicz et al. 2013). Because of the reported health risks to the mother and infant after elective deliveries prior to 39 weeks of GA, sub-grouping the term birth into 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 has been recommended (American College of Obstetricians and Gynecologists ACOG 2014, Spong 2013). The health problems of early-term, late-term and post-term infants are milder and less common than in the most premature groups but may result in a substantial public health burden due to the high number of infants (ACOG 2014; Gill & Boyle 2017).

It has been suggested that not only GA at birth but also some peri- and neonatal factors may play a role in the development of asthma and atopic dermatitis (Martino & Prescott 2011) and may increase the risk of infections in early childhood (Kristensen & Henriksen 2016). Intrauterine and postnatal period have been suggested to be a phase, when specific exposures may have an influence on later disease risk by modifying the development of lungs and immune system. Many obstetrical decisions during the final weeks of a pregnancy involve weighing the risks and benefits of delivering an infant prior or after the due date (Rusconi et al. 2017). A more precise understanding of the risks including long-term respiratory morbidity

related to GA is necessary. Most previous studies have focused on long-term respiratory health following very preterm birth. There has been rather little research on respiratory health-related outcomes of MP and LP births and term subgroups in later childhood.

This study compared the incidence and risk of long-term respiratory morbidity and severe atopic dermatitis in MP and LP children with those in very preterm and term children by seven years of age in a national register-based birth cohort. This study also aimed to evaluate the association of early-term, late-term and post-term birth with later risk of asthma, atopic dermatitis and LRTIs. Additionally, the study explored maternal-, delivery- and newborn-related factors associated with increased long-term respiratory morbidity and atopic dermatitis in relation to GA at birth.

2 REVIEW OF THE LITERATURE

2.1 Gestational age (GA) groups

Gestational age indicates the duration of pregnancy, dated from the first day of the last menstrual period. The more accurate assessment of GA is done by measuring the crown-rump length of the fetus during a first-trimester ultrasonographic examination. The general practice in Finland is that the estimation of GA is corrected according to ultrasonographic evaluation if there is a discrepancy of more than 5–7 days compared with GA based on the last menstrual period (National Institute for Health and Welfare, THL). In Finland, ultrasonographic evaluation of pregnancy has been performed in clinical practice since 1980s (Saari-Kemppainen et al. 1990).

2.1.1 Preterm birth and birth weight

Preterm birth is defined by the World Health Organization (WHO) as birth before 37 completed weeks of gestation (WHO 1977). Preterm birth can be classified based on GA as extremely preterm (22^{+0}-27^{+6} weeks), very preterm (28^{+0}-32^{+0} weeks), moderately preterm (MP, 32^{+0}-33^{+6} weeks) and late preterm (LP, 34^{+0}-36^{+6} weeks) (Figure 1).

Low birth weight is defined as weight of less than 2,500g, very low birth weight as less than 1,500g and extremely low birth weight as less than 1,000g (WHO 2004). Birth weight for gestational age can be defined in all GA groups. Small for GA (SGA) infants are defined as those with a birth weight more than 2.0 standard deviations (SD) below the average for GA and large for GA (LGA) infants as those with a birth weight more than 2.0 SD above the mean weight for GA according to sex-specific fetal growth curves (Pihkala et al. 1989).

2.1.2 Term and post-term birth

Term birth has been defined as a birth between 37 and 42 weeks of gestation and post-term birth as a birth at or beyond 42 weeks of gestation, respectively. Recent recommendations suggest sub-categorization of birth after 37 weeks to provide more accurate descriptions of deliveries and their outcomes (ACOG 2014; Spong 2013). These subgroups of children born after 37 weeks are: 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^{+0} weeks and beyond) (Figure 1).

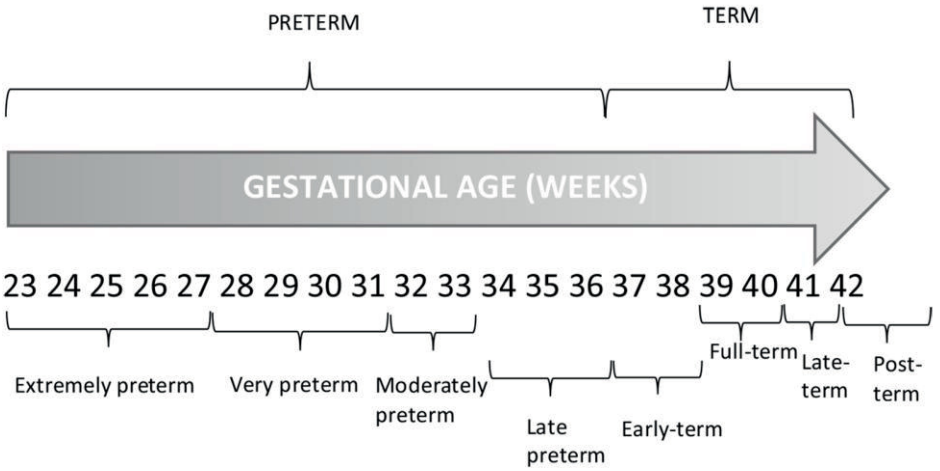

Figure 1. Gestational age groups (modified from Gill & Boyle 2017).

2.1.3 Epidemiology of preterm, term and post-term birth

Approximately 11.1% of all live births worldwide are preterm births with rates ranging from 5.0% in Europe to 18.0% in Africa (Blencowe et al. 2012). Preterm birth rates have increased during recent decades, mostly due to the increase in LP births in several countries, especially in the U.S (Davidoff et al. 2006; Shapiro-Mendoza & Lackritz 2012). Recently the rates in the U.S began to decrease because of declining elective late preterm deliveries (Ananth et al. 2018). The rates of LP

births range from 3.0% to 6.0% of live singleton births and constitute between 65% and 75% of preterm births in high-income countries according to data from 2010 (Delnord et. al 2019). The preterm birth rate in Finland has been approximately 5% and has not increased markedly over the last decade (Jakobsson et al. 2008; THL perinatal statistics Finland). Worldwide the complications of preterm birth are the second highest cause of early childhood mortality, after pneumonia (Liu et al. 2012).

Early-term births are approximately five times more common than LP births, with percentges ranging from 15% to 30% internationally (Delnord et. al 2019; Richards et al. 2016). Trends in early-term births vary by mode of onset. Early-term birth rates are estimated to range between 9.8% and 16.6% for spontaneous and 4.3% and 15.5% for iatrogenic early-term births (Delnord et al. 2019).

The incidence of post-term birth is approximately 3%–5% of all births. This varies depending on population characteristics, such as the percentage of primigravidas in the population, the prevalence of obesity, numbers of parturients with a history of previous post-term pregnancy, genetic predisposition and local management practices (Timonen 2015). Recent recommendations suggest induction of labor after 42^{+0} weeks and by 42^{+6} weeks of gestation, given evidence of an increase in perinatal morbidity and mortality (ACOG 2014). In Finland national guidelines have recommended clinical assessment at 41-42 weeks of gestation and possible induction of labor 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 (Timonen 2015, THL perinatal statistics Finland).

2.2 Aspects of respiratory and immunological maturation

2.2.1 Lung development

The prenatal growth and development of the human lung have traditionally been divided into five stages (Joshi & Kotecha 2007). This is illustrated in Figure 2 and Table 1.

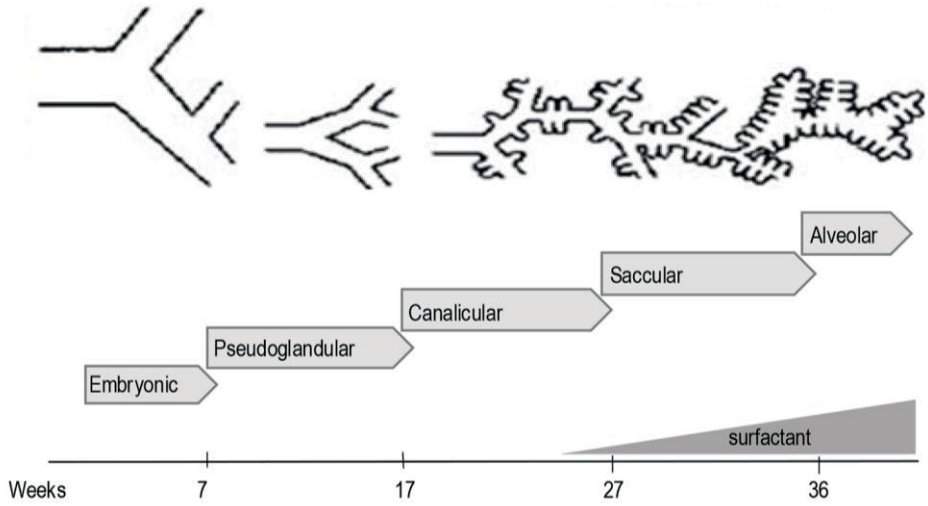

Figure 2. Stages of lung development (modified based on the text by Joshi & Kotecha 2007).

Table 1. Stages of lung growth and maturation (modified from Joshi & Kotecha 2007).

Embryonic	0–7 weeks	Formation of lung bud, trachea, right and left main bronchi and segmental bronchi, vasculogenesis around air bugs
Pseudoglandular	7–17 weeks	Formation of conduction airway and terminal bronchioles, formation of pulmonary arteries and veins
Canalicular	17–27 weeks	Formation of respiratory bronchioles, alveolar ducts and primitive alveoli, formation of alveolar capillary barrier
Saccular	28–36 weeks	Formation of saccules, alveolar ducts and air sacs, increment in gas exchange areas
Alveolar	36 weeks–2 years	Septation and multiplication of alveoli
Microvascular maturation	Birth to 2–3 years	Fusion of double alveolar capillary network into a single layer

The conducting airways are formed mainly during embryonic and pseudoglandular stages. The formation of alveolar structures in the canalicular and saccular stages of lung development enables gas exchange (Joshi & Kotecha 2007). The third trimester of pregnancy represents a rapid stage of lung growth, characterized by transition from the terminal sac period to the alveolar period of

development. During the saccular stage, numbers of bronchi are increasing, saccules start to form alveoli, and surfactant production occurs. The alveolar stage of lung development starts at 36 weeks gestation, and continues into childhood. Preterm birth at the canalicular or saccular stage disrupts normal lung development (Joshi & Kotecha 2007). Alveoli are not completely mature until 36 weeks of GA (Langston et al. 1984). This causes inadequate maintenance of functional residual capacity, decreased compliance, and smaller airway diameters compared to term infants (Colin et al. 2010). Total lung volume increases during the last trimester of gestation, the air-space walls decrease in thickness, and a fourfold increase in air-space surface area occurs. At 34 weeks of GA lung volume only reaches 47% of the final volume at term (Langston et al. 1984). The immature lung structure present before term may be associated functionally with delayed intrapulmonary fluid absorption, surfactant insufficiency, and inefficient gas exchange (Mahoney & Jain 2013). In addition to very preterm infants, these physiologic deficiencies may contribute to the vulnerability of MP and LP infants to respiratory morbidity both in the neonatal period and long-term.

Alveolar multiplication continues in the postnatal period at least up to the age of 2–3 years and alveolar size and surface increase until after adolescence. Besides the multiplication and enlargement of airspaces, the stage of microvascular maturation occurs after birth (several months to 2–3 years). During this period of postnatal lung growth, new alveolar septa can be formed as a result of angiogenesis and alveolization (Burri 2006).

2.2.2 Early-life immune maturation and the microbiota

The fetus and newborn face many immunological demands, including protection against infection, avoidance of harmful inflammatory immune responses that can lead to preterm delivery, and balancing the transition from intra-uterine environment to the outside world, which is rich in foreign antigens. This process of immune maturation is driven by a variety of cell-intrinsic and extrinsic factors. The newborn is mainly dependent on innate immunity and maternal antibodies, most of which are passively acquired during the third trimester (Ygberg 2012). Innate immunity provides the first line of immune defense against pathogens. The slower adaptive immune response follows the innate response and generates the immunological memory.

Preterm infants have immature immune responses, both innate and adaptive immunity. In comparison to term infants, preterm infants present with a smaller pool of monocytes and neutrophils, impaired ability of these cells to kill pathogens, and lower production of cytokines which limits T cell activation and reduces the ability to fight bacteria and detect viruses in cells (Melville et al. 2013). It has been suggested that the development of antigen-specific immune responses is restricted to the period after birth; however, in utero exposure to environmental antigens has been detected in cord blood and amniotic fluid (Pastor-Vargas et al. 2016).

The two integral subgroups of T cells in adaptive immunity with separate immune functions are CD4+ helper T cells and CD8+ cytotoxic T cells. T helper cells can be subdivided into effector cells and regulatory cells (Ygberg 2012). Traditionally T helper cells are further divided into T helper 1 (Th1) and T helper 2 (Th2) cells, with specific roles in immune responses according to their cytokine production, but this classification has recently been considered to be more plastic in terms of Th cell subtypes and their functions (Zhu 2018).

During pregnancy normal fetal development occurs in a Th2-biased environment that protects the fetus from the maternal immune response (McFadden et al 2015). The immunologic competence of the newborn progresses rapidly in the first three months of life when acquired immunity cells mature and gain antigenic experience. The mature Th1/Th2 balance is acquired through exposure to microbial antigens during infancy. Regulatory T cells are considered key mediators in this balance by maintaining immune system homeostasis and tolerance to self-antigens. Stimulation of the Th1-type immune response by viral infections may attenuate the Th2-type response. As suggested by the 'hygiene hypothesis' diminished microbial exposure in early childhood may lead to Th1/Th2 imbalance favoring the Th2-type immune response and an increased risk of allergic diseases (Strachan 1989). However, recent findings suggests that timing of exposure, antigen dose and the genetic background of the child also influence whether antigen exposure will lead to beneficial or harmful effects (Ygberg 2012).

The development of the microbiota has been assumed to start at birth, but recent observations suggest that gut colonization may already be initiated in utero (Collado et al. 2016). The bacterial colonization of the infant gut continues during early infancy and is influenced by several maternal and environmental factors such as the mode of delivery. GA at birth has a strong impact on gut microbiota development and in comparison to term infants, the gut microbiota of preterm infants is characterized by delayed colonization and by limited microbial diversity (Henderickx et al. 2019). Vaginal delivery exposes the infant to the maternal vaginal and intestinal

flora. In contrast, the intestinal microbiota in infants born by cesarean section is enriched by skin flora. Some other factors, such level of hygiene, early antibiotic exposure and breastfeeding, may also have influence on the composition of the infant's intestinal microbiota (Collado et al. 2016; Rautava et al. 2012). The microbiota colonizing the gut after birth is thought to have an impact on the immune maturation process during the neonatal period and may have far-reaching consequences for later health. A current hypothesis suggests that the process and interaction between genetic factors, early environmental exposures, and alterations in the microbiota might influence a child's susceptibility to asthma and atopic diseases, especially in early life when the immune system is maturating (Jackson et al. 2017; Liu 2015).

2.3 Asthma in childhood

2.3.1 Definitions

Asthma is considered a heterogeneous disease, usually characterized by chronic variable airway inflammation, airway obstruction, and airway hyperresponsiveness. According to the recently updated definition by the Global Initiative for Asthma (GINA), asthma is defined as a history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness, and cough that varies over time and in intensity, together with variable expiratory airflow limitation, which reverses either spontaneously or after use of medication (GINA 2018). The direct application of this definition to pediatric patients remains limited, especially in patients less than six years of age (Papadopoulos et al. 2019). The individual clinical symptom patterns are diverse and wheezing is common during early childhood. Different wheezing phenotypes based on different pathogenesis, progression and outcomes have been identified in earlier studies (Martinez et al. 1995; Taussig et al. 2003). Majority of early-life wheezing children have transient symptoms only during respiratory tract infections and they become gradually asymptomatic after the age of three years and have small asthma risk. About half of wheezing children have continuous symptoms from the age of three until six years of age and half of these children become sensitized to an allergen and have persistent symptoms reflecting underlying chronic inflammation and increased asthma risk (Martinez et al. 1995; Taussig et al. 2003, Reddy et al. 2016). In older children, this may lead to permanent structural alterations

of the airway wall (airway remodeling) and potentially a more severe asthma phenotype (Taussig et al. 2003). Traditionally asthma is classified into non-allergic and allergic asthma and this classification has been recommended in Finnish guidelines for pediatric asthma (Pelkonen et al. 2006; Current Care Guidelines 2012). Allergic asthma is a common asthma phenotype in childhood and it is associated with IgE sensitization and Th2-type immune response (Wenzel 2006). Childhood asthma can also be classified into different phenotypes depending on the age of the children or on the underlying mechanism/trigger, such as viruses, exercise or allergens (Ducharme et al. 2014; Reddy et al. 2016; GINA 2018). Recently, asthma has not been considered a single disease entity but rather a variety of clinical presentations (phenotypes) and underlying mechanisms (endotypes), coupled with the presence of overlapping symptoms (Papadopoulos et al. 2012 & 2019; GINA 2018). These classifications can help to understand the underlying genetics and pathophysiology and to modify the treatment (Papadopoulos et al. 2019).

2.3.2 Epidemiology of childhood asthma

Globally asthma is one of the most common chronic diseases and is considered as a major public health burden throughout the world (Masoli et al. 2004). Asthma prevalence among children has increased very considerably in recent decades, being highest in Western countries, approximately 10% of children in the European Union and North America, and lowest in Asia (Asher et al. 2006; Papadopoulos et al. 2012; Papadopoulos et al. 2019). In Finland, asthma is also the most common chronic disease in childhood (Säynäjäkangas et al. 2007) The overall incidence of asthma is 7-9%, and a similar percentage of children have asthma-like symptoms (von Hertzen et al. 2006; Haahtela et al. 2013). The incidence of asthma has increased slightly over the past two decades, especially in younger age groups (Haahtela et al. 2013). Conversely, hospitalizations for asthma and the costs of asthma have decreased (Haahtela et al. 2006, 2017). In 1994, the Finnish national 10-year asthma program was established to lessen the burden of asthma to individuals and society. In 2002, the childhood asthma mini-program was launched to resolve specific problems related to pediatric asthma. After releasing more precise diagnostic criteria for asthma, the number of children receiving reimbursements for asthma medication has decreased by approximately 30% during the last ten years (Social Insurance Institution statistics). The reduction has been most prevalent among young children aged 0-4 years (Haahtela et al. 2013).

2.3.3 Diagnosis and treatment of childhood of asthma

The diagnosis of childhood asthma is based on internationally accepted criteria (Current Care Guidelines 2012; Haahtela et al. 2013; GINA 2018; Papadopoulos et al. 2019). In Finland according to national guidelines, a specialist, usually a pediatrician in specialized health care unit, confirms the final diagnosis and the need for long-term medication. The diagnosis is based on the presence of typical symptoms and signs and/or pulmonary function tests confirming the variable or reversible airway obstruction depending on the age of the child (Papadopoulos et al. 2012 & 2019; Martinez & Vercelli 2013). Further examinations in order to exclude alternative diagnoses (i.e. chest X-rays) should be considered (Papadopoulos et al. 2012 & 2019). Lung function tests, such as oscillometry, spirometry, peak expiratory flow tests or plethysmography, are recommended for children more than three years of age. Clinical exercise test, and inhaled methacholine/histamine challenge tests can also be used. Fractional exhaled nitric oxide measurements are used in assessing airway inflammation. Skin prick tests or serum allergen-specific IgE-tests against common allergens are used in the evaluation of atopy. (Current Care Guidelines 2012)

A short treatment trial with inhaled asthma medication is suggested for children under three years of age. In infants having had physician-diagnosed wheezing episodes three times per year, the diagnosis can be confirmed by using a special (asthma predictive) index score based on three main criteria, family history of asthma, atopic dermatitis diagnosed by a physician, and sensitization to inhaled allergens, and side criteria such as IgE-mediated food allergy and wheezing without respiratory infection or eosinophilia. A need for inhaled corticosteroid treatment for more than six months is considered as diagnostic for asthma. (Current Care Guidelines 2012; Papadopoulos et al. 2012; Haahtela et al. 2013)

The treatment aim is to use the lowest possible amount of medication to achieve adequate symptom control and to reduce future risks (Tesse et al. 2018). Anti-asthmatic drugs are divided into beta-2 agonists, corticosteroids and leukotriene-modifiers. In Finnish guidelines, anti-inflammatory inhaled corticosteroids have been recommended as first-line regular therapy for pediatric asthma. Non-steroid-based biologic treatments (i.e. omalizumab) are also available for children >6 years (Papadopoulos et al. 2019). Pharmacological treatment is selected by age and a stepwise approach according to the severity of the disease (Current Care Guidelines 2012; Tesse et al. 2018). Currently children must have a regular asthma medication for at least six months before entitlement to special reimbursement. Allergen-specific

immunotherapy can be considered for treatment of allergic asthma in children (Papadopoulos et al. 2012; Haahtela et al. 2013). The non-pharmacological treatment approaches include education and trigger avoidance. The evaluation and monitoring of asthma and treatment adequacy is recommended at least once or twice a year (Papadopoulos et al. 2019; Haahtela et al. 2013).

2.3.4 Asthma medication reimbursement

In Finland, reimbursement for medication expenses is based on the Health Insurance Act. Certain diagnostic criteria set by the Social Insurance Institution of Finland (KELA) must be fulfilled to be eligible for reimbursement payments under the special reimbursement category. The lower special rate of reimbursement for asthma medication is 65% of the costs (KELA 2019). Entitlement to special reimbursement for asthma medication can be granted for five years among children under the age of 16 and for two years among children under the age of three (KELA 2019).

2.4 Atopic dermatitis in childhood

2.4.1 Definition and clinical presentation

Atopic dermatitis is a chronic, pruritic, inflammatory skin disease (Kantor et al. 2016; Kapur et al. 2018). It follows a relapsing course with acute flares. Severe atopic dermatitis can significantly impact on the quality of life of affected children as well as their families and may result in hospitalization for the management of the disease and its complications. Although the pathogenesis of atopic dermatitis is not completely understood, it appears to result from the complex interplay between defects in skin barrier function, environmental and infectious agents, and immune dysregulation (Kapur et al. 2018). Atopic dermatitis is characterized by dry and pruritic skin, immune dysfunction, and dermatitis in typical anatomical sites. The clinical manifestations of atopic dermatitis vary depending on the age of onset and the natural course of the disease. Different phenotypes of atopic dermatitis have been suggested (Roduit et al. 2017). In infants, dermatitis usually appears on the cheeks. Older children often experience rashes in the folds of the knees or elbows, on the backs of hands or on the scalp. "Atopic" means that there is typically a genetic

tendency toward allergic disease. The diagnosis of atopic dermatitis is made clinically and is based on specific criteria (criteria proposed by Williams et al. 1994), which take into account the patient's history and clinical manifestations. The diagnostic criteria in Finnish guidelines include an itching dermatitis in typical areas plus three or more of the following: history of flexural involvement, a history of asthma/hay fever, a history of a generalized dry skin, onset of rash under the age of two years, or visible flexural dermatitis (Current Care Guidelines 2016). In more than 60% of children the disease starts within the first two years of life (Kapur et al. 2018). Many children will outgrow the disease; in others it will persist. Atopic dermatitis is often the initial indication of later development of asthma and allergic rhinitis (Roduit el al. 2017).

2.4.2 Epidemiology of atopic dermatitis

Atopic dermatitis in childhood is common, with a rate of 10-20%, but its occurrence varies greatly throughout the world (Flohr et al 2014; Williams et al. 2008; Henriksen et. al 2015; Roduit 2017; Asher et al. 2006). In a European cohort, including Finland, the rate of atopic dermatitis was 27 % in four year old children (Roduit 2012). The incidence has increased by two- to three-fold during the recent decades in industrialized countries. The latest worldwide data showed that while atopic dermatitis seems to have reached a plateau in the countries with the highest prevalence such as the UK and New Zealand, atopic dermatitis continues to increase in low-income countries, such as those in Latin America or Southeast Asia, specifically in young children (Asher et. al 2006).

2.4.3 Treatment of atopic dermatitis

Self-management with moisturizers, periodical topical corticosteroids, daily bathing with water and avoiding irritating agents are the basis of the treatment. In Finland, children with a more severe atopic dermatitis or underlying food allergy are referred to specialized health care consultation. In cases of more severe atopic dermatitis, topical calcineurin inhibitors are used. Topical corticosteroids and calcineurin inhibitors can also be used twice weekly to reduce relapses (Current Care Guidelines 2016). Recent trials have demonstrated the effectiveness of early, consistent application of emollients for infants at increased risk (Horimukai et al. 2014; Simpson et al 2014). These results suggest that reinforcing skin barrier function in

the neonatal period is a promising strategy for the prevention of atopic dermatitis. The administration of Lactobacillus rhamnosus GG starting 4 weeks prenatally and continuing for six months after birth may decrease the development of atopic dermatitis up to two years of age (Doege et al. 2012)

2.5 Lower respiratory tract infections (LRTIs) in childhood

2.5.1 Bronchiolitis, wheezing bronchitis and bronchitis

2.5.1.1 Definition and clinical presentation

Bronchiolitis in infancy is a lower respiratory tract infection caused by viral pathogens. The pathogenesis of bronchiolitis includes acute inflammation, edema and necrosis of epithelial cells in small airways, increased mucus production and bronchospasm (Meissner 2016). Acute wheezing in children under three years of age covers two clinical conditions, bronchiolitis and wheezing bronchitis. These are different in terms of causative agents, clinical symptoms, and outcomes (Tapiainen et. al 2016). In previous literature, these conditions are often included in the same studies. The term bronchiolitis is used for children under 24 months of age with wheezing in the U.S, but in Europe including Finland, it is restricted to children under 12 months of age experiencing their first virus-induced wheezing episode (Ralston et al. 2014; Mecklin et al. 2014). In Finland, wheezing (obstructive) 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 6 to 12 months (Mecklin et al. 2014; Tapiainen et al 2016). Recently it is also suggested that instead of using a certain cutoff age to diagnose bronchiolitis, the viral etiology could be used as the differentiating factor (Jartti et al. 2019). Acute childhood bronchitis is considered as an acute cough associated with a viral respiratory infection lasting less than three weeks (Tapiainen et al. 2016). However, these conditions may have a significant clinical overlap.

The diagnosis of bronchiolitis is clinical. Typical clinical symptoms and signs associated with bronchiolitis are rhinitis, cough, wheezing, signs of respiratory distress such as tachypnea, the use of accessory muscles, and apneas in young babies, and widespread crackles on auscultation (Ralston et al. 2014; Smyth 2006). Bronchiolitis is most often seen in infants under six months of age during respiratory

syncytial virus (RSV) epidemics (Smyth 2006). In older children signs of respiratory distress and expiratory wheezing during acute respiratory viral infection are typical for wheezing bronchitis (Current Care Guidelines 2015).

2.5.1.2 Epidemiology

Bronchiolitis is a common disease with a high health care burden (Smyth 2006). According to population-based birth cohort studies, the occurrence of bronchiolitis is approximately 18-32% in the first year and 9-17% in the second year of life (Jartti & Korppi 2011). Approximately 3% of all infants are admitted to hospital for bronchiolitis during the first year of life, and 2-6% of these need intensive care unit treatment due to acute respiratory distress (Green et al. 2016, Smyth 2006). In a Finnish cohort of infants younger than six months with bronchiolitis, the incidence of emergency department visits was 37/1,000 per year. Seventy percent of these patients were hospitalized (Pruikkonen et al. 2014). In developed countries, the mortality rate for bronchiolitis has been low and is associated with underlying illnesses, such as chronic lung disease, neuromuscular disease, congenital heart disease, and immunodeficiency (Thorburn 2009). In the US and UK, the mortality rate for bronchiolitis has been at two to three per every 100,000 live births (Holman et al. 2003, Smyth & Openshaw 2006). Generally, wheezing associated with respiratory infection (i.e. wheezing bronchitis) occurs in approximately 30% of all children during the first three years of their lives (Martinez et al. 1995; Brand al. 2014; Henderson et al. 2008; Taussig et al. 2003). The majority of wheezing children grow out of the wheezing tendency by the age of 8 years. Those who continue to wheeze are later prone to developing asthma (Martinez et al. 1995; Taussig et. al 2003; Henderson et al. 2008).

2.5.1.3 Microbiologic etiology of bronchiolitis and wheezing bronchitis

The RSV is the most common virus causing bronchiolitis and is responsible for 50-70% of all hospitalizations for bronchiolitis (Miller et al. 2013; Meissner 2016; Tapiainen et al 2016). In Finland, RSV epidemics used to occur every other year, but during the last few years RSV epidemics appear to be happening every year with the peak in the winter months (Tapiainen et al. 2016). Rhinoviruses are particularly associated with wheezing bronchitis and are detected more steadily throughout the year. Accordingly, RSV is the most important virus that causes wheezing in children

under one year of age and rhinoviruses are the most important in older children. The recently recognized respiratory viruses are the human metapneumovirus, which is associated with bronchiolitis, and the human bocavirus, which is associated with wheezing bronchitis. Coinfections are common in infants hospitalized with acute bronchiolitis up to 61% of all cases (Skjerven et al. 2016). Bacteria do not usually cause bronchiolitis or wheezing bronchitis in children (Tapiainen et al. 2016).

2.5.1.4 Treatment of bronchiolitis and wheezing bronchitis

A child with bronchiolitis should be admitted to hospital if his/her general condition is weakened or the oxygen saturation is decreased. Infants who experience bronchiolitis during the first weeks of life should usually be properly monitored due to a risk of apnea and deteriorating respiratory symptoms. Over the past decades, bronchiolitis has been treated with medication reflecting that of asthma treatment (i.e. corticosteroids, inhaled agents). However, these medications have failed to alleviate the course of disease (Meissner 2016). The current guidelines, including the Finnish Current Care Guidelines for the treatment of LRTIs in children published in 2015, recommend supportive care, i.e. monitoring of oxygenation, administration of supplemental oxygen and maintaining adequate hydration, as the goal of the treatment (Meissner 2016; Tapiainen et al. 2016). Inhalations of racemic epinephrine or nebulized hypertonic saline may be given for severe symptoms. Acute respiratory failure is treated with respiratory support such as continuous positive airway pressure and high-flow nasal oxygenation (Sinha 2015). Two to three percent of hospitalized infants require invasive ventilation (Hasegawa et al. 2015). Immunoprophylaxis with palivizumab can be used to prevent severe RSV bronchiolitis symptoms in high risk groups, such as those with chronic lung disease or heart disease (Meissner 2016).

Salbutamol inhalations administered via a holding chamber may relieve the symptoms of wheezing bronchitis. Glucocorticoid inhalations are not recommended for the prevention of expiratory wheezing episodes induced by viral infections in children. Currently available drugs are not effective in relieving cough symptoms (Tapiainen et al. 2016).

2.5.2 Pneumonia

2.5.2.1 Definition and clinical presentation

The definition of pneumonia includes viral or bacterial infection of the pulmonary alveoli or interstitial tissue. It can be diagnosed by chest radiography and/or on the basis of clinical findings, such as the presence of fever and acute respiratory symptoms (McIntosh 2002; Don et al. 2010; Tapiainen et al. 2016). Community-acquired pneumonia can be defined as the presence of signs and symptoms of pneumonia acquired outside the hospital in a previously healthy child (McIntosh 2002; Harris et al. 2011). Pneumonia can be diagnosed on a clinical basis (Harris et al. 2011; Tapiainen et al. 2016). The most common indicative symptoms and findings of pneumonia are fever, cough and dyspnea and fine crepitations or silenced breath sounds on auscultation. Chest radiography showing a typical lung infiltration is useful for severely ill hospitalized children and in cases of complicated pneumonia, or a poor response to antimicrobial treatment (Tapiainen et al. 2016). Laboratory tests for infection and microbiological etiology could be considered.

2.5.2.2 Epidemiology

The annual incidence of community-acquired pneumonia in children of less than 5 years of age has been reported to range from 0.2–0.33% to 3.5–4% (Don et al. 2010). Approximately half of the children with pneumonia in this age group and 20% of children aged between 5 and 10 years are treated in hospital (Heiskanen-Kosma et al. 1998; Don et al. 2010). In western countries the mortality due to pneumonia is low among previously healthy children without underlying conditions, but pneumonia in children younger than 5 years of age is responsible for 18.4% of mortality worldwide (Liu et al. 2012; Bhutta et al. 2013).

2.5.2.3 Microbiologic etiology of pneumonia

Respiratory viruses, such as the RSV, cause one-third of childhood pneumonia cases. Viruses combined with bacteria account for another third and bacteria alone for the remaining third (Tapiainen et al 2016). Viral pneumonia is more common in children less than two years of age and bacterial etiology predominates at school age (Don et

al. 2010). The most common pathogen has been Streptococcus pneumoniae (Don et al. 2010), but pneumococcal bacteremia cases have markedly decreased since the introduction of pneumococcal vaccines (Korppi et al. 2013). Mycoplasma pneumoniae typically causes pneumonia in school-aged children (Don et al. 2010). Chlamydia pneumoniae has been found in less than 10% of pneumonia cases in children (Don et al. 2010).

2.5.2.4 Treatment of pneumonia

In the Finnish guidelines orally administered amoxicillin is suggested for the treatment of pneumonia in previously healthy children whose clinical condition do not require hospitalization. Administration of G-penicillin intravenously is suggested if hospital treatment is required. Macrolides may be beneficial in treating pneumonia caused by Mycoplasma pneumoniae. Antiviral treatment against influenza should be considered. Children with suspected complications of pneumonia (i.e. empyema, lung abscess) should be treated in hospital (Current Care Guidelines 2015).

2.6 Long-term respiratory morbidity and atopic dermatitis by gestational age at birth

2.6.1 Children born preterm

2.6.1.1 Asthma after preterm birth

Systematic reviews and meta-analyses have shown that preterm birth (<37 weeks) is associated with an increased risk of asthma (Jaakkola et al. 2006; Sonnenschein-van der Voort et al. 2014), and the risk is particularly high among children born very preterm (<32 weeks) (Been et al. 2014). The associations between MP and LP birth and asthma in childhood have also been reported by previous studies (Been et al. 2014; Boyle et al. 2012; Harju et al. 2014, Trønnes et al. 2014). In a retrospective cohort study persistent asthma and use of inhaled corticosteroids by 18 months were more common in LP infants compared with those born at term (Goyal et al. 2011). The incidence of asthma and wheeze were increased at 3 and 5 years of age in MP or LP children compared with term children, as was the risk of needing asthma

treatment with increasing prematurity (Boyle et al. 2012). Harju and associates also noted that LP children, born at 33–36 weeks' gestation, had a higher adjusted OR 1.7 (95% CI 1.4–2.0) of developing asthma compared with children born at 39–40 weeks' gestation (Harju et al. 2012). In contrast, no association was found between LP birth and the risk of asthma in a population of approximately 500 LP infants aged 2–83 months (Abe et al. 2010). In the large UK Avon Longitudinal Study of Parents and Children (ALSPAC), the children born at 33–34 weeks of gestation had spirometry measures that were all significantly lower than those of term-born children at 8–9 years, the effect being similar to that seen in children born very preterm. The approximate differences compared with term infants after adjustment for age, gender and height were -143 ml for forced expiratory volume in 1 second (FEV1), -98 ml for forced vital capacity (FVC) and -253 ml/s for forced expiratory flow at 25-75% (FEF25–75) in the 33-34-week gestation group. By 14–17 years, FEV1 and FVC had improved, approaching values similar to those born at term, but differences in FEV1/FVC and forced expiratory flow at FEF25–75/FVC remained significant (Kotecha et al. 2012).

2.6.1.2 Atopic dermatitis after preterm birth

Preterm birth and very low birth weight (≤ 1500 g) have been linked to a decreased long-term risk of atopic sensitization (Siltanen et al. 2011), but the findings are inconsistent (Kvenshagen et al. 2009). One previous study on two independent cohorts of premature infants found that birth at very low GA (< 29 weeks) was associated with a reduced risk of atopic dermatitis compared with birth at 29–34 weeks and term GA (Barbarot et al. 2013). Recent meta-analysis of 18 observational studies, including data from more than 2 million individuals, found that very preterm birth predicted a reduced risk of developing atopic eczema later in life (Zhu et. al 2018). Compared with full-term infants, there were no associations between MP birth and eczema (Zhu et al 2018). Low birth weight <2500g has been presented as a protective factor for the development of atopic dermatitis in the meta-analysis of 10 studies (Panduru et al. 2014).

2.6.1.3 LRTIs after preterm birth

Children born very preterm (<32 weeks) are at an increased risk of respiratory tract infections, the risk persisting into early childhood (Greenough 2013). Previous

studies have also confirmed the association between MP and LP birth and an increased incidence of hospital admissions for LRTIs (Boyle et al. 2012; Miller et al. 2016; Parajonthy et al. 2013; Blanken et al. 2016; Vrijlandt et al. 2013). A Canadian retrospective health record linkage study of a total of 35,733 infants including 2,051 LP (33-36 weeks) births revealed an increased risk of acute bronchiolitis/bronchitis (OR 1.64, 95%CI 1.13-2.39) and pneumonia (OR 1.17, 95% CI 1.05-1.30) in the first 3 years of life in LP infants compared with term infants (Berard et al. 2012). The systematic review by Been and associates reported that children born at 32–36 weeks' gestation had an increased risk of wheezing with an unadjusted OR 1.49 (95% CI, 1.34–1.66) compared with term-born children (Been et al. 2014). This study also showed that this risk was threefold in those born very preterm (Been et al. 2014). Moreover, several studies in LP infants have shown increased hospital admission rates of RSV bronchiolitis during the first year of life (Helfrich et al. 2015; Isayama et al. 2017). LP infants with RSV bronchiolitis have a three-fold higher risk of respiratory support in comparison to full-term infants (Helfrich et al. 2015).

2.6.2 Children born early-term and term

2.6.2.1 Asthma after early-term and term birth

Early-term birth has been associated with an increased risk of childhood asthma in comparison with full-term birth (Vogt et al. 2011; Boyle et al. 2012; Edwards et al. 2015; Harju et al 2014). In a large Swedish cohort of 1,100,826 children and adolescents (6-19 years old), early-term children had an increased risk of inhaled corticosteroid use, evaluated by registered drug retrievals, compared with those born at 39-41 weeks of gestation (Vogt et al. 2011). A hospital-based Finnish register study found that the burden of asthma in children was particularly associated with deliveries at 37-38 weeks of gestation (Harju 2014). In the UK ALSPAC cohort the spirometry measures at 8–9 years were lower in the early-term children compared with full-term born children, but the measures between the two groups were similar at 14–17 years of age (Kotecha et al. 2016).

2.6.2.2 Atopic dermatitis after early-term and term birth

In previous reports on the prevalence and risk of atopic dermatitis, early-term-born children have often been included in the GA at group 37-42 weeks and thus the risk of atopic dermatitis is thought to be somewhat equal.

2.6.2.3 LRTIs after early-term and term birth

A population-based prospective cohort study of all singleton deliveries in a single tertiary center revealed an association between early-term birth and long-term respiratory morbidity (i.e. asthma, bronchiolitis, pneumonia) up to the age of 18 years when compared with births at full-term and late-term (Walfisch et al. 2017). In a large Australian register study in which follow-up lasted from birth to 18 years of age, increased relative risks of admission for LRTIs were found in children born at 37–38 weeks of GA, whereas birth at 41 weeks or later was associated with modestly reduced rates of admission (Miller 2016). In another cohort study in which children born via induced early-term delivery were compared with those born full-term or late-term, 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 had received intensive care and/or respiratory care in the neonatal period (Tickell et al. 2015).

2.6.3 Children born late- and post-term

2.6.3.1 Asthma after late- and post-term birth

In previous reports late-term (Harju et al. 2014) and post-term (Harju et al. 2014; Källen et al. 2013) births have been associated with a decreased risk of childhood asthma compared with full-term birth. In a birth cohort study of 8327 Chinese children followed up to 12 years of age post-term births (≥42 weeks) were associated with a decreased risk of hospitalization for asthma and other wheezing disorders HR 0.56 (95% CI 0.32, 0.98). In late-term births (41 to <42 weeks), HR did not reach statistical significance HR 0.77 (95% 0.59, 1.01) (Leung et al. 2016).

2.6.3.2 Atopic dermatitis after late- and post-term birth

A large Norwegian birth cohort study of 1,000,000 children is the only earlier report suggesting an increased risk of atopic dermatitis by school age in children born post-term (Trønnes et al. 2013).

2.6.3.3 LRTIs after late- and post-term birth

In a large Australian register study by Miller et al., birth at 41 weeks or later was associated with modestly reduced rates of admission for LRTIs (Miller et al. 2016). In another population-based cohort study, late-term birth also predicted a decreased risk of long-term respiratory infectious morbidity (i.e. bronchiolitis, pneumonia) up to the age of 18 years, while no significant association was seen with post-term birth (Walfisch et al. 2017).

2.6.4 Limitations in comparing outcome studies

Some important factors should be taken into account when comparing outcome studies of early childhood asthma, wheezing, atopic dermatitis and LRTIs. The definitions may be heterogeneous between studies. The definition of GA categories in the preterm and term birth groups may vary among studies. GA group comparisons and exclusion criteria may also be different. The clinical assessment, diagnostic methods and recording practices may vary between sites and time periods. The definition of acute bronchiolitis in particular may vary in terms of age but also in terms of symptoms. The use of terminology in allergic disorders may also be inconsistent in different study designs and this should be recognized when comparing prevalence and time trends of asthma and allergies. In addition, treatment practices in peri- and neonatal care have changed and improved over time. For example there may be variations in the indications for cesarean delivery and non-invasive ventilation practices have been improved.

Routinely collected health data obtained for administrative and clinical purposes are increasingly used in epidemiological studies. The reliability and validation of the used register data, standardization in terminology and information on disease severity are important in the comparison of study results.

2.7 Early-life risk factors for childhood asthma, atopic dermatitis and LRTIs

The risks of developing heterogeneous diseases, asthma and atopic dermatitis, are related to a complex interaction between genetic susceptibility and early-life exposures. Many genetic, epidemiological and environmental factors that have not been fully explored are linked to later childhood respiratory morbidity and atopic tendency. In recent years, research interest has been focused on identifying specific genes connected to susceptibility to asthma and allergies (Vercelli et al. 2008) and also to bronchiolitis occurrence and severity (Pasanen et al. 2017). Increasing research evidence also suggests that epigenetic variation (such as DNA methylation) can contribute to asthma as well as to bronchiolitis susceptibility (Xu et al. 2018; Elgizouli et al. 2017). However, these explain only a part of the variation in this risk. The rapid increase in the prevalence of allergic diseases proposes that environmental factors and early-life exposures might play an important role in the pathogenesis of these diseases. Most of the studied early-life risk factors are related to maternal factors, to the maturation of the immune system, and to lung development and the maturity of the newborn. As proposed by previous birth cohort and epidemiological studies, specific exposures in the fetal and early postnatal periods may influence lung growth and immune development (Keil et al. 2004; Hofman et al. 2004; Taussig et al. 2003; Martino 2011) and modify later risk of allergic diseases (McKeever et al. 2002; Prescott et al. 2013) and LRTIs (Vissing et al. 2018).

2.7.1 Maternal, pregnancy and delivery related factors

2.7.1.1 Maternal age and socioeconomic status (SES)

A higher maternal age has been related to adverse neonatal risks, but maternal age at birth may also reflect other health and social processes (Goisis et al. 2017). Advanced maternal age ≥40 years has been previously associated with the development of asthma in the offspring (Aspberg et al. 2010), but this has not been studied extensively. Risks associated with maternal age are linked with maternal SES and smoking. Young maternal age and low SES have been associated with an increased risk of hospital admission for bronchiolitis (Green et al. 2013, Lanari et al. 2015). Smoking during pregnancy correlates strongly with lower maternal SES in Finland

(Ekblad et al. 2014; Rumrich et al. 2018). Mothers with lower SES tend to continue smoking after delivery and breastfeed their offspring less often compared with mothers with higher SES (Ruijsbroek et al. 2011). In a previous Finnish register-based study maternal SES played a substantial role in preterm births after adjustment for numerous birth characteristics and reproductive risk factors (Räisänen et al. 2013). The incidence of preterm births was mostly higher among blue-collar compared to white-collar workers. In some reports, lower maternal education has been associated with preterm birth (Ruiz et al 2015). In other words, many of these factors linked to maternal SES may influence the burden of later childhood respiratory morbidity via indirect pathways.

2.7.1.2 Maternal smoking during pregnancy

The association between maternal smoking during pregnancy and later childhood asthma has been established in numerous studies (Burke et al. 2012; Jaakkola et al. 2004; Silvestri et al. 2015). Maternal smoking during pregnancy affects fetal lung development, inducing long-lasting structural changes, and it may predispose to preterm delivery (McEvoy et al. 2017). According to a meta-analysis, exposure to prenatal smoking has increased the risk of wheezing in <6-year-old children and the risk of wheezing or asthma in ≥6-year-old children (Silvestri et al. 2015). A recent review and meta-analysis concluded that pre- or postnatal passive smoke exposure increases the incidence of wheeze and asthma in children and young people by at least 20% (Burke et al. 2012). Results of the study using data from eight European birth cohorts showed that maternal smoking during pregnancy also increased the risk of wheeze and asthma among children who were not exposed to maternal smoking after birth (Neuman et al. 2012). Maternal smoking during pregnancy is also associated with bronchiolitis in infancy (Green et al. 2016). Tobacco smoke exposure during pregnancy might preclude sensitization through an immunosuppressive effect (Thacher et al. 2016) and might alter the later risk of development of atopic dermatitis.

2.7.1.3 Maternal diabetes and obesity

Fetal exposure to hyperglycemia affects lung growth and alveolization (Koskinen 2014) and may increase the risk of neonatal respiratory problems (Michael Weindling 2009) and thus the subsequent development of asthma. A previous register-based

study by Aspberg and associates showed a weak association between maternal diabetes and increased prescription of anti-asthmatic medication during childhood (Aspberg et al. 2010). However, in a pooled analysis of 14 European birth cohorts after adjusting for several complications of pregnancy, no association was found between gestational and/or pregestational diabetes with the risk of wheezing up to 24 months of life (Rusconi et al. 2018). Maternal obesity has been associated with increased asthma and wheezing among offspring, especially with non-atopic asthma (Forno et al. 2014). Maternal obesity is related to fetal growth (Duijts 2012) and is also associated with other underlying conditions, such as hypertension and the need for cesarean delivery. Thus, it seems to indirectly increase the risk of wheezing and asthma in the offspring (Rusconi et al. 2018).

2.7.1.4 Maternal infection and antibiotic use

Maternal infection and antibiotic therapy during pregnancy are associated with a higher risk of childhood asthma (Stokholm et al. 2014) Chorioamnionitis is a cause of fetal inflammation. It increases the risk of developing lung morbidity and thus may increase the risk of developing asthma (Kumar et al. 2008). The Danish National Birth Cohort confirmed the increased risk of asthma hospitalization HR 1.17(1.00-1.36) and use of inhaled corticosteroids HR 1.18(1.10-1.27) in children below the age of five if mothers had been exposed to antibiotics at any time during pregnancy. No association was found in terms of a child's risk of eczema (Stensballe et. al 2013).

2.7.1.5 Maternal asthma and atopy

Maternal asthma is the main risk factor associated with the development of childhood asthma (Litonjua et al. 1998). A meta-analysis conducted by Lim et al. showed that children of mothers with maternal asthma had approximately a threefold risk of asthma compared with those children without maternal asthma (Lim et al. 2010). Maternal atopy is associated with higher prevalence of asthma, atopy and allergic rhinitis in the offspring (Wang et al. 2012).

2.7.1.6 Mode of delivery

Previous studies have revealed an association between delivery by cesarean section and childhood asthma and infectious respiratory morbidity (Thavagnanam et al. 2008; Huang et al. 2015; Kristensen et al. 2016; Leung et al. 2015; Moore et al. 2012; Sevelsted et al. 2015). A meta-analysis has shown a 20% increase in childhood asthma risk after birth by cesarean delivery (Huang et al. 2015).). In previous reports, the risk of later asthma has been increased particularly after elective cesarean section (Kristensen et al. 2016), but in another study also after emergency cesarean section (Tollånes et al. 2008). According to a recent Danish national register-based cohort study, children delivered by elective cesarean section also had an increased risk of LRTIs (Kristensen et al. 2016). Infants born by cesarean section, especially by elective cesarean section, are exposed differently to maternal hormones and microbiota compared with those born by vaginal delivery, and these differences could predispose an infant to an adverse respiratory outcome (Kotecha et al. 2016; Vissing et al. 2018). The indication of cesarean section could also be a reflection of other risk factors influencing the outcome. Children born by vaginal delivery are exposed to diverse microbiological flora from the birth canal and subsequent colonization of the gut and airways alters immune modulation and susceptibility to LRTIs (Kotecha et al. 2016; Vissing 2018). The association of the mode of delivery with the risk of atopic dermatitis is controversial. Some studies have found no association (Bager et al. 2008; Kvenshagen et al. 2009) whereas others have associated atopic dermatitis with cesarean delivery (Yu et al. 2015).

2.7.2 Gestational age at birth

Preterm-born children are at risk of later respiratory morbidity due to birth at an immature stage of lung development and influenced by complications of preterm birth and medical interventions such as mechanical ventilation. Bronchopulmonary dysplasia is a chronic respiratory disease associated with premature birth that primarily affects infants born at less than 28 weeks of GA (Greenough 2013). Bronchopulmonary dysplasia is associated with bronchiolitis, recurrent wheezing, and asthma in early childhood (Greenough 2013; Davidson et al. 2017). Preterm birth and later respiratory morbidity may also have common genetic components. Some prenatal exposures that could induce preterm birth, such as smoking, could also influence the risk of asthma postnatally (McEvoy et al. 2017; Leps 2018). Preterm infants are also more often delivered by cesarean section than term infants

(Zeitlin et al. 2010). Antenatal corticosteroid therapy administered for fetal lung maturation in cases of imminent preterm delivery, has previously been associated with childhood asthma (Pole et al. 2009). The effects of corticosteroids on fetal growth (Murphy et al. 2012), the hypothalamus-pituitary axis, the immune function (Prescott 2009), and kidneys, as well as subsequent hypertension, and subsequently may have a role in the development of asthma (Pole et al. 2009). Susceptibility to LRTIs during early infancy in very preterm, but also in MP and LP born infants, might be caused by incomplete transfer of maternal antibodies as a result of premature birth and immaturity of the neonatal immune system. Final maturation of the immune system occurs during the first six months of life (Ygberg et al. 2012). The association of early-term birth with an increased risk of long-term respiratory morbidity 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 (Gill & Boyle 2017).

It is unclear why very preterm birth is associated with a reduced risk of atopic dermatitis and post-term birth with an increased risk on the other hand. Many underlying mechanisms have been proposed. Antenatal exposures or earlier exposure to the extrauterine environment may modulate the disease risk by influencing the Th1/Th2 balance (Martino 2011). The epidermal maturation of the skin is complete by 34 weeks of GA and stratum corneum is fully formed a few weeks after birth (Oranges et al. 2015; Goedicke-Fritz et al. 2017). Preterm infants have functionally impaired skin barriers resulting in early transcutaneous exposure to antigens and the development of tolerance (Barbarot et al. 2014; Goedicke-Fritz et al. 2017). Very preterm infants also have reduced diversity of intestinal microflora, and this could influence the acquisition of immune tolerance and lead to a reduced risk of atopic dermatitis (Barbarot et al. 2014). As previously suggested, Th2 predominance leads to increased secretion of proinflammatory and Th2 cytokines, and this might promote immunoglobulin E production and, subsequently, atopic inflammation and diseases (Martino 2011). A shorter period of exposure to Th2 cytokines during pregnancy could also modulate the fetal immune system toward less atopy, which is contrary with post-term infants (Goedicke-Fritz et al. 2017; Zhu et al. 2018). Health risks associated with post-term birth, including increased risk of atopic dermatitis, might be related to underlying maternal risk factors for post-term pregnancy, such as obesity and advanced age (Galai et al. 2012). Other hormonal and immunological processes or the decreased capacity of the placenta to transport oxygen and nutrients to fetus after expected date of delivery might be contributing

to this. However, the pathogenesis of post-term pregnancy is not yet clearly understood (Galai et al. 2012).

2.7.3 Newborn-related and postnatal factors

Restricted fetal growth through adaptive processes in utero may predispose infants to reduced lung function with smaller airways and respiratory diseases later in life (Duijts 2012). Previous results suggest that SGA children seem to carry a greater risk of bronchiolitis/bronchitis (Miller et al. 2016; Paranjothy et al. 2013; Green et al. 2016). A link between low birth weight and childhood wheezing disorders has been reported, although some results have been inconsistent (Mebrahtu et al. 2015). A meta-analysis assessed the association of preterm birth (gestational age <37 weeks) and low birth weight (<2,500 g) with childhood asthma outcomes. Associations between low birth weight adjusted for gestational age at birth with preschool wheezing (pooled OR, 1.10; 95% CI, 1.00-1.21) and school-age asthma (pOR, 1.13; 95% CI, 1.01-1.27) were detected. An increased risk of preterm birth was, however, seen independent of birth weight (Sonnenschein-der Voort et al. 2014). An association between anthropometric parameters at birth and later atopic tendency has been suggested, but the findings in relation to atopic dermatitis have been inconsistent (Bolte et al. 2004).

Male sex has been associated with wheezing (Taussig et al. 2003; Blanken et al. 2016; Caudri et al. 2013), as well as an increased risk of asthma (Trønnes et al. 2013; Göskor et al. 2013) and atopic dermatitis (Moore et al. 2004) in infancy and childhood. A large worldwide systematic analysis found a consistently higher incidence of admissions for severe acute LRTIs in boys than in girls (Nair et al. 2013). The physiological basis for this incidence is not fully understood, but in boys growth of the airways lags behind that of the lung parenchyma resulting in disparity between airway caliber and lung size compared with girls (Liptzin et al. 2015; Kotecha el al. 2018).

Some reports have linked early antibiotic exposure during the first week of life to asthma (Göskor et al. 2011; Raymond et al. 2017; Stromberg et al. 2018), but the link to LRTIs is not yet well established. Antibiotics affect the infant's gastrointestinal microbiota and maturation of the immune system and may disrupt the development of immunological tolerance (Zwittink et al. 2017). The first weeks of life probably represent the most important time window for changes in the intestinal microbiota caused by antibiotics (Collado et al. 2015). This mechanism is suggested for the

association with early antibiotics and atopic dermatitis (Tsakok et al. 2013). 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 (Stromberg et al. 2018).

Infants needing mechanical ventilation in the neonatal period have increased risks of wheezing and asthma later in life (Greenough 2013) and also after adjustment for GA (Källen et al. 2013). Neonatal ventilator-induced lung injury especially to structurally immature, compliant airway structures in preterm infants has been previously well described (Reyburn et al. 2012). It seems that regardless of the etiology of lung disease, ventilator therapy in the neonatal period may be associated with long-term respiratory consequences. Asthma and airway hyperresponsiveness after preterm birth have been suggested to differ from typical childhood asthma, showing more association with neonatal respiratory problems and oxygen therapy than with current inflammation (Halvorsen et al. 2005).

2.7.4 Other risk factors

Other environmental factors after birth such as nutrition may influence the risk of asthma and atopic dermatitis. Breastfeeding (minimum of three months) may have a protective effect against childhood asthma (Sonnenschein-van der Voort et al. 2012). Instead, the meta-analysis by Yang et al. showed no strong evidence of a protective effect of at least three months' exclusive breastfeeding against atopic dermatitis (Yang et al. 2009).

Postnatal exposure to smoking is a known risk factor for wheezing in early childhood and LRTIs in pre-school children (Jones et al. 2011). It is also suggested that exposure to tobacco smoke might be a trigger of lower respiratory symptoms, such as cough and wheeze, rather than enhancing the susceptibility to infections (Vissing et al. 2018).

Air pollution has also been a risk factor for asthma (Burbank & Peden 2018). In a recent Taiwanese study, relative risks of hospitalization due to asthma in children associated with exposure to varying levels of air pollutants were identified. The relative risks for asthma hospitalization associated with air pollutants were higher among children aged 0-5 years than aged 6-18 years and were higher among males than females. The effects of air pollution on childhood asthma were greater in the higher-level air pollution regions, while no association was observed in the lower-level air pollution regions (Kuo et al. 2019).

Being the first-born child has been found to be protective against childhood wheezing (Lodge et al. 2014), but first-born children have presented with a greater risk of atopic dermatitis (Upchurch et al. 2010). Twins also seem to be less prone to develop asthma and atopic dermatitis than singletons (McKeever et al 2001). The presence of older siblings has been associated with a higher risk of early wheezing but with a lower risk of late-onset asthma or wheeze (Ball et al. 2000; McKeever et al. 2001). In addition, a higher number of siblings has been protective against the development of atopic dermatitis (McKeever et al. 2001; Karmaus et al. 2002). The mechanisms behind this process are unclear but increased exposure to infections transmitted by siblings and maternal microbial pressure affecting the in utero environment have been suggested (Benn et al 2004). Previous results also suggest that the presence of older siblings and day care attendance increase the risk of RSV infection hospitalization (Haerskjold et al. 2016) and transient wheezing in early childhood (Blanken et al. 2016; Caudri et al. 2013). It has been previously proposed that early-life LRTIs caused by RSV and rhinovirus are strongly associated with an increased asthma risk ("viral march") (Jartti 2011; Lukkarinen et al. 2017). It is also suggested that early-life contact with microbes can be protective against allergy, but severe early-life infection can lead to prolonged Th2-type responses (Strachan 1989; von Mutius 2007).

As suggested by the 'hygiene hypothesis', recent changes in lifestyle and reduced microbial exposure during childhood may lead to an imbalance in the developing immune system and subsequently increase the risk of allergic diseases. In contrast, the protective effect of the farm environment, regular contact with farm animals and farm milk consumption, in childhood has been associated with a lower risk of asthma and allergies in later life in previous studies (von Mutius & Vercelli 2010). Previous research on the association between household pet keeping and the development of childhood asthma or allergies has shown contradictory results. In a meta-analysis including children from European birth cohort studies, no association was found between contact with furry pets in early life and asthma or allergic rhinitis (Lødrup Carlsen et al. 2012). Recently the prevalence of allergic disease (any of asthma, allergic rhinoconjunctivitis, or eczema) in children aged 7-9 years has been reported to be reduced in a dose-dependent fashion with the number of household pets living with the child during their first year of life (Hesselmar et al. 2018). Living with furry pets has been associated with changes in the child's gut microbiota in infancy (Stewart et al. 2018). Accordingly, so called "biodiversity hypothesis" proposes that contact with diverse environmental microbiome and natural environments enriches

the human microbiota, promotes immune balance and protects from allergy and inflammatory disorders (Haahtela 2019).

In summary, possible pathways and early-life risk factors associated with respiratory morbidity (asthma, LRTIs) and atopic dermatitis are illustrated in Figure 3. Several factors seem to play a role especially in the respiratory vulnerability of premature infants: prenatal factors, prematurity with its inherent developmental and physiologic components, neonatal respiratory morbidity, increased susceptibility to viruses (i.e. RSV) and other environmental factors (Colin et al. 2010; Greenough 2013; Kugelman & Colin 2013).

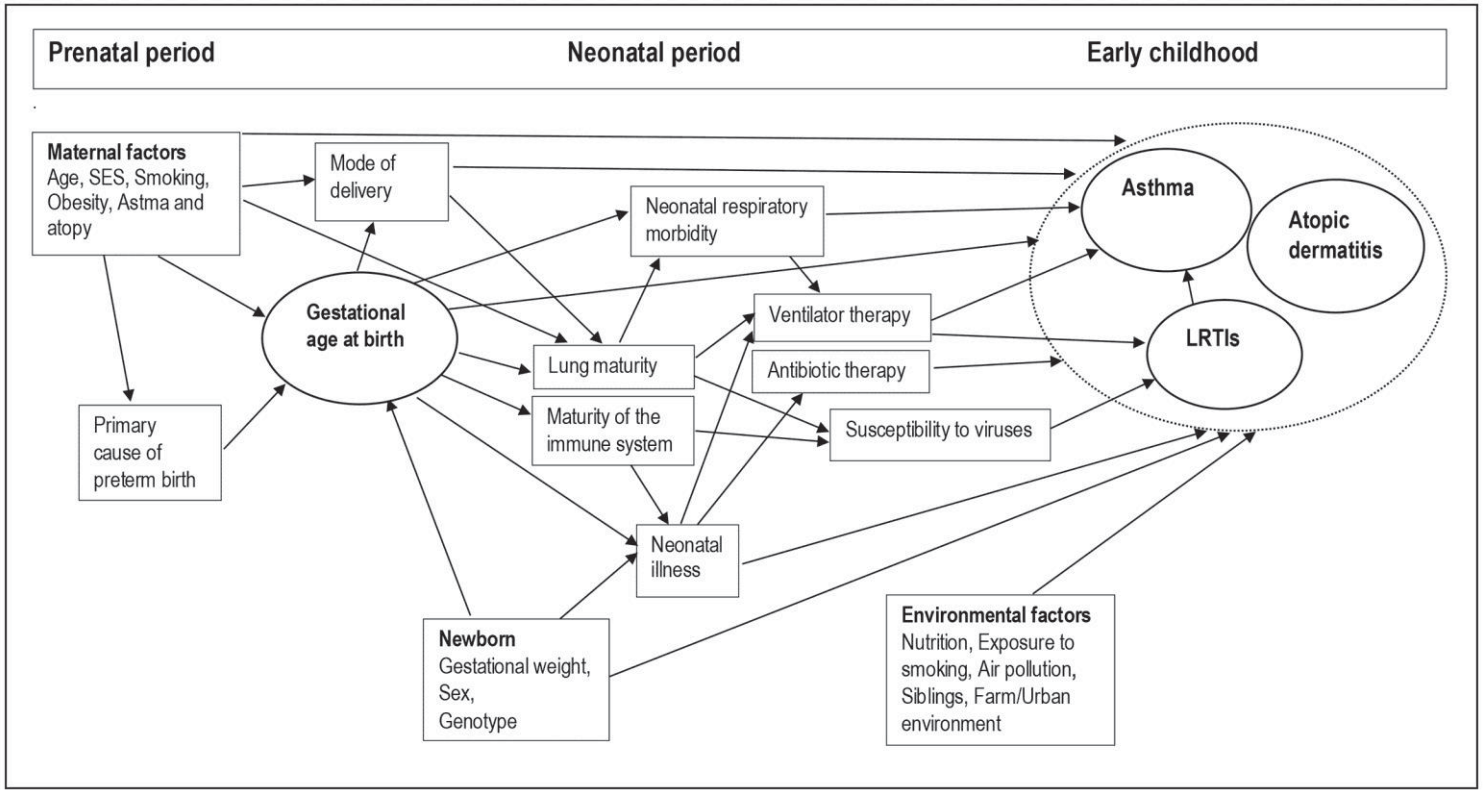

Figure 3. A model suggesting possible pathways and early-life risk factors associated with respiratory morbidity and atopic dermatitis.

3 AIMS OF THE STUDY

The aims of this study were to evaluate the long-term respiratory outcomes and atopic dermatitis among moderately preterm (MP) and late preterm (LP) infants in relation to very preterm and term infants and among the term subgroups of infants. An additional aim was to identify perinatal and neonatal risk factors associated with a risk of asthma, atopic dermatitis and lower respiratory tract infections (LRTIs) in relation to gestational age (GA) at birth.

The specific aims were:

1. To evaluate the association between MP and LP births and the risk of asthma and severe atopic dermatitis and to compare the peri- and neonatal risk factors for asthma and atopic dermatitis by school age among very preterm, MP, LP and term groups. A further aim was to assess the risk factors for childhood asthma and atopic dermatitis according to the degree of prematurity (I).

2. To evaluate whether or not MP and LP birth increase the risk of hospital admissions for LRTIs and to assess the role of perinatal and neonatal risk factors for LRTI hospitalization up to the age of seven years (II).

3. To evaluate the incidence and risk factors of asthma and atopic dermatitis by seven years of age in term subgroups of the children: early-term, full-term, late-term and with a special emphasis on post-term children (III).

4. To determine the association of early-, late- and post-term birth on the rate of hospital admissions for LRTIs up to the age of seven years. An additional aim was to explore maternal and perinatal factors associated with the risk of admissions for LRTIs in these GA groups, also focusing especially on the post-term group (IV).

4 MATERIALS AND METHODS

4.1 Study design

This is a retrospective register study, based on a cohort of population derived from national administrative health registers. The data were linked from several national registers, and the primary cohort consisted of all live born children in Finland between 1991 and 2008 according to the Medical Birth Register (MBR). A flow chart of the study is presented in Figure 3.

4.1.1 National health registers

4.1.1.1 Medical Birth Register (MBR)

The MBR maintained by the National Institute for Health and Welfare (THL) contains data from maternity hospitals and home births, the Population Information System of the Population Register Centre, and Statistics Finland. Data collection and reporting to the register-holding authority are obligated by Finnish legislation (Act on National Personal Data Registers Kept under the Health Care System). The MBR includes data on live births and stillbirths of fetuses with a birth weight of at least 500 g or with a gestational age of at least 22 weeks. The data content of the mothers includes information on personal background factors and previous and present pregnancies and deliveries. It also includes data on the infants' care interventions and diagnoses by the age of seven days. The MBR was established in 1987. The reforms of the Register in 1990, 1996, and 2004 were aimed at improving its reliability. The MBR data have been shown to be well established and validated, and reliable in register studies (Teperi 1993; Gissler et al. 1995; Gissler & Shelley 2002).

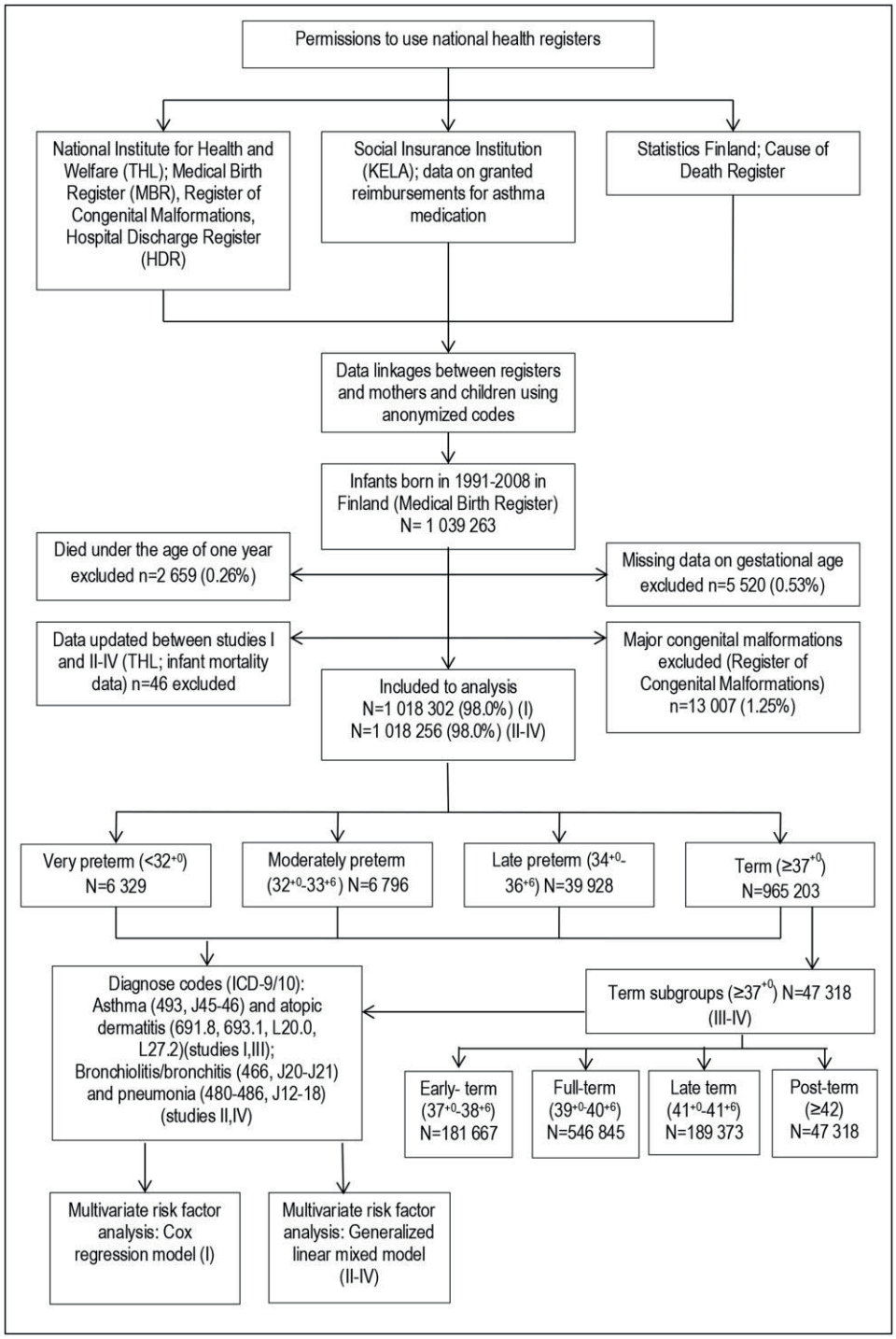

Figure 4. Flow chart of the study.

4.1.1.2 Hospital Discharge Register (HDR)

The HDR maintained by the THL contains information on patients discharged from hospitals between 1969 and 1993. The term HDR was replaced with the Care Register for Health Care in 1994. The Care Register has more comprehensive data on admission and discharge dates, diagnoses and procedures regarding all inpatient visits to all hospitals in Finland and since 1998 specialized outpatient healthcare in all public hospitals. Diagnoses are coded according to the International Classification of Diseases, 9th Revision (ICD-9) in 1987-1995 and according to the 10th Revision (ICD-10) from 1996. The data derived from both HDR and the Care Register for Health Care are used in the present study and considered to be reliable in register studies (Sund 2012).

4.1.1.3 Register of Congenital Malformations

The THL maintains the Register of Congenital Malformations, which contains data on congenital structural anomalies and chromosomal abnormalities. The data are obtained from birth hospitals and genetic laboratories, as well as from other health registers including the MBR and the HDR. Diagnoses are coded according to ICD codes, and minor abnormalities are excluded according to international consensus (EUROCAT Guide 1.3 and reference documents, 2005).

4.1.1.4 Causes of Death Register, Statistics Finland

Statistics Finland keeps the Causes of Death Register, which is based on death certificates that are complemented with data on deaths from the Population Information System. This validated register contains data on causes of death, demographic factors, and the circumstances of death, as well as data on perinatal, neonatal, and infant mortality (Lahti & Penttilä 2001).

4.1.1.5 Register of Social Insurance Institution (KELA)

KELA keeps a register of granted reimbursements for medicine expenses. Entitlement to special reimbursement for medication can be granted for chronic diseases if certain diagnostic criteria set by KELA are fulfilled. The KELA database

is considered a valid source of prevalence data and the ability to accurately identify, for example, asthma cases in the general population (Nwaru et al. 2011).

4.2 Study population

4.2.1 Cohort

The study population was derived from the MBR cohort of all live births (n=1,039,263) in Finland between 1991 and 2008. Infants who died before one year of age (n=2,659) were excluded, had at least one major congenital anomaly (n=13,007) or whose profile had missing data on GA (n=5,520) were excluded (studies I-IV). The infant mortality data were updated between studies I and II, leading to exclusion of 46 infants who died before the age of one year in studies II-IV (Figure 3).

4.2.2 Gestational age groups

The remaining cohort of 1,018,256 infants was divided according to GA into four subgroups: very preterm (< 32^{+0} weeks, n=6,329), MP (32^{+0}-33^{+6} weeks, n=6,796), LP (34^{+0}-36^{+6} weeks, n=39,928) and term (≥37 weeks, n=965,203) (studies I and II). The distribution of excluded infants who died before one year of age in each GA group was: very preterm (n=1,419), MP (n=107), LP (n=179) and term (n=919). In addition, children born after 37 weeks (n=965,203) were divided into four subgroups: early-term (37+0-38+6 weeks, n=181,667), full-term (39^{+0}-40^{+6} weeks, n=546,845), late-term (41^{+0}-41^{+6} weeks, n=189,373) and post-term (≥42, n=47,318) (studies III and IV).

4.3 Main end points

Diagnoses of main end points, respiratory morbidity and atopic dermatitis were retrieved from the HDR and the register of the KELA using ICD codes. These collected diagnoses were coded according to the ICD-9 for 1991–1995 and according to ICD-10 from 1996. All dates of specialized health care hospital admissions to and discharges from public hospitals with these as the main or

secondary diagnoses were collected. Diagnoses were also collected separately for three age categories: 0-11 months, 12-35 months and 36-84 months (studies II and IV). The age at diagnosis was the age of the child when the first detection was recorded in the registers. Data of the children were followed up to seven years of age or to the end of 2009.

4.3.1 Asthma (I, III)

A child was considered to have asthma if ICD-9 code 493 and ICD-10 code J45, J46 (including allergic, non-allergic, unspecified and acute severe asthma) or asthma medication reimbursement was recorded in the registers. According to the Finnish Current Care Guidelines, the diagnosis of childhood asthma is based on the presence of typical symptoms and signs and/or pulmonary function tests confirming the variable or reversible airway obstruction depending on the age of the child. In small children, aged less than three years, the diagnostic criteria for asthma include three to four episodes of wheezing bronchitis within one year. The final asthma diagnosis is confirmed by a specialist, usually a pediatrician. To be eligible for the asthma medication reimbursement, a patient must provide a doctor's certificate confirming an asthma diagnosis and preceding need for inhaled corticosteroid treatment for more than six months (Current Care Guidelines 2012).

4.3.2 Atopic dermatitis (I, III)

A child was considered to have atopic dermatitis if the following diagnoses were detected in the register: ICD-9 codes 691.8 and 693.1 and ICD-10 L20.0 and L27.2 for atopic dermatitis or dermatitis due to ingested food. These diagnoses were combined in analyses of atopic dermatitis. The definition of atopic dermatitis is a chronic, pruritic, inflammatory skin disease with dermatitis in typical anatomical sites. The diagnosis of atopic dermatitis is made clinically and is based on specific criteria that take into account the patient's history and clinical manifestations. Children hospitalized due to atopic dermatitis are those with a more severe disease who need specialized care consultation or treatment.

4.3.3 Bronchiolitis/Bronchitis (II, IV)

The diagnostic parameters for bronchiolitis/bronchitis used in the present study covered all hospital admissions due to acute bronchiolitis and bronchitis, including wheezing bronchitis. The collected diagnoses for bronchiolitis/bronchitis were all ICD-9 codes 466 and ICD-10 codes J20-J21. The ICD-10 code J21.9 for acute wheezing bronchitis was available between 1996 and 2008. The diagnoses were collected directly from the register and definitions presented below did not directly influence the case definition and selection. According to the Finnish guidelines, bronchiolitis is defined as the first virus-induced wheezing episode in infants under the age of 12 months. Acute childhood bronchitis is defined as an acute cough associated with viral respiratory infections lasting less than three weeks. Wheezing (obstructive) 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. The diagnosis of bronchiolitis and wheezing bronchitis is clinical and based on typical symptoms and signs (Current Care Guidelines 2015).

4.3.4 Pneumonia (II, IV)

With regard to outcome measures, the study subjects were considered to have had pneumonia if ICD-9 codes 480-486 and ICD-10 codes J12-18 for pneumonia (including all viral, bacterial or unspecified pneumonia codes) had been recorded. The general definition of pneumonia includes viral or bacterial infection of the pulmonary alveoli or interstitial tissue, and pneumonia can be diagnosed by chest radiography and/or on the basis of clinical findings, such as the presence of fever and acute respiratory symptoms (Current Care Guidelines 2015).

4.4 Predictive variables

Maternal background characteristics, pregnancy- and delivery-related factors; and infants' characteristics, procedures and treatments provided during the neonatal period were considered risk factors for respiratory morbidity and atopic dermatitis.

Maternal smoking included smoking during pregnancy and diabetes included the mother's gestational diabetes and type 1 and 2 diabetes. Cesarean sections were classified as elective (decided upon and undertaken before labor) or emergency (undertaken according to maternal or fetal indications during labor) procedures.

SGA infants were defined as those with a birth weight more than 2.0 SD below the average for GA and LGA infants as those with a birth weight above than 2.0 SD over the mean weight for GA (Pihkala et al. 1989). Resuscitation at birth included intubation and/or chest compressions in the delivery unit. Ventilator therapy included invasive ventilation (i.e. all endotracheal mechanically assisted ventilation). Antibiotic therapy included administration of antibiotics during the first week of life. Finland was divided into five geographical areas according to level III hospital catchment regions (IV).

4.5 Data linkages

Statistics Finland performed data linkages between registers by using unique personal identity codes anonymized by the register-holding authorities. The study group received unidentifiable data using a very secure system called the Micro Data Remote Access System, which is run by the Finnish Information Centre for Register Research and the IT Center for Science Ltd (a non-profit, state-owned company administered by the Ministry of Education and Culture).

4.6 Statistical analysis

The background characteristics of infants and their mothers were described by means and SDs in the case of normal distributed continuous variables and by medians with an interquartile range (IQR) in skew distributed variables and were expressed as numbers and percentages if the variables were categorical. The background characteristics of the study population and differences between the GA groups were analyzed using Pearson's chi-square test and Fisher's exact test (categorical variables), and continuous variables were analyzed using the Mann-Whitney U test, the one-way analysis of variance (ANOVA), Welch's t-test or the Kruskal-Wallis test. Non-normal distributions were first normalized by base e-logarithm. P-values <0.001 were considered statistically significant in group comparisons (I–IV).

Risk factors for asthma medication reimbursement and hospital visits due to atopic dermatitis were sought with Cox regression analysis using a multivariable model for each GA group. All variables were entered simultaneously into the model for each GA group (I). The association between GA groups and asthma medication

reimbursement or hospital visits due to atopic dermatitis was studied by including GA groups in the multivariable model using the term group as a reference. Results were expressed as hazard ratios (HR) and 95 % confidence intervals (95 % CI). Cox regression models were performed on IBM SPSS Statistics version 23.0 (SPSS, Chicago, Illinois).

A Generalized linear mixed model was used to search for risk factors for respiratory morbidity (asthma and LRTIs) and atopic dermatitis (II-IV). To take into account the number of deliveries by one mother, the Generalized linear mixed model with an *lmer* function was used. All explanatory variables were modeled as fixed variables and the number of deliveries per mother was added as a random effect. The analyses were performed in the whole study population and also in the post-term subgroup (III, IV). Results were presented as ORs with 95% CIs. All p-values were two-tailed and values <0.001 (I, II, IV) or <0.05 (III, IV) were considered statistically significant in the multivariable models. The Generalized Linear Mixed Model analyses were performed with the Statistical Package R version 3.3.0 package lme4 (www.r-projcet.org).

Population attributable risks (PARs, %) for the variables included in the multivariable models were calculated to assess the risk factors for asthma medication reimbursement and hospital visits due to atopic dermatitis (III). PAR was calculated by equation: PAR (f [OR − 1]) / (1 + f [OR − 1]), where f is the frequency of the risk factor in the population and OR is the OR for disease due to that exposure (III) (Rockhill et al. 1998).

4.7 Ethical aspects

This study was based on register data and patients were not contacted. Study subjects were pseudo-anonymized by codes in the register-holding institutions. Permissions to use registries were obtained from THL (Dnro THL/1637/5.05.00/2009), KELA (Kela 75/522/2009), and Statistics Finland (TK-53-1541-09). An approval statement was obtained from the national data protection ombudsman. The regional Ethics Committee of Tampere University Hospital approved the study (ETL R09218).

5 RESULTS

5.1 Characteristics of the infants and their mothers (I-IV)

Peri- and neonatal characteristics are presented separately for the whole study population in Table 2 (I, II) and for the term subgroups in Table 3 (III, IV). Of all live-births, the preterm birth rate was 5.1%. MP and LP births accounted for 88.1% of all preterm births (Figure 3). Early-term births accounted for 18.8% and post-term births for 4.9% of all term births (Figure 4). Maternal smoking during pregnancy was more common in the preterm groups and in the post-term group. During the study period the cesarean section rate was 16.1% and 38.8% of preterm infants were delivered by cesarean section. Among the term subgroups, the frequency of elective cesarean section was highest in the early-term group and emergency cesarean section was most common in the post-term group.

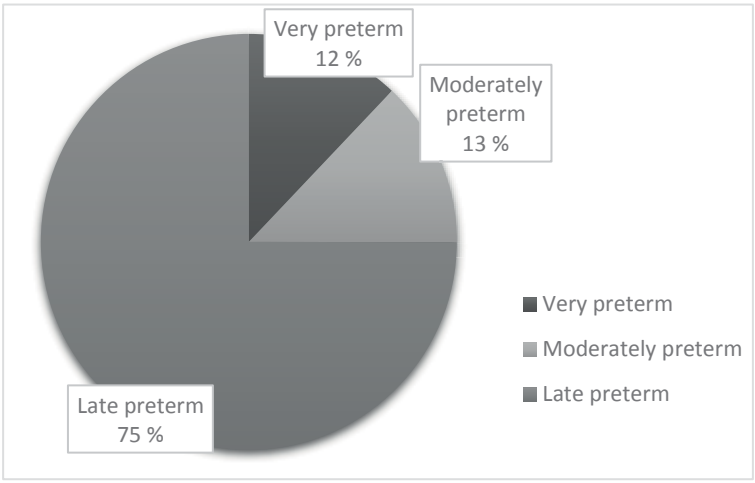

Figure 5. Proportions of preterm births between 1991 and 2008 in Finland (n=53,053).

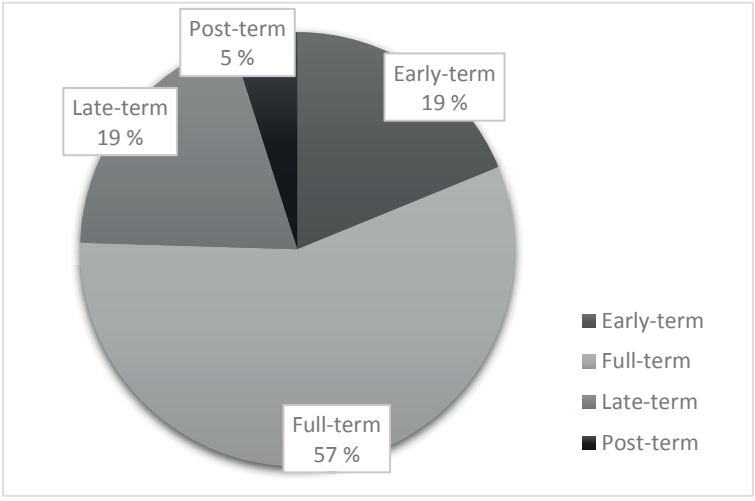

Figure 6. Proportions of term births between 1991 and 2008 in Finland (n=965,203).

Table 2. Characteristics of infants and their mothers among the whole study population; years 1991–2008 (N =1,018,302).

	Very preterm <32 wk (n=6,329)		Moderately preterm 32+0-33+6 wk (n=6,796)		Late preterm 34+0-36+6 wk (n=39,928)		Term ≥37 wk (n=965,203)	
Mother								
Age, Mean (SD)	30.2	(5.8)	29.8	(5.7)	29.7	(5.5)	29.2	(5.3)
Smoking, n (%)	1,187	(18.8)	1,184	(17.4)	6,602	(16.5)	144,094	(14.9)
First delivery, n (%)	3,314	(52.4)	3,792	(55.8)	20,040	(50.2)	392,574	(40.7)
Number of fetuses at birth, n (%)								
1	4,517	(71.4)	4,591	(67.6)	31,062	(77.8)	948,695	(98.3)
2	1,614	(25.5)	1,954	(28.8)	8,548	(21.4)	16,489	(1.7)
3-4	198	(3.1)	251	(3.7)	318	(0.8)	19	(<0.1)
Place of birth, n (%)								
University hospital (level III)	4,943	(78.1)	3,993	(58.8)	17,154	(43.0)	299,470	(31.0)
Central hospital (level II)	1,340	(21.2)	2,726	(40.1)	17,551	(44.0)	444,952	(46.1)
Other[a]	41	(0.6)	77	(1.1)	5,220	(13.1)	220,654	(22.9)
Mode of delivery, n (%)								
Vaginal	2,524	(39.9)	3,211	(47.2)	26,685	(66.8)	820,942	(85.1)
Cesarean section	3,793	(59.9)	3,582	(52.7)	13,210	(33.1)	143,491	(14.9)
Newborn								
Boys, n (%)	3,428	(54.2)	3,728	(54.9)	21,658	(54.2)	490,211	(50.8)
Birth weight, g, Md (IQR)	1290	(1000-1570)	1970	(1730-2200)	2670	(2360-2985)	3590	(3276-3910)
Gestational weight, n (%)								
SGA	1,019	(16.1)	883	(13.0)	3,245	(8.1)	16,662	(1.7)
AGA	4,972	(78.6)	5,637	(82.9)	34,681	(86.9)	919,970	(95.3)
LGA	284	(4.5)	276	(4.1)	2,002	(5.0)	28,571	(3.0)
Apgar 1 min 0-3, n (%)	1,001	(15.8)	325	(4.8)	890	(2.2)	7,491	(0.8)
Admission to neonatal unit, n (%)	5,692	(89.9)	5,972	(87.9)	19,155	(48.0)	58,365	(6.0)
Ventilator therapy, n (%)	3,656	(57.8)	1,413	(20.8)	1,667	(4.2)	2,793	(0.3)
Phototherapy, n (%)	4,202	(66.4)	3,821	(56.2)	14,153	(35.4)	36,671	(3.8)
Antibiotic therapy, n (%)	4,505	(71.2)	2,958	(43.5)	5,038	(12.6)	23,849	(2.5)
Death by 7 years of age	31	(0.5)	7	(0.1)	40	(0.1)	648	(0.1)

Statistical differences were assessed by Pearson chi-square test or Fisher's exact or by Mann-Whitney test; *Regional hospital, private hospital, health center, home birth.
AGA, appropriate for gestational age; IQR, interquartile range; LGA, large for gestational age; Md, median; SD, standard deviation; SGA, small for gestational age.

Table 3. Characteristics of infants and their mothers among term subgroups; years 1991-2008 (N=965,203).

	Early-term 37+0–38+6 wk (n=181,667)		Full-term 39+0–40+6 wk (n=546,845)		Late-term 41+0–41+6 wk (n=189,373)		Post-term ≥ 42 wk (n=47,318)	
Mother								
20 years or less, n (%)	7,987	(4.4)	25,772	(4.7)	9,894	(5.2)	2,613	(5.5)
21-25 years, n (%)	33,861	(18.6)	111,065	(20.3)	40,451	(21.4)	10,330	(21.8)
26-30 years, n (%)	61,757	(34.0)	195,178	(35.7)	67,818	(35.8)	16,677	(35.2)
31-35 years, n (%)	50,759	(27.9)	146,777	(26.8)	49,834	(26.3)	12,296	(26.0)
36 years or more, n (%)	27,303	(15.0)	68,053	(12.4)	21,376	(11.3)	5,402	(11.4)
Smoking, n (%)	28,215	(15.5)	79,713	(14.6)	28,414	(15.0)	7,752	(16.4)
First delivery, n (%)	71,578	(39.4)	214,262	(39.2)	81,677	(43.1)	25,057	(53.0)
Number of fetuses at birth, n (%)								
1	168,239	(92.6)	543,815	(99.4)	189,325	(100)	47,316	(100)
2 or more	13,428	(7.4)	3,030	(0.6)	48	(0.0)	2	(0.0)
Place of birth, n (%)								
University hospital (level-III)	59,972	(33.0)	167,964	(30.7)	55,942	(29.5)	15,592	(33.0)
Central hospital (level-II)	81,413	(44.8)	252,010	(46.1)	89,406	(47.2)	22,123	(46.8)
Other[a]	40,260	(22.2)	126,798	(23.2)	44,003	(23.2)	9,593	(20.3)
Region of birth, n (% of infants in region)								
Southern	59,775	(32.9)	186,039	(34.0)	67,602	(35.7)	18,932	(40.0)
Eastern	26,898	(14.8)	83,073	(15.2)	27,940	(14.8)	6,393	(13.5)
Western	35,099	(19.3)	107,307	(19.6)	36,701	(19.4)	8,723	(18.4)
Southwest	31,973	(17.6)	83,974	(15.4)	28,275	(14.9)	5,484	(11.6)
Northern	27,741	(15.3)	85,907	(15.7)	28,687	(15.1)	7,768	(16.4)
Mode of delivery, n (%)								
Vaginal	139,104	(76.6)	473,812	(86.6)	169,151	(89.3)	38,875	(82.2)
Elective cesarean section	26,168	(14.4)	39,932	(7.3)	3,178	(1.7)	1,092	(2.3)
Emergency cesarean section	16,259	(8.9)	32,642	(6.0)	16,904	(8.9)	7,316	(15.5)
Newborn								
Boys, n (%)	96,029	(52.9)	275,714	(50,4)	94,257	(49.8)	24,211	(51.2)
Birth weight, g, Md (IQR)	3,275	(2970-3590)	3,600	(3310-3900)	3,775	(3490-4080)	3,850	(3560-4150)
Gestational weight, n (%)								
SGA	6346	(3.5)	8,056	(1.5)	1,958	(1.0)	302	(0.6)
AGA	167,611	(92.3)	523,946	(95.8)	182,891	(96.6)	45,522	(96.2)
LGA	7,710	(4.2)	14,843	(2.7)	4,524	(2.4)	1,494	(3.2)
Apgar 1 min, Md (IQR)	9	(9-9)	9	(9-9)	9	(8-9)	9	(8-9)
0-3	1,573	(0.9)	3,609	(0.7)	1,691	(0.9)	618	(1.3)
Resuscitation at birth, n (%)	655	(0.4)	1,385	(0.3)	716	(0.4)	318	(0.7)
Admission to neonatal unit, n (%)	18,386	(10.1)	26,681	(4.9)	10,067	(5.3)	3,231	(6.8)
Ventilator therapy, n (%)	827	(0.5)	1,163	(0.2)	575	(0.3)	228	(0.5)
Antibiotic therapy, n (%)	4,810	(2.6)	11,464	(2.1)	5,626	(3.0)	1,949	(4.1)

Statistical differences were assessed by Pearson's chi-square test or the Kruskal-Wallis test.; *Regional hospital, private hospital, health center, home birth. Abbreviations as in Table 2.

5.2 Asthma and atopic dermatitis (I, III)

5.2.1 Cumulative incidence of asthma and atopic dermatitis

Of all 1,018,302 children, whose data were recorded up to the age of seven years, 39,991 (3.9 %) received reimbursement for asthma medication. In all, 51,532 (5.1%) needed hospital care due to asthma and 52,191 (5.1%) due to atopic dermatitis. Children in 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 very preterm children (15.4%). Hospital visits due to asthma were more common among MP (10.6%) and LP (7.3%) children than term children (4.8%) but less common than in very preterm children (20.1%). Hospital visits due to atopic dermatitis was more frequent among term children (5.2%) compared with MP (4.2%), LP (4.7%), and very preterm (3.9%) children. The decreasing trend was seen in the cumulative incidence of hospital visits due to asthma with increasing GA while hospital visits due to atopic dermatitis became more common with increasing GA (Figure 5).

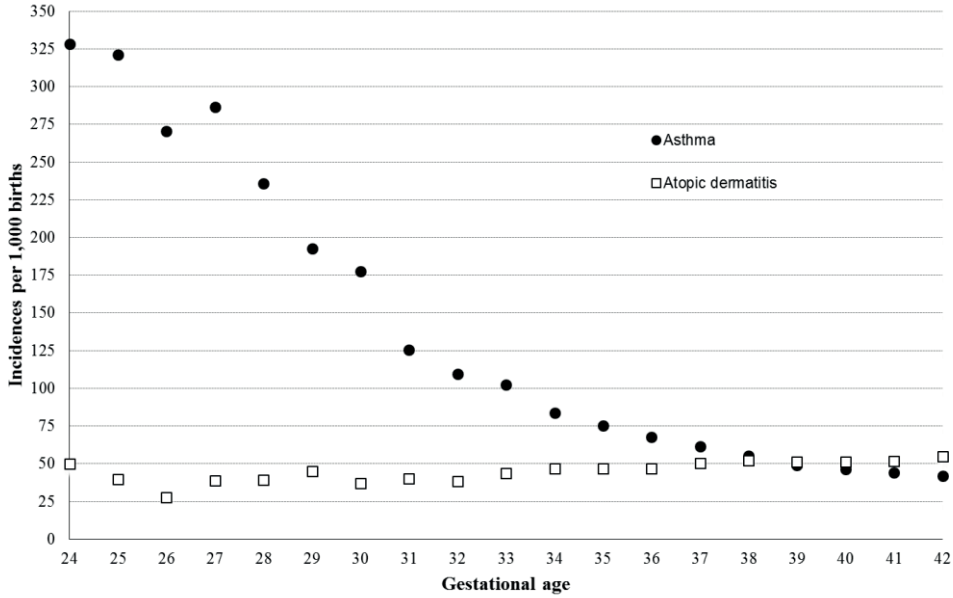

Figure 7. Cumulative incidences of hospital visits due to asthma and atopic dermatitis per 1,000 births by seven years of age in relation to gestational age week at birth, birth years 1991-2008 (N=1,018,302).

Among term-born children (n= 965,203), the frequencies of asthma medication reimbursement and hospital visits due to asthma were highest in the early-term group, and hospital visits due to atopic dermatitis were most common in the post-term group (Table 4).

Table 4. Reimbursement for asthma medication and hospital visits due to asthma and atopic dermatitis in infants born at ≥37 weeks of gestation in 1991–2008 and followed-up to seven years of age (N=965,203).

	Early term 37^{+0}-38^{+6} wk (n=181,667)		Full term 39^{+0}-40^{+6} wk (n=546,845)		Late term 41^{+0}-41^{+6} wk (n=189,373)		Post term ≥42 wk (n=47,318)	
Reimbursement for asthma medication, n (%)	**8,166**	**(4.5)**	**20,180**	**(3.7)**	**6,330**	**(3.3)**	**1,534**	**(3.2)**
Age at 1st reimbursement, Md (IQR) in years	2.7	(1.6-4.3)	2.9	(1.8-4.5)	3.0	(1.8-4.6)	3.0	(1.8-4.5)
Hospital visits due to asthma, n (%)	10,351	(5.7)	25,937	(4.7)	8,372	(4.4)	1,976	(4.2)
Hospital visits due to atopic dermatitis, n (%)	**9,359**	**(5.2)**	**28,032**	**(5.1)**	**9,836**	**(5.2)**	**2,568**	**(5.4)**
Age at 1st visit, Md (IQR)	1.1	(0.6-2.4)	1.1	(0.6-2.4)	1.1	(0.6-2.4)	1.0	(0.6-2.3)

Statistical differences were tested by Pearson's chi-square test, Fishers exact test, or the Kruskall-Wallis test.
IQR, interquartile range; Md, median

5.2.2 Predictors for asthma and atopic dermatitis

5.2.2.1 Association of gestational age at birth

In the fully adjusted models, compared with the term-born children, preterm birth was associated with an increased hazard of asthma medication reimbursement and HRs were for very preterm group 3.18 (95 % CI 2.91–3.46), MP group 1.77 (95 % CI 1.61–1.94), and LP group 1.40 (95 % CI 1.33–1.47). However, preterm birth was associated with a decreased hazard of hospital visits due to atopic dermatitis compared with the term group, as follows: very preterm group HR 0.64 (95 % CI 0.56–0.74), MP group HR 0.67 (95 % CI 0.59–0.76), and LP group HR 0.84 (95 % CI 0.79–0.88).

Among term subgroups of children early-term birth was associated with an increased odds of asthma OR 1.20 (95% CI 1.17-1.23), while late-term birth OR 0.91 (95% CI 0.89-0.93) and post-term birth OR 0.87 (95% CI 0.83-0.92) associated with decreased odds of asthma. Post-term birth predicted atopic dermatitis with an OR 1.06 (95% CI 1.01-1.10).

5.2.2.2 Gestational age group-specific risk factors

Ventilator therapy was associated with asthma medication reimbursement among all preterm groups: very preterm (HR 1.43, 95% CI 1.22-1.46), MP (HR 1.26, 95% CI 1.01-1.57) and LP (HR 1.42, 95% CI 1.18-1.71). Maternal smoking during pregnancy was associated with asthma medication among MP (HR 1.32, 95% CI 1.08-1.63), LP (HR 1.21, 95% CI 1.09-1.35), and term groups (HR 1.14, 95% CI 1.11-1.18), but such an association was not seen in the very preterm group. Maternal diabetes seemed to predict asthma medication in the MP group (HR 1.62, 95% CI 1.02–2.58). Antenatal steroid was associated with asthma medication in LP (HR 1.46, 95% CI 1.46-2.09) and term groups (HR 1.72, 95% CI 1.27-2.33) but such an association was not seen in the very preterm group (HR 0.69, 95% CI 0.49-0.95).

The risk factor analyses for hospital visits due to atopic dermatitis showed weaker association with peri- and neonatal factors. Male sex was associated with hospital visits due to atopic dermatitis among MP (HR 1.35, 95% CI 1.06–1.72), LP (HR 1.29, 95% CI 1.17–1.41) and term children (HR 1.25, 95% CI 1.23–1.28). Maternal diabetes was associated with atopic dermatitis in very preterm (HR 2.25, 95% CI 1.09-4.63) and term groups (HR 1.42, 95% CI 1.31-1.54). Early antibiotic therapy seemed to predict atopic dermatitis in very preterm (HR 1.61, 95% CI 1.13-2.30) and term groups (HR 1.19, 95% CI 1.12-1.26). Being first-born or a twin in the LP and term groups was negatively associated with atopic dermatitis.

5.2.2.3 Common risk factors in all gestational age groups and among term-born children

Male sex was associated with receiving asthma medication reimbursement among all GA groups: very preterm (HR 1.60, 95% CI 1.41–1.83), MP (HR 1.74, 95% CI 1.46–2.09), LP (HR 1.65, 95% CI 1.51–1.80) and term (HR 1.73, 95% CI 1.70–1.77). Birth by cesarean section was associated with asthma medication only in the term group (HR 1.17, 95% CI 1.14-1.21). Being first-born or being born in a level II hospital was negatively associated with asthma medication in all GA groups.

Among term-born children the most relevant risk factors for asthma medication reimbursement from a population point of view were male sex, hospital visits due to atopic dermatitis (as a surrogate for atopic tendency), maternal smoking during pregnancy, and birth by elective cesarean section. Maternal age of 40 years or more, being first-born or being born in a level II hospital were associated with a decreased risk of asthma. According to PAR analyses, male sex, being first-born, birth in a level

II hospital and birth by emergency cesarean section were the most relevant risk factors for atopic dermatitis, whereas smoking during pregnancy and place of birth other than a level III or level II hospital were associated with a reduced risk.

In the subgroup analysis among post-term children, no association was found between birth by cesarean section and asthma medication reimbursement. Ventilator therapy OR 1.78 (95% CI 1.00-3.18) was associated with an increased risk of asthma medication reimbursement. Birth by emergency cesarean section OR 1.19 (95% CI 1.07-1.33) emerged as a risk factor for hospital visits due to atopic dermatitis, whereas birth by elective cesarean section did not.

5.3 Lower respiratory tract infections (II, IV)

5.3.1 Cumulative incidence of bronchiolitis/bronchitis and pneumonia

In all, 60,588 (6.0%) children had been admitted to hospital for bronchiolitis/bronchitis and 25 575 (2.5%) for pneumonia by seven years of age. Of all, 4,738 (7.8%) bronchiolitis/bronchitis admissions and 1,639 (6.4%) pneumonia admissions occurred among MP and LP children. Hospital admissions for LRTIs were more common in the MP and LP groups than in the term group but less common than in the very preterm group (Table 5, Figure 8). The length of hospital stay due to bronchiolitis/bronchitis was longer in the MP and LP groups than in the term group (Table 5). The frequency of both viral and bacterial LRTI decreased with increased gestational age (Table 6).

Table 5. Hospital admissions for LRTIs up to the age of seven years among very preterm, MP, LP and term groups, years 1991-2008 (n=1,018,256).

	Very preterm <32 wk (n=6,329)		Moderately preterm 32^{+0}-33^{+6} wk (n=6,796)		Late preterm 34^{+0}-36^{+6} wk (n=39,928)		Term ≥37 wk (n=965,203)	
Acute bronchiolitis/bronchitis, n (%)	**1,542**	**(24.4)**	**942**	**(13.9)**	**3,796**	**(9.5)**	**54,308**	**(5.6)**
Age at diagnosis								
0-11 months, n (%)	920	(59.7)	600	(63.7)	2,184	(57.5)	27,787	(51.2)
12-35 months, n (%)	513	(33.3)	279	(29.6)	1,295	(34.1)	20,589	(37.9)
36-84 months, n (%)	109	(7.1)	63	(6.7)	317	(8.4)	5,932	(10.9)
Number of visits, Md (IQR)	2	(1-3)	2	(1-3)	2	(1-3)	2	(1-2)
Days in hospital, Md (IQR)	6	(3-14)	6	(3-11)	5	(2-10)	4	(2-7)
Pneumonia, n (%)	**560**	**(8.8)**	**307**	**(4.5)**	**1,332**	**(3.3)**	**23,376**	**(2.4)**
Age at diagnosis								
0-11 months, n (%)	121	(21.6)	67	(21.8)	225	(16.9)	3,562	(15.2)
12-35 months, n (%)	270	(48.2)	150	(48.9)	656	(49.2)	11,799	(50.5)
36-84 months, n (%)	169	(30.2)	90	(29.3)	451	(33.9)	8,015	(34.3)
Number of visits, Md (IQR)	1	(1-2)	1	(1-2)	1	(1-2)	1	(1-2)
Days in hospital, Md (IQR)	5	(3-10)	4	(1-6)	4	(2-7)	4	(2-5)

Statistical differences were tested by Pearson's chi-square test or by Welch test.
IQR, interquartile range; Md, median

Table 6. The distribution of LRTI diagnoses with viral or bacterial etiology between years 1996-2008 (N = 709,534).

	Very preterm <32 wk (n=4,549)		Moderately preterm 32^{+0}-33^{+6} wk (n=4,859)		Late preterm 34^{+0}-36^{+6} wk (n=28,151)		Term ≥37 wk (n=671,975)		Total (n=709,534)	
	n	%	n	%	n	%	n	%	n	%
RSV pneumonia (J12.1)	13	(0.3)	3	(0.1)	21	(0.1)	250	(0.04)	287	(0.04)
Other viral pneumonia (J12)	37	(0.8)	18	(0.4)	77	(0.3)	874	(0.1)	1,006	(0.1)
Bacterial pneumonia (J13-18)	441	(9.7)	257	(5.3)	1,104	(3.9)	20,140	(3.0)	21,942	(3.1)
RSV bronchiolitis (J21.0)	378	(8.3)	230	(4.7)	850	(3.0)	10,353	(1.5)	11,811	(1.7)
Viral or bacterial wheezing bronchitis (J21.9)	712	(15.7)	454	(9.3)	1,822	(6.5)	25,579	(3.8)	28,567	(4.0)

Statistical differences were tested by Pearson's chi-square test.

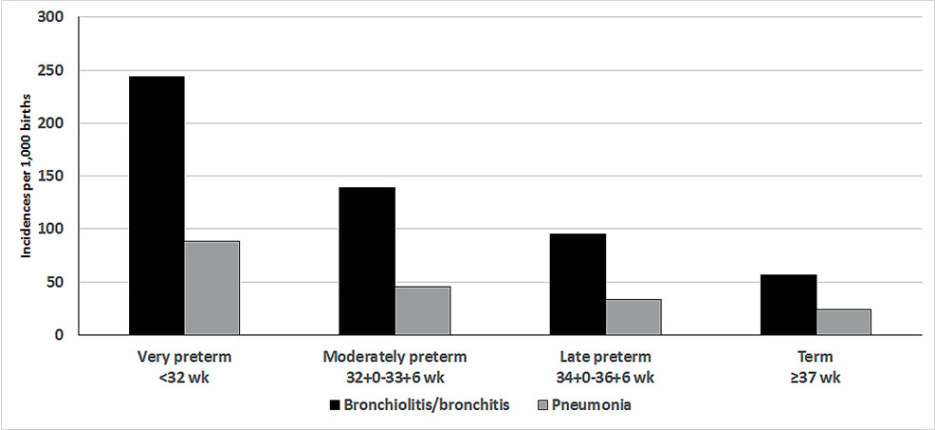

Figure 8. Cumulative incidences of hospital admissions for LRTIs per 1000 births by seven years of age in relation to GA group at birth, birth years 1991-2008 (N = 1,018,256).

Among infants born at ≥37 weeks of gestation, the rates of hospital admission for LRTIs were highest in the early-term group (Table 7). Post-term children were admitted at an older age. The majority of all admissions because of LRTIs in all GA groups took place before the age of 36 months, representing approximately 90% of bronchiolitis/bronchitis and 65% of pneumonia admissions.

Table 7. Hospital admissions for LRTIs up to the age of seven years among early-, full-, late- and post-term children, years 1991–2008 (N=965,203).

	Early-term 37+0–38+6 wk (n=181,667)		Full-term 39+0–40+6 wk (n=546,845)		Late-term 41+0–41+6 wk (n=189,373)		Post-term ≥ 42 wk (n=47,318)	
Acute bronchiolitis/bronchitis, n (%)	**12,359**	**(6.8)**	**30,086**	**(5.5)**	**9,605**	**(5.1)**	**2,258**	**(4.8)**
Age at diagnosis, Md (IQR), in months	10	(4-21)	11	(4-21)	12	(4-23)	12	(4-24)
0-11 months, n (%)	6,747	(54.6)	15,197	(50.5)	4,728	(49.2)	1,115	(49.4)
12-35 months, n (%)	4,434	(35.9)	11,538	(38.4)	3,769	(39.2)	848	(37.6)
36-84 months, n (%)	1,178	(9.5)	3,351	(11.1)	1,108	(11.5)	295	(13.1)
Pneumonia, n (%)	**5,012**	**(2.8)**	**12,926**	**(2.4)**	**4,372**	**(2.3)**	**1,066**	**(2.3)**
Age at diagnosis, Md (IQR), in months	25	(15-43)	25	(15-43)	26	(15-44)	27	(16-45)
0-11 months, n (%)	828	(16.5)	1,965	(15.2)	621	(14.2)	148	(13.9)
12-35 months, n (%)	2,452	(48.9)	6,599	(51.1)	2,231	(51.0)	517	(48.5)
36-84 months, n (%)	1,732	(34.6)	4,362	(33.7)	1,520	(34.8)	401	(37.6)

Statistical differences were tested by Pearson's chi-square test or the Kruskal-Wallis test.
IQR, interquartile range; Md, median

5.3.2 Predictors for bronchiolitis/bronchitis and pneumonia

5.3.2.1 Association of gestational age at birth

In the fully adjusted models, compared with the term group, very preterm, MP and LP birth were associated with bronchiolitis/bronchitis (very preterm OR 3.33; 95% CI 3.09-3.59, MP 1.89; 1.75-2.03, LP 1.51; 1.45-1.56) and pneumonia (very preterm OR 2.59; 95% CI 2.32–2.89, MP 1.49; 1.32-1.67, LP 1.25; 1.18-1.33) admissions.

Among infants born at ≥37 weeks of gestation, early-term birth was associated with an increased risk of admission for bronchiolitis/bronchitis (OR 1.23, 95% CI 1.20, 1.25) and pneumonia (OR 1.16, 95% CI 1.12, 1.20), while late-term (OR 0.93, 95% CI 0.91, 0.95) and post-term births (OR 0.89, 95% CI 0.85, 0.93) were associated with a decreased risk of bronchiolitis/bronchitis admission.

5.3.2.2 Common risk factors in all gestational age groups and among term-born children

In risk factor analyses regarding the whole study population, in the fully adjusted models, maternal smoking during pregnancy (adjusted OR 1.47; 95% CI 1.44–1.50),

being first-born (1.74; 1.14–1.21), birth by cesarean section (1.15; 1.13–1.18), male sex (1.61; 1.58–1.64), being born SGA (1.09; 1.03-1.15), admission to a neonatal unit (1.24; 1.20-1.29), ventilator therapy (1.27; 1.18-1.36) and neonatal antibiotic therapy (1.15; 1.09-1.20) were associated with an increased risk of hospital admissions for bronchiolitis/bronchitis. Weaker associations were found between hospital admissions for pneumonia and perinatal and neonatal factors. Maternal smoking (1.10; 1.07–1.14), birth by cesarean section (1.08; 1.04–1.12), male sex (1.13; 1.10-1.16), admission to a neonatal unit (1.21; 1.15-1.27) and ventilator therapy (1.32; 1.19-1.46) were associated with pneumonia.

When analyzing infants born at ≥37 weeks of gestation, young maternal age (<20 years), maternal smoking, male sex, cesarean section, ventilator therapy and neonatal antibiotic therapy were associated with an increased risk of admission for all LRTIs. Being first-born, SGA and having a low 1-min Apgar score predicted admission for bronchiolitis/bronchitis. Being born in a level II hospital and in the Northern region reduced the risk of admission for all LRTIs. Higher maternal age (>31 years) and being a twin were associated with a decreased risk of admission for bronchiolitis/bronchitis.

In the post-term subgroup, maternal smoking, birth in other than the Northern region, ventilator therapy and neonatal antibiotic therapy were associated with an increased risk of all admissions for LRTIs. Young maternal age (<20 years), being first-born and male sex remained risk factors for admission for bronchiolitis/bronchitis. No significant association was found between birth by cesarean section and LRTIs.

5.4 Summary of the results (I-IV)

The results of the study are shown in Figure 9 as cumulative incidences of respiratory morbidity (asthma, bronchiolitis/bronchitis and pneumonia) and atopic dermatitis. There is a decreasing trend in the cumulative incidences of respiratory morbidity with increasing GA. Conversely, the cumulative incidence of atopic dermatitis shows slight increasing trend with increasing GA.

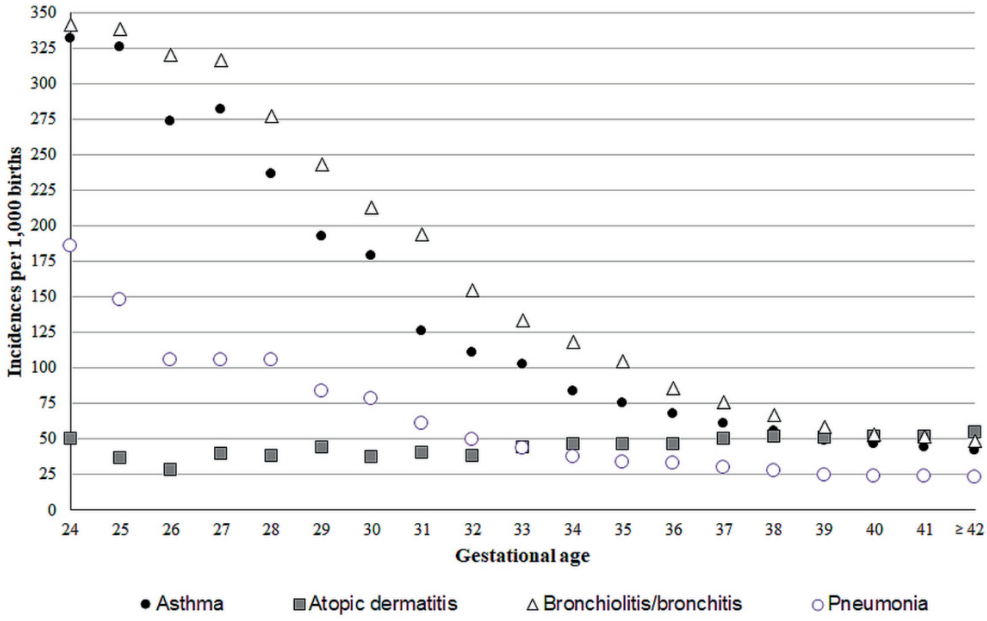

Figure 9. Cumulative incidences of respiratory morbidity and atopic dermatitis per 1000 births by seven years of age in relation to gestational age week at birth in 1991-2008.

The results of the associations of respiratory morbidity and atopic dermatitis according to different preterm GA groups compared with the term group (≥37 weeks) are summarized in Table 8 and according to term sub-groups compared with the full-term group (39^{+0}-40^{+6}) are summarized in Table 9.

Table 8. Summary of the results from separate multivariable models: The associations of respiratory morbidity and atopic dermatitis by seven years of age with birth in preterm GA group using term (≥37 weeks) group as reference (adjusted HR/OR, 95%CI), years 1991-2008 (N = 1 018 256).

	Very preterm <32 wk (n=6,329)		Moderately preterm 32+0-33+6 wk (n=6,796)		Late preterm 34+0-36+6 wk (n=39,928)		Term ≥37+0 wk (n=965,203)	
	n	OR/HR (95% CI)	n	OR/HR (95% CI)	n	OR/HR (95% CI)	n	OR/HR (95% CI)
Asthma[1]	979	**3.18** (2.92-3.47)	543	**1.77** (1.61-1.94)	2,259	**1.40** (1.34-1.46)	36,210	1.00
Atopic dermatitis[1]	249	**0.64** (0.56–0.74)	283	**0.67** (0.59–0.76)	1,864	**0.84** (0.79–0.88)	49,795	1.00
Bronchiolitis/ bronchitis[2]	1,542	**3.33** (3.09-3.59)	942	**1.89** (1.75-2.03)	3,796	**1.51** (1.45-1.56)	54,308	1.00
Pneumonia[2]	560	**2.59** (2.32–2.89)	307	**1.49** (1.32-1.67)	1,332	**1.25** (1.18-1.33)	23,376	1.00

[1] Cox regression multivariable model, results given as the HRs and 95% CIs (Study I)
[2] Multivariable generalized linear mixed model, results given as the ORs and 95% CIs (Study III-IV)

Table 9. Summary of the results from separate multivariable models: The associations of respiratory morbidity and atopic dermatitis by seven years of age with birth in term sub-groups using full-term (39+0-40+6) group as reference (adjusted OR, 95%CI), years 1991-2008 (N = 965,203).

	Early term 37+0-38+6 wk (n=181,667)		Late term 41+0-41+6 wk (n=189,373)		Post term ≥42 wk (n=47,318)		Full-term 39+0-40+6 wk (n=546,845)	
	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Asthma	8,166	**1.20** (1.17-1.23)	6,330	**0.91** (0.89-0.93)	1,534	**0.87** (0.83-0.92)	20,180	1.00
Atopic dermatitis	9,359	**0.99** (0.96-1.01)	9,836	**0.99** (0.99-1.04)	2,568	**1.06** (1.01-1.10)	28,032	1.00
Bronchiolitis/ bronchitis	12,359	**1.23** (1.20-1.25)	9,605	**0.93** (0.91-0.95)	2,258	**0.89** (0.85-0.93)	30,086	1.00
Pneumonia	5,012	**1.16** (1.12-1.20)	4,372	**0.98** (0.95-1.01)	1,066	**0.96** (0.90-1.02)	12,926	1.00

Multivariable generalized linear mixed model, results given as the ORs and 95% CIs (Study III-IV)

6 DISCUSSION

6.1 Asthma and atopic dermatitis (I, III)

In this large national register study, the overall frequency of asthma medication reimbursement and hospital visits due to asthma by seven years of age corresponded to the expected rate in Finland (Current Care Guidelines 2012). The significant finding was that MP and LP children received reimbursement for asthma medication and needed hospital care due to asthma more often than the term controls but less frequently than very preterm children by seven years of age. These findings are in accordance with previous reports on the association between MP and LP birth and asthma in childhood (Been et al. 2014; Harju et al. 2015; Trønnes et al. 2013). The present study also found a decreasing trend of GA in the frequency of asthma medication reimbursement and the need for hospital visits due to asthma by seven years of age in children born at ≥37 weeks of GA. After controlling for several perinatal and neonatal confounding factors, early-term birth was associated with an increased risk of asthma, whereas late- and post-term births appeared to reduce this risk. The finding of an increased risk of asthma in early-term children is in accordance with previous studies (Vogt et al 2011; Boyle et al. 2012; Edwards et al. 2015; Harju et al. 2014). Moreover, in a large Swedish cohort study, early-term children had an increased risk of inhaled corticosteroid use, evaluated by registered drug retrievals, compared with those born at 39-41 weeks of gestation (Vogt et al. 2011). A previous Finnish hospital-based register study found that the burden of asthma in children was particularly associated with deliveries at 37-38 weeks of gestation (Harju et al. 2014). In the Millenium Cohort Study in the UK, the incidence of asthma and wheeze was increased at three and five years of age in MP, LP and early-term compared with term children, as was the risk of needing asthma treatment with increasing prematurity (Boyle et al. 2012). It may be explained by that both spontaneous and iatrogenic preterm and early-term deliveries have common causes and that there are similar exposures to postnatal treatments such as those needed for neonatal respiratory problems (Sengupta et al. 2013). In the current study, post-term birth was associated with a decreased risk of early childhood asthma despite the increased frequency of neonatal respiratory problems defined as the need for

ventilator therapy in the post-term group. Similar findings among late-term (Harju et al. 2014) and post-term (Leung et al. 2016) children have previously been reported. This seems to represent part of a continuum of the first study, in which the decreased risk of asthma was associated with increasing GA from very preterm birth to term, possibly due to continuous intrauterine maturation of the airways.

Of all children followed up to the age of seven years, 5.1% needed hospital care due to atopic dermatitis, which represents those children with a more severe disease needing specialized care consultation or treatment. The true incidence of atopic dermatitis could not be analyzed in the present cohort due to the lack of data on cases of mild atopic dermatitis usually diagnosed and treated in the primary health care system at this age group. Risk factors for severe disease may be different than those for mild and moderate diseases. The important finding of the present study is that hospital visits due to atopic dermatitis became more frequent with increasing GA, and post-term birth emerged as a risk factor for hospital visits due to atopic dermatitis. In accord with these results, others have observed an increased risk of atopic dermatitis with increasing GA and the risk may be reduced in children born preterm (Barbarot et al. 2013; Zhu et al. 2018). Instead, a previous prospective follow-up study on 609 children (193 preterm and 416 term) found no difference in the prevalence of atopic dermatitis between preterm and term children in the first two years of life (Kvenshagen et al. 2009). Supporting the results of the present study, an increased risk of atopic dermatitis by school age in children born post-term was seen in a large Norwegian birth cohort study (Trønnes et al 2013).

The findings in the first study suggest that some peri- and neonatal risk factors for asthma are the same in all GA groups (e.g., maternal smoking during pregnancy, male sex) and some differ in term and preterm groups (e.g., ventilator therapy). This supports the concept of different asthma etiologies in preterm and term infants (Halvorsen et al. 2005). The first study found that asthma was more common in preterm children while atopic dermatitis was more frequent in term children suggesting that assisted ventilation could induce non-allergic asthma. In other words, asthma in preterm children might be associated with neonatal respiratory complications, reduced airway size, and decreased lung function (Havoresn et al 2005). Some of the risk factors were previously well described, such as male sex, maternal smoking and birth by cesarean section. Maternal diabetes seemed to be associated with asthma in the MP group and this finding may also be related to other underlying factors that complicate diabetic pregnancy (Rusconi et al. 2017). Accordingly, among term subgroups of children, from a population point of view, the most relevant risk factors for asthma were male sex, atopic tendency, maternal

smoking during pregnancy and elective cesarean section, and those of atopic dermatitis were male sex, being first-born, birth in a level II hospital, and birth by emergency cesarean section. Among term subgroups of children, hospital visits due to atopic dermatitis were used as a surrogate for severe atopic tendency in the risk-factor analyses for asthma. There are only a few previous studies evaluating the association of antibiotic therapy during the first week of life and the risk of asthma or atopic dermatitis (Goksör et al. 2013; Raymond et al. 2017; Stromberg et al. 2018). The present study found an association between antibiotic therapy and both asthma medication reimbursement and atopic dermatitis, suggesting long-lasting effects of neonatal antibiotic exposure. However, this risk factor was not very relevant from a population point of view among term subgroups, having low PAR% values. Birth in a level II hospital was associated with a decreased risk of the need for asthma medication in all GA groups, probably because high-risk infants, who need invasive treatments, are more commonly born in level III hospitals. In contrast, birth in other than a level III or level II hospital seemed to decrease the risk of atopic dermatitis.

6.2 Lower respiratory tract infections (II, IV)

In this large cohort, the associations between GA and LRTI hospitalization were detected both in incidences and adjusted ORs. The clinical pictures of LRTIs may overlap and it is especially challenging to differentiate between diagnoses of bronchiolitis and wheezing bronchitis. As in many previous studies, we analyzed bronchiolitis and wheezing bronchitis together. In the present study, 6% of all children were hospitalized because of bronchiolitis/bronchitis by the age of seven years, about half of them by 12 months of age. This is in accordance with previous reports, which shows that 2-3% of all children were hospitalized because of bronchiolitis during their first year of life (Green et al. 2016). In all, 2.5% of all children were admitted for pneumonia by seven years of age. The true incidence of pneumonia could not be analyzed in this cohort due to the lack of data on cases of pneumonia diagnosed and treated in primary health care settings. Current hospital admission rates due to pneumonia are in accordance with the reported annual incidence of community-acquired pneumonia ranging from 0.2-0.33% to 3.5-4% in children of less than five years of age. Approximately half of the children with pneumonia at this age group are treated in hospital (McIntosh 2002; Tapiainen et al. 2016).

The present study found that MP and LP children were more often admitted to hospital for LRTIs than term controls but less often than very preterm children up to the age of seven years. These results on the association between MP and LP birth and an increased incidence of hospital admissions for LRTIs are in line with previous findings (Miller et al. 2016, Parajonthy et al. 2013, Blanken et al. 2016, Vrijlandt et. al 2013). No data could be obtained on bronchiolitis confirmed by positive RSV tests, but the distribution of the ICD 10 diagnoses supports the previous findings on the increased risk of hospital admission for RSV in children born MP and LP (Helfrich et al. 2015). Susceptibility to LRTIs during infancy in children born MP and LP might be a consequence of preterm birth and immature development of the immune system and the lungs (Pike et al. 2015).

The major finding among term subgroups of children was that early-term birth emerged as a risk factor for hospital admission for all LRTIs up to seven years of age, while increasing GA, as well as late- and post-term birth, were associated with a decreased risk of admission for bronchiolitis/bronchitis. These results on the association between early-term birth and the risk of hospital admission for LRTIs support previous findings (Tickell et al. 2016; Walfisch et al. 2017; Miller et al. 2016). 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 admissions (Miller et al. 2016). Similarly, the present study also found lower rates of admission for all LRTIs in children born late- and post-term. This association could be partly explained by continuous intrauterine maturation of the airways. On the other hand, the last weeks of gestation represent a critical period of lung growth and development with both short- and long-term health consequences in early-term infants (Colin et al. 2010; Pike et al. 2015).

The perinatal and neonatal risk factors for hospital admissions for LRTIs among the whole study population included maternal smoking, cesarean delivery, male sex, admission to a neonatal unit and ventilator therapy. In addition, being first-born, being born SGA, and neonatal antibiotic therapy were associated with bronchiolitis/bronchitis. Generally, hospital admissions for pneumonia showed weaker associations with perinatal and neonatal factors. Among term subgroups of children, several maternal and perinatal factors remained risk factors for LRTIs after exclusion of preterm infants and those with congenital anomalies. The most relevant risk factors for admission for LRTIs were maternal smoking during pregnancy, cesarean section, male sex, neonatal ventilator therapy and early antibiotic therapy. Infants admitted to a neonatal unit are usually those suffering from early neonatal

respiratory morbidity or infections, and this could explain the association with an increased risk of LRTIs. Differences in early microbial exposure related to the mode of delivery may also have an impact on immunomodulation. Studying respiratory outcomes after early-term birth is confounded by higher rates of deliveries by cesarean section in this GA group (Kotecha et al. 2016). Current results suggest that both early-term birth and cesarean delivery are independent risk factors for admission for LRTIs. Interestingly, no association was found between cesarean delivery and LRTIs in the post-term subgroup. This could be explained by the higher rate of elective cesarean section in the early term group, and emergency cesarean section was most frequent in the post-term group. Infants born by elective cesarean delivery are exposed differently to maternal hormones and microbiota compared with those born by vaginal delivery, and these differences could predispose the infant to an adverse respiratory outcome (Indraccolo et al. 2019). The process of labor may promote the production of various cytokines and activate the immune system (Moore et al. 2012). 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. Interestingly and in contrast to the results of a previous study (Lodge et al. 2014), in the present study, first-born children had an increased risk of bronchiolitis/bronchitis, but this association was not seen for pneumonia. It is suggested that children with older siblings suffer from more respiratory infections than first-born children, but on the other hand, children with older siblings may experience an earlier immune maturation and a subsequent improved resistance against infections later in childhood (Vissing et al. 2018). This might also be related to the suggestion that first-born children may have a reduced anti-inflammatory profile in their T-cells at birth and thus an enhanced risk of later developing immune-related diseases (Kragh et al. 2016).

6.3 Strengths and limitations (I-IV)

The study population was substantial consisting of 98% of all infants born between 1998 and 2008 in Finland. The strengths of this study are the reliable national population-based well established and validated register data (Gissler et al. 1995; Gissler et al 1998; Gissler & Sheleley 2002; Sund & Lahti 2012). By using this large register data in the present study, it was possible to explore common childhood diseases and take into account many confounding peri- and neonatal factors, which

is challenging in clinical settings. In Finland, public healthcare is easily accessible to all and all children's hospitals are public. Therefore, in this age group all hospital admissions for asthma and atopic dermatitis, as well as LRTIs, can be derived reliably from the registers. In Finnish guidelines, an asthma diagnosis made by a pediatrician, is required to qualify for medication reimbursement. The KELA database is held as a valid source of prevalence data and affords researchers the ability to accurately identify asthma cases in the general population (Nwaru et al. 2011). Due to difficulties in ascertaining the diagnosis of asthma in infants, asthma medication reimbursement was used, a parameter based on national criteria, as the main outcome measure in the risk factor analyses. 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 settings.

The current study has some limitations. The recording practices for administrative health register data may vary among staff and regions and over time periods. During the earlier years of the catchment period the diagnosis and treatment of asthma in young children aged less than five years differed from the current practice. Regional variations between hospital districts in the diagnosis and treatment of childhood asthma also existed based on a previous research in Finland (Virta & Mäki 2003). The national asthma program in 1994 emphasized earlier diagnosis and active treatment with inhaled corticosteroids also in young children. Since 1995 asthma medication reimbursement was granted for children aged less than five years when the need of regular maintenance medication was considered to continue at least for six months. After releasing more precise diagnostic criteria for pediatric asthma, the number of children receiving reimbursements for asthma medication was reduced in the early 2000s and turned downwards during the recent decade (Haahtela et al. 2013). In spite of differences in the treatment practices over the time periods, the GA groups were comparable throughout the study period in the present study setting.

In this study the infants, who died before one year of age were excluded. It is possible that this changes the composition of the surviving preterm population in terms of the risk of asthma and atopic dermatitis. This can be regarded as a weakness. However, most of the mortality in very preterm infants usually occurs already during the neonatal period. The current study did not take into account children, who emigrated during the study period. According to Statistics Finland the proportion of children aged 0-14 years who emigrated from Finland during the years 1987-2014 was low, approximately 0.1-0.2% (Kivijärvi & Peltola 2016).

Some unknown confounding factors may exist in the large register data. Because of the study design, children born in the most recent years of the study period had shorter follow-up times than those born in earlier years. However, the median age at first reimbursement for asthma medication was 2.0-2.9 years, and approximately 90% of admissions for bronchiolitis/bronchitis and 65% of those for pneumonia occurred before the age of three and most infants were followed up for longer than that. No data were obtained on parental asthma, indications for cesarean delivery, psychosocial factors, duration of breastfeeding, postnatal smoke exposure, or other environmental conditions. Reliable data on maternal socioeconomic status were also unavailable. However, the information on maternal smoking can be regarded as a surrogate marker of SES, because smoking during pregnancy correlates strongly with lower maternal SES in Finland (Rumrich et al. 2018). Generally, it is a time-consuming process of acquiring permissions and data collection with linkages preceding access to national health data, and this creates a gap between follow-up time and published data.

6.4 Implications for clinical practice

Much is still unknown about the risk factors for childhood asthma, atopic dermatitis and LRTIs, but the current results suggest that early-life exposures seem to play an important role. Methods of affecting significant underlying risk factors should be considered. Avoidance of smoking during pregnancy and following strict indications for cesarean delivery may improve the respiratory outcome of the offspring. Minimizing the duration and invasiveness of ventilator therapy might be beneficial for all infants with respect to later risk of asthma or LRTIs. Indications to use antibiotics during the neonatal period should be considered.

Recently updated Finnish guidelines recommend administration of antenatal corticosteroids to women at risk for delivery at 35^{+0}-36^{+6} weeks to reduce the rate of neonatal respiratory complications and in cases of elective cesarean delivery (Current care guidelines 2018). All infants, especially MP and LP born infants, should be properly monitored after birth for the possible complications without interfering normal adaptation. Family centered care, encouraging mothers for breastfeeding and parents for providing early skin-to-skin contact is important also for preterm infants.

6.5 Challenges for future research

As the results the of this study revealed, children born MP, LP and early-term are at risk of long-term respiratory morbidity in childhood, and many peri- and neonatal factors are associated with this risk. In the field of perinatal care, it is still important to develop methods for identifying fetal risks and the timing of delivery according to the competing risks of continuing pregnancy and possible consequences of preterm or early-term delivery. Strict medical indications for elective induction of labor and elective cesarean section should be addressed and followed. Trials on cases, where elective cesarean section cannot be avoided, are needed and going on, in order to find ways to modulate the adverse effects of the elective cesarean section on the microbiome of the infant. It is a challenge to recognize whether there is a specific group of MP/LP and early-term infants at particular risk for later morbidity related to their GA at birth and to potentially target early intervention for these infants. In the field of neonatal care, a better understanding of how GA at birth affects the developing immune system and susceptibility to infection, and how extensive antibiotic treatment early in life affects the long-term outcome, including asthma, atopic dermatitis and LRTIs, are important points. Studying multifactorial diseases is challenging since it is important to adequately control for the known confounders and to find out new relevant connections. In addition, future studies are needed concerning long-term consequences after MP/LP and early-term birth in adolescence and adulthood (Kajantie et al. 2019). It still remains partly unclear why preterm infants have a reduced risk of atopic dermatitis compared with term-born infants and why post-term birth may increase this risk, and future research should further explore potential pathways behind this.

7 CONCLUSIONS

The following conclusions can be drawn on the basis of the present register linkage follow-up study:

1. Children born moderately preterm (MP) and late preterm (LP) received asthma medication reimbursement and were hospitalized due to asthma more often than term controls but less frequently than very preterm children. There is a decreasing trend in hospital visits due to asthma with increasing gestational age (GA). Conversely, the incidence of hospital visits due to atopic dermatitis rises with increasing GA. Male sex, maternal smoking, maternal diabetes, and ventilator therapy were associated with asthma medication in the MP and/or LP children.

2. Children born MP and LP were admitted to hospital for lower respiratory tract infections (LRTIs) more often than the term controls but less frequently than very preterm children. Preterm children had longer hospital stays due to bronchiolitis/bronchitis. These results suggest that, in addition to very preterm birth, MP and LP births also have a significant impact on the use of health-care services due to LRTIs. Associated risk factors for LRTIs included maternal smoking, birth by cesarean section, male sex, admission to a neonatal unit and ventilator therapy.

3. Early-term birth was a predictor of asthma, and post-term birth was associated with an increased risk of atopic dermatitis. Late- and post-term births appeared to be associated with a decreased risk of asthma compared with full-term birth. The most relevant risk factors for asthma were male sex, smoking during pregnancy, and birth by elective cesarean section, while for atopic dermatitis, the most relevant risk factors were male sex, being first-born, birth in a level II hospital, and birth by cesarean section.

4. Early-term birth was associated with increased rates and risk of hospital admission for all LRTIs, while late- and post-term birth reduced the risk of admission for bronchiolitis/bronchitis compared with full-term birth. Modifiable risk factors for LRTIs were smoking during pregnancy, elective cesarean delivery, ventilator therapy and neonatal antibiotic therapy.

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PUBLICATIONS

PUBLICATION I

Asthma and atopic dermatitis in children born moderately and late preterm

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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 but less frequently than VP children followed by 7 years of age. Hospitalization due to atopic dermatitis becomes 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

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.

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 birth 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=2 576, 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=6 347, 0.6%), MP (32^{+0}-33^{+6} weeks, n=6 799, 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 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 [11,33]. 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, 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 labour more than 24 hours 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 (Table 3, 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, Illinois). 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, 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 is shown in Figure 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 LP group 1.40 (95% CI 1.33-1.47).

Hospital visits due to atopic dermatitis became more common with increasing GA (Table 2, Figure 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 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 [34]. 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 makes 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 hyperglycaemia 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 association being strongest between 3 and 5 years of age [29]. The effects of corticosteroids on the hypothalamus-pituitary-axis, 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 covers 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 [10,11,33]. The present study population was substantial. In Finland, asthma diagnoses given by a pediatrician, preceded by the need of inhaled corticosteroid treatment for six months, is required to qualify for medication reimbursement [2]. Social Insurance Institution database is as a valid source of prevalence data and able to 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 disease.

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. Counselling 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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Compliance with Ethical Standards

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Conflict of interest: The authors declare that they have no conflict of interest.

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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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 wk (n=6,347)		Moderately preterm 32^{+0}-33^{+6} wk (n=6,799)		Late preterm 34^{+0}-36^{+6} wk (n=39,932)		Term ≥37 wk (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	(5.8)	29,8	(5.7)	29,7	(5.5)	29,2	(5.3)	p<0.001	p<0.001	p<0.001	p<0.001
Smoking, n (%)	1,192	(18.8)	1,186	(17.4)	6,605	(16.5)	144,097	(14.9)	p<0.001	p<0.001	p<0.001	p<0.001
First delivery, n (%)	3,329	(52.4)	3,792	(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[1], n (%)	92	(1.4)	148	(2.2)	969	(2.4)	8,468	(0.9)	p=0.002	p<0.001	p<0.001	p<0.001
Assisted reproductive technology, n (%)	609	(9.6)	768	(11.3)	2,764	(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	4,525	(71.3)	4,593	(67.6)	31,065	(77.8)	948,715	(98.3)				
2	1,621	(25.5)	1,955	(28.8)	8,549	(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)	1,282	(3.2)	3,518	(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)	4,957	(78.1)	3,995	(58.8)	17,156	(43.0)	299,477	(31.0)				
Central hospital (level II)	1,343	(21.2)	2,727	(40.1)	17,553	(44.0)	444,961	(46.1)				
Other[2]	42	(0.7)	77	(1.1)	5,220	(13.1)	220,659	(22.9)				
Mode of delivery, n (%)									p<0.001	p<0.001	p<0.001	p<0.001
Vaginal	2,537	(40.0)	3,212	(47.2)	26,687	(66.8)	820,961	(85.1)				
Cesarean section	3,798	(59.8)	3,584	(52.7)	13,212	(33.1)	143,493	(14.9)				
Newborn												

Boys, n (%)	3,441	(54.2)	3,730	(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	1,021	(16.1)	883	(13.0)	3,245	(8.1)	16,664	(1.7)				
AGA	4,974	(78.4)	5,639	(82.9)	34,685	(86.9)	919,989	(95.3)				
LGA	284	(4.5)	277	(4.1)	2,002	(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 (%)	1,014	(16.0)	326	(4.8)	891	(2.2)	7,495	(0.8)	p<0.001	p<0.001	p<0.001	p<0.001
Apgar 1 min 4-10, n (%)	5,223	(82.3)	6,397	(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 (%)	1,909	(30.1)	626	(9.2)	795	(2.0)	3,076	(0.3)	p<0.001	p<0.001	p<0.001	p<0.001
Admission to neonatal unit, n (%)	5,703	(89.9)	5,975	(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 (%)	3,665	(57.7)	1,416	(20.8)	1,667	(4.2)	2,797	(0.3)	p<0.001	p<0.001	p<0.001	p<0.001
Phototherapy, n (%)	4,203	(66.2)	3,822	(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 (%)	4,511	(71.1)	2,961	(43.6)	5,038	(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*
[1]= Register data available for 1991-2003, [2]=Regional hospital, private hospital, health center, home birth
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

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

	Very preterm <32 wk (n=6,437)		Moderately preterm 32+0-33+6 wk (n=6,799)		Late preterm 34+0-36+6 wk (n=39,932)		Term ≥37 wk (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)**	**2,259**	**(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 (%)	**1,277**	**(20.1)**	**718**	**(10.6)**	**2,901**	**(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)**	**1,864**	**(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

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

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 as following time separately for four gestation-week categories (N=1,018,302).

	Very preterm <32 wk (n=979/N=6,347)		Moderately preterm 32+0-33+6 wk (n=543/N=6,799)		Late preterm 34+0-36+6 wk (n=2,259/N=39,932)		Term ≥37 wk (n=36,210/N=965,224)	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Mothers' age	**0.99**	**(0.98-1.00)**	1.00	(0.98-1.02)	**0.98**	**(0.97-0.99)**	**0.98**	**(0.98-0.98)**
Smoking								
No	1.00		1.00		1.00		1.00	
Yes	1.15	(0.98-1.34)	**1.32**	**(1.08-1.63)**	**1.21**	**(1.09-1.35)**	**1.14**	**(1.11-1.18)**
First delivery								
No	1.00		1.00		1.00		1.00	
Yes	**0.70**	**(0.61-0.80)**	**0.79**	**(0.66-0.94)**	**0.77**	**(0.71-0.85)**	**0.82**	**(0.80-0.84)**
Diabetes[1]								
No	1.00		1.00		1.00		1.00	
Yes	0.96	(0.58-1.69)	**1.62**	**(1.02-2.58)**	0.78	(0.63-1.11)	1.09	(0.99-1.21)
Assisted reproduction technology								
No	1.00		1.00		1.00		1.00	
Yes	1.01	(0.78-1.29)	0.77	(0.54-1.11)	1.20	(1.00-1.43)	**1.21**	**(1.12-1.31)**
Antenatal steroid[2]								
No	1.00		1.00		1.00		1.00	
Yes	**0.69**	**(0.49-0.95)**	1.01	(0.62-1.64)	**1.46**	**(1.46-2.09)**	**1.72**	**(1.27-2.33)**
Number of fetuses								
1	1.00		1.00		1.00		1.00	
2	0.93	(0.79-1.09)	**0.81**	**(0.65-1.00)**	**0.85**	**(0.76-0.96)**	1.01	(0.94-1.10)
3 or 4	0.86	(0.57-1.28)	0.56	(0.30-1.05)	0.74	(0.44-1.22)	1.02	(0.14-7.22)
PROM								
No	1.00		1.00		1.00		1.00	
Yes	**0.67**	**(0.45-0.98)**	0.67	(0.38-1.15)	0.74	(0.54-1.03)	**0.75**	**(0.59-0.96)**
Birth hospital								
University (level III)	1.00		1.00		1.00		1.00	
Central (level II)	**0.72**	**(0.61-0.85)**	**0.79**	**(0.66-0.94)**	**0.88**	**(0.80-0.96)**	**0.85**	**(0.83-0.88)**
Other[3]	0.64	(0.26-1.57)	1.33	(0.70-2.53)	0.94	(0.82-1.07)	**0.96**	**(0.93-0.99)**
Mode of delivery								

Vaginal	1.00		1.00		1.00		1.00	
Cesarean section	1.04	(0.91-1.20)	1.06	(0.88-1.27)	1.10	(1.01-1.20)	**1.17**	**(1.14-1.21)**
Sex								
Boy	**1.60**	**(1.41-1.83)**	**1.74**	**(1.46-2.09)**	**1.65**	**(1.51-1.80)**	**1.73**	**(1.70-1.77)**
Girl	1.00		1.00		1.00		1.00	
Gestational weight								
SGA	1.11	(0.93-1.32)	1.11	(0.86-1.42)	1.02	(0.87-1.19)	1.06	(0.98-1.14)
AGA	1.00		1.00		1.00		1.00	
LGA	**0.63**	**(0.44-0.90)**	0.90	(0.59-1.37)	0.88	(0.73-1.08)	1.02	(0.96-1.09)
Admission to neonatal unit								
No	1.00		1.00		1.00		1.00	
Yes	**0.79**	**(0.64-0.99)**	0.84	(0.65-1.09)	**1.13**	**(1.03-1.24)**	**1.15**	**(1.10-1.21)**
Ventilator therapy								
No	1.00		1.00		1.00		1.00	
Yes	**1.43**	**(1.22-1.67)**	**1.26**	**(1.01-1.57)**	**1.42**	**(1.18-1.71)**	1.12	(0.94-1.33)
Antibiotic therapy								
No	1.00		1.00		1.00		1.00	
Yes	**0.83**	**(0.70-0.98)**	1.09	(0.89-1.33)	1.12	(0.97-1.28)	1.07	(0.99-1.16)

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 **bolded**. Categories of missing values not shown.
[1]= Register data available for 1991-2003. [2]= Register data available from 2004, years 2004-2008 analyzed. [3]= Regional hospital, private hospital, health center, home birth.
AGA=appropriate for gestational age; LGA=large for gestational age; PROM=premature rupture of membranes; SGA=small for gestational age

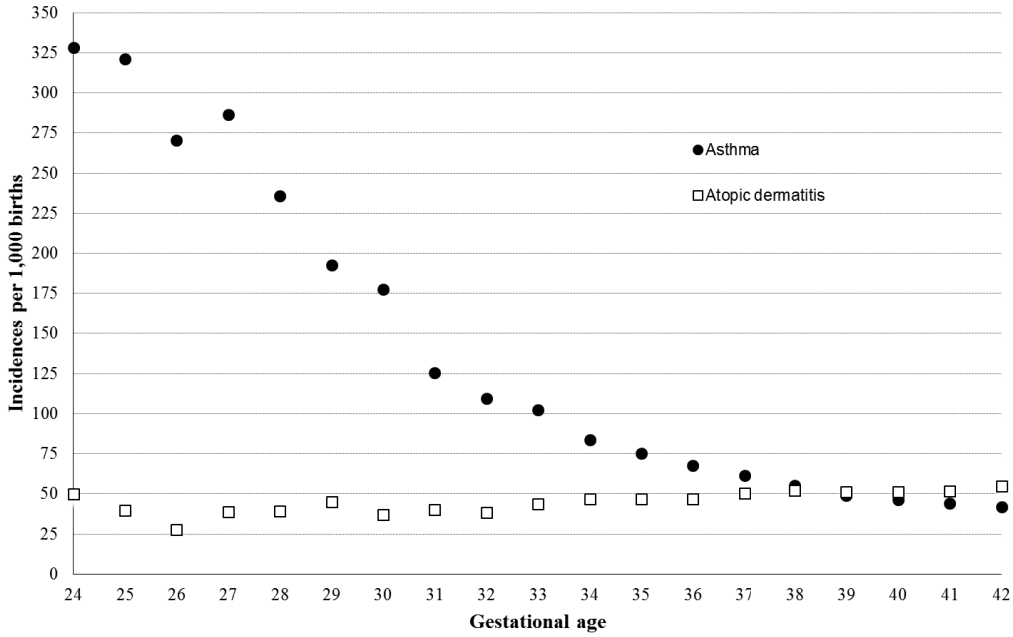
Table 4. Risk factor analysis for hospital visits due to atopic dermatitis (n=52,191) in the years 1991-2008 by the age of 7 years using time from birth to the first hospital visit as following time separately for four gestation-week categories (N=1,018,302).

	Very preterm <32 wk (n=249/N=6,347)		Moderately preterm 32+0-33+6 wk (n=283/N=6,799)		Late preterm 34+0-36+6 wk (n=1,864/N=39,932)		Term ≥37 wk (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[1]								
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[2]	*		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 **bolded**. Categories of missing values not shown.
*= Cannot be computed due to small sample size. [1]= Register data available for 1991-2003. [2] = Regional hospital, private hospital, health center, home birth.
AGA=appropriate for gestational age; LGA=large for gestational age; PROM=premature rupture of membranes; SGA=small for gestational age

Figure 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).



PUBLICATION II

Hospital admissions for lower respiratory tract infections in children born moderately/late preterm

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ORIGINAL ARTICLE: RESPIRATORY INFECTIONS

WILEY PEDIATRIC PULMONOLOGY

Hospital admissions for lower respiratory tract infections in children born moderately/late preterm

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Abstract

Objective: To evaluate the frequency and predictors of hospital admissions for lower respiratory tract infections (LRTIs) in moderately preterm (MP, 32^{+0} to 33^{+6} weeks) and late preterm (LP, 34^{+0} to 36^{+6} weeks) infants compared to term (T ≥37 weeks) and very preterm (VP, $<32^{+0}$ weeks) infants.

Study Design: This national register-based study covered all infants born in Finland in 1991-2008. Data on 1 018 256 infants were analyzed in four gestational age-based groups: VP (*n* = 6329), MP (*n* = 6796), LP (*n* = 39 928), and T (*n* = 965 203) groups. Data on hospital admissions due to bronchiolitis/bronchitis and pneumonia were collected up to the age of 7 years.

Results: Hospital admissions for LRTIs were more common in the MP and LP groups than in the T group but less frequent than in the VP group: bronchiolitis/bronchitis (VP 24.4%, MP 13.9%, LP 9.5%, and T 5.6%) and pneumonia (VP 8.8%, MP 4.5%, LP 3.3%, and T 2.4%). Compared to the term group, MP and LP birth predicted bronchiolitis/bronchitis (MP OR 1.89; 95%CI 1.75-2.03, LP 1.51; 1.45-1.56) and pneumonia (MP 1.49; 1.32-1.67, LP 1.25; 1.18-1.33) admissions. Statistically significant risk factors for LRTIs included maternal smoking, cesarean section, male sex, admission to a neonatal unit and ventilator therapy. In addition, being first-born, being born SGA and neonatal antibiotic therapy were associated with bronchiolitis/bronchitis.

Conclusions: MP and LP births, in addition to VP birth, have a significant impact on respiratory infectious morbidity and the need of hospital admissions for LRTIs.

KEYWORDS
bronchiolitis, bronchitis, hospitalization, pneumonia, wheezing bronchitis

1 | INTRODUCTION

Moderately preterm (MP, born at 32^{+0} to 33^{+6} weeks) and late preterm (LP, born at 34^{+0} to 36^{+6} weeks) infants account for over 80% of all preterm births.[1] These infants have an increased risk of early-childhood as well as later respiratory morbidity, such as asthma.[2,3] Lower respiratory tract infections (LRTIs) are the leading cause of hospitalization in preschool children.[4] Many previous studies have focused on the

Abbreviations: AGA, appropriate for gestational age; CI, confidence interval; GA, gestational age; HDR, hospital discharge register; HR, hazard ratio; ICD, International Classification of Diseases; IQR, interquartile range; LGA, large for gestational age; LP, late preterm; LRTI, lower respiratory tract infection; MBR, medical birth register; MP, moderately preterm; OR, odds ratio; RSV, respiratory syncytial virus; SD, standard deviation; SGA, small for gestational age; T, term; VP, very preterm.

respiratory health outcome of children born very preterm (VP), that is, before 32 weeks of gestational age (GA). Less data is available on LRTI hospitalizations among MP and LP children. Findings from recent population-based cohort studies[5–7] and also from those focusing on MP and LP children[8,9] have shown an increasing risk of hospital admission for respiratory infections with decreasing GA. It has also been suggested that not only prematurity but also some perinatal factors such as mode of delivery or being born small for gestational age (SGA) may increase the risk of infections in early childhood.[10,11]

We have previously analyzed data on all 1 018 256 infants born in Finland in 1991-2008, using national registers.[12,13] According to our results, hospitalization for asthma was more common in MP and LP groups than among term controls, but less common than in the VP group.[12] On the other hand, hospitalization for atopic dermatitis was more common among term controls than in the MP or LP groups.[12] The aims of the present study were to evaluate whether or not moderately and late preterm birth increases the risk of hospital admissions for LRTI in the same population and to assess the role of perinatal and neonatal risk factors of LRTI hospitalization up to the age of 7 years.

2 | MATERIALS AND METHODS

The national register-based study population was acquired from the Finnish Medical Birth Register (MBR), which collects information on maternal health and interventions during pregnancy and delivery, and on infant health and medical procedures undergone during the first week of life. The data were linked to data from the Cause of Death Register and the Register of Congenital Malformations. Data collection has been described in more detail in our previous publications.[12,13] Altogether, 1 039 263 infants were born alive in Finland between 1991 and 2008. Infants who died before 1 year of age (n = 2 659, 0.25%), or who had at least one major congenital anomaly (n = 13 007, 1.25%), or with missing data on GA (n = 5520, 0.5%) were excluded. The remaining cohort of 1 018 256 infants (98.0% of all) was analyzed in four GA-based groups: VP (<32^{+0} weeks, n = 6 329, 0.6%), MP (32^{+0} to 33^{+6} weeks, n = 6 796, 0.7%), LP, (34^{+0} to 36^{+6} weeks, n = 39 928, 3.9%) and term (≥37 weeks, n = 965 203, 94.8%).

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. A correction to GA was made if the ultrasonographic estimation showed a discrepancy of more than 5-7 days compared with GA based on the last menstrual period. Morbidity data were collected from the Hospital Discharge Register (HDR). This data includes admission and discharge dates, diagnoses and procedures regarding all specialized outpatient healthcare in all public hospitals (since 1998) and inpatient visits to all hospitals in Finland. Infants were followed up to 7 years of age or to the end of 2009.

With regard to outcome measures, the study subjects were considered to have had LRTI if the following diagnoses had been recorded in the HDR by the end of 2009 (International Classification of Diseases 9th Revision ICD-9 in 1991-1995 and 10th Revision ICD-10 in 1996-2008): acute bronchiolitis/bronchitis (all ICD-9 codes 466 and ICD-10 codes J20-J21) and pneumonia (all ICD-9 codes 480-486 and ICD-10 codes J12-18). All dates of hospital admissions and discharges with these 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 ICD-10 diagnoses between years 1996 and 2008 were also collected separately as respiratory syncytial virus (RSV) pneumonia (J12.1), other viral pneumonia (J12), bacterial pneumonia (J13-18), RSV bronchiolitis (J21.0), and viral or bacterial wheezing bronchitis (J21.9). All data linkages were carried out by using a unique anonymized identification code.

2.1 | Definitions

The parameter bronchiolitis/bronchitis used in the present study covered all hospital admissions due to acute bronchiolitis and bronchitis, including wheezing bronchitis, a diagnosis commonly used in the Nordic countries.[14] We collected the diagnoses directly from the register, using both primary and secondary diagnoses. The definitions presented below did not directly influence the case definition and selection.

According to the Finnish Current Care Guidelines (www.kaypahoito.fi), bronchiolitis is defined as the first virus-induced wheezing episode in infants under the age of 12 months.[15] Acute childhood bronchitis is defined as an acute cough associated with viral respiratory infections lasting less than three weeks.[15] The ICD-10 code for acute wheezing bronchitis was available in 1996-2008. In Finland, wheezing (obstructive) bronchitis is defined as any wheezing in children aged 12-36 months during an acute respiratory viral infection or repeated wheezing in children aged 6-12 months.[15,16] The definition of pneumonia includes viral or bacterial infection of the pulmonary alveoli or interstitial tissue and can be diagnosed by chest radiography and on the basis of clinical findings, such as the presence of fever and acute respiratory symptoms.[15,17,18]

2.2 | Ethics

The regional Ethics Committee approved the study. The National Institute for Health and Welfare and Statistics Finland gave their permission to use sensitive health data for research.

2.3 | Statistical analysis

The background parameters of the study population and differences between the GA groups were analyzed by using Pearson's chi-square test (categorical variables) and continuous variables were analyzed by using One-way Anova or Welch test or Kruskal-Wallis test (Tables 1–3). Non-normal distributions were first normalized by base e-logarithm (Table 2). Only variables that have been reliably recorded with good validity and very low amount of missing or false data in the registers were analyzed.[19]

To take into account for the number of deliveries per one mother, risk factors for hospital visits due to bronchiolitis/bronchitis and pneumonia were sought by Generalized Linear Mixed Model with an

TABLE 1 Characteristics of infants and their mothers

	Very preterm <32 wk (*n* = 6329)	Moderately preterm 32^{+0}-33^{+6} wk (*n* = 6796)	Late preterm 34^{+0}-36^{+6} wk (*n* = 39 928)	Term ≥37 wk (*n* = 965 203)
Mother				
Age, Mean (SD)	30.2 (5.8)	29.8 (5.7)	29.7 (5.5)	29.2 (5.3)
Smoking, *n* (%)	1187 (18.8)	1184 (17.4)	6602 (16.5)	144 094 (14.9)
First delivery, *n* (%)	3314 (52.4)	3792 (55.8)	20 040 (50.2)	392 574 (40.7)
Previous deliveries, Md (IQR)	0 (0-1)	0 (0-1)	0 (0-1)	1 (0-2)
Number of fetuses at birth, *n* (%)				
1	4517 (71.4)	4591 (67.6)	31 062 (77.8)	948 695 (98.3)
2	1614 (25.5)	1954 (28.8)	8548 (21.4)	16 489 (1.7)
≥3	198 (3.1)	251 (3.7)	318 (0.8)	19 (<0.1)
Place of birth, *n* (%)				
University hospital (level III)	4943 (78.1)	3993 (58.8)	17 154 (43.0)	299 470 (31.0)
Central hospital (level II)	1340 (21.2)	2726 (40.1)	17 551 (44.0)	444 952 (46.1)
Other[a]	41 (0.6)	77 (1.1)	5220 (13.1)	220 654 (22.9)
Mode of delivery, *n* (%)				
Vaginal	2524 (39.9)	3211 (47.2)	26 685 (66.8)	820 942 (85.1)
Cesarean section	3793 (59.9)	3582 (52.7)	13 210 (33.1)	143 491 (14.9)
Newborn				
Boys, *n* (%)	3428 (54.2)	3728 (54.9)	21 658 (54.2)	490 211 (50.8)
Birth weight, g, Md (IQR)	1290 (1000-1570)	1970 (1730-2200)	2670 (2360-2985)	3590 (3276-3910)
Gestational age, *n* (%)				
SGA	1019 (16.1)	883 (13.0)	3245 (8.1)	16 662 (1.7)
AGA	4972 (78.6)	5637 (82.9)	34 681 (86.9)	919 970 (95.3)
LGA	284 (4.5)	276 (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)
Apgar 1 min 0-3, *n* (%)	1001 (15.8)	325 (4.8)	890 (2.2)	7491 (0.8)
Resuscitation at birth, *n* (%)	1901 (30.1)	625 (9.2)	795 (2.0)	3074 (0.3)
Admission to neonatal unit, *n* (%)	5692 (89.9)	5972 (87.9)	19 155 (48.0)	58 365 (6.0)
Ventilator therapy, *n* (%)	3656 (57.8)	1413 (20.8)	1667 (4.2)	2793 (0.3)
Phototherapy, *n* (%)	4202 (66.4)	3821 (56.2)	14 153 (35.4)	36 671 (3.8)
Antibiotic therapy, *n* (%)	4505 (71.2)	2958 (43.5)	5038 (12.6)	23 849 (2.5)

Years 1991-2008 (*N* = 1 018 256; infants who died under 1 year of age and infants with major congenital malformations excluded). Statistical differences were tested by Pearson chi-square test or by One-way Anova or by Kruskall-Wallis test. All *P* values between GA groups were $P < 0.001$.
AGA, appropriate for gestational age; IQR, interquartile range; LGA, large for gestational age; Md, median; SD, standard deviation; SGA, small for gestational age.
[a]Regional hospital, private hospital, health center, home birth.

lmer function (Table 4). All explanatory variables were modeled as a fixed variable and the number of deliveries per mother were added as random effect. Results were presented as odds ratios (OR) with 95% confidence intervals (CI). Values of p less than 0.001 (two-tailed) were considered statistically significant. The independent maternal and delivery-related factors (age, smoking, first delivery, number of fetuses, level of hospital, mode of delivery) and newborn-related factors (sex, gestational weight, admission to a neonatal unit, ventilator, and antibiotic therapy) with good validity in the registers were included in the mixed models.

The Generalized Linear Mixed Model analyses were performed with the Statistical Package R version 3.3.0 package lme4 (www.r-

TABLE 2 Hospital admissions for lower respiratory tract infections up to the age of 7 years among very preterm, moderately preterm, late preterm and term 1 year survivors

	Very preterm <32 wk (n−= 6329)	Moderately preterm 32^{+0}-33^{+6} wk (n = 6796)	Late preterm 34^{+0}-36^{+6} wk (n = 39 928)	Term ≥37 wk (n = 965 203)
Acute bronchiolitis/bronchitis (466, J20-J21), *n* (%)	1542 (24.4)	942 (13.9)	3796 (9.5)	54 308 (5.6)
Age at diagnosis				
0-11 months, *n* (%)	920 (59.7)	600 (63.7)	2,184 (57.5)	27,787 (51.2)
12-35 months, *n* (%)	513 (33.3)	279 (29.6)	1,295 (34.1)	20,589 (37.9)
36-84 months, *n* (%)	109 (7.1)	63 (6.7)	317 (8.4)	5,932 (10.9)
Number of visits, Md (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-2)
Days in hospital, Md (IQR)	6 (3-14)	6 (3-11)	5 (2-10)	4 (2-7)
Pneumonia (480-486, J12-18), *n* (%)	560 (8.8)	307 (4.5)	1332 (3.3)	23 376 (2.4)
Age at diagnosis				
0-11 months, *n* (%)	121 (21.6)	67 (21.8)	225 (16.9)	3,562 (15.2)
12-35 months, *n* (%)	270 (48.2)	150 (48.9)	656 (49.2)	11,799 (50.5)
36-84 months, *n* (%)	169 (30.2)	90 (29.3)	451 (33.9)	8,015 (34.3)
Number of visits, Md (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)
Days in hospital, Md (IQR)	5 (3-10)	4 (1-6)	4 (2-7)	4 (2-5)

Years 1991-2008 (*n* = 1 018 256). Differences between GA groups were assessed by using Pearson's chi-square test or by Welch test. All *P* values were $P < 0.001$. Non-normal distributions were first normalized by base e-logarithm.
IQR, interquartile range; Md, median.

projcet.org) and the remaining analyses by using IBM SPSS Statistics version 23.0 software (IBM SPSS, Chicago, IL).

3 | RESULTS

Background characteristics of the infants and their mothers are presented in Table 1. Overall, 60 588 (6.0%) children followed for up to 7 years of age had experienced hospital admission for bronchiolitis/bronchitis, and 25 575 (2.5%) for pneumonia. In all, 4738 (7.8%) bronchiolitis/bronchitis admissions and 1639 (6.4%) pneumonia admissions occurred among MP and LP children. Hospital admissions for LRTIs were more common in the MP and LP groups than in the T group but less frequent than in the VP group (Table 2). The data showed a decreasing trend with GA in the incidence of hospital admissions for LRTI (Table 2, Figure 1). The majority of all admissions because of LRTIs took place before the age of 36 months. The figures were 93.0% (VP group), 93.3% (MP group), 91.6% (LP group), and 89.0% (T group) for bronchiolitis/bronchitis admissions, and 69.8% (VP group), 70.7% (MP group), 66.1% (LP group), and 65.7% (T group) for pneumonia admissions. The length of hospital stay due to bronchiolitis/bronchitis was longer in the MP and LP groups than in the T group (Table 2). The distribution of LRTI diagnoses with viral or bacterial etiology between years 1996-2008 (*N* = 709 534) is presented in Table 3. The frequency of both viral and bacterial LRTI seemed to decrease by increasing gestational age.

In the risk factor analyses, maternal smoking, being first-born, cesarean section, male sex, being born SGA, admission to neonatal unit, ventilator therapy, and neonatal antibiotic therapy were associated with an increased risk of hospital admissions for bronchiolitis/bronchitis (Table 4). The OR for hospital admission due to bronchiolitis/bronchitis (compared to the term controls) was 3.33 (95%CI 3.09-3.59) in the VP group, 1.89 (95%CI 1.75-2.03) in the MP group and 1.51 (95%CI 1.45-1.56) in the LP group. The risk factor analysis regarding hospital admissions for pneumonia showed weaker associations with perinatal and neonatal factors. Maternal smoking, cesarean section, male sex, admission to a neonatal unit and ventilator therapy were associated with pneumonia. Correspondingly, the OR for hospital admission for pneumonia (compared with the term controls) was 2.59 (95%CI 2.32-2.89) in the VP group, 1.49 (95%CI 1.32-1.67) in the MP group, and 1.25 (95%CI 1.18-1.33) in the LP group. Lower maternal age and birth in a level-II hospital seemed to decrease the risk of hospital admission for LRTI.

4 | DISCUSSION

Moderately preterm and LP children were more often admitted to hospital for LRTIs than term controls, but less often than VP children, up to the age of seven. We detected associations between GA and LRTI hospitalization both in incidences and adjusted ORs. The perinatal and neonatal risk factors regarding hospital admissions for LRTIs included maternal smoking, cesarean section, male sex, admission to a neonatal unit and ventilator therapy. In addition, being first-born, being born SGA and neonatal antibiotic therapy were associated with bronchiolitis/bronchitis.

Strengths of this study include the large amount of population-based register data with national coverage, and the substantial number

TABLE 3 Lower respiratory tract infection diagnoses according to viral or bacterial etiology up to the age of 7 years among very preterm, moderately preterm, late preterm and term 1 year survivors between years 1996 and 2008 (N = 709 534)

	n%				
	Very preterm <32 wk (n = 4549)	**Moderately preterm 32^{+0}-33^{+6} wk (n = 4859)**	**Late preterm 34^{+0}-36^{+6} wk (n = 28 151)**	**Term ≥37 wk (n = 671 975)**	**Total (n = 709 534)**
RSV pneumonia (J12.1)	13 (0.3)	3 (0.1)	21 (0.1)	250 (0.04)	287 (0.04)
Other viral pneumonia (J12)	37 (0.8)	18 (0.4)	77 (0.3)	874 (0.1)	1006 (0.1)
Bacterial pneumonia (J13-18)	441 (9.7)	257 (5.3)	1104 (3.9)	20 140 (3.0)	21 942 (3.1)
RSV bronchiolitis (J21.0)	378 (8.3)	230 (4.7)	850 (3.0)	10 353 (1.5)	11 811 (1.7)
Viral or bacterial wheezing bronchitis (J21.9)	712 (15.7)	454 (9.3)	1822 (6.5)	25 579 (3.8)	28 567 (4.0)

Differences between GA groups were assessed by using Pearson's chi-square test. All P values were $P < 0.001$.
RSV, respiratory syncytial virus.

of infants. The reliability of the Finnish MBR and HDR has been demonstrated in previous studies.[20,21] In Finland there are only public children's hospitals, and therefore all hospital admissions for LRTIs we consider to have been derived reliably from the registers. The available data allowed adjustments with multiple maternal-, delivery-, and newborn- related background factors.

The weaknesses of our study, as in all register-based studies and analyses of routinely collected data, include the fact that recording practices may vary between regions and time periods. Undoubtedly, the definitions also varied during the 18 years of follow-up. Misclassification in the coding of diagnoses in regard to hospital admissions and discharges is possible. Because of our study design, the children born after 2002 had a follow-up period shorter than 7 years. However, approximately 90% of bronchiolitis/bronchitis and 65% of pneumonia admissions occurred before the age of 3 years and most infants were followed up for longer than that. Data on general-practice visits could not be obtained in this study. Owing to the lack of data on parental asthma and duration of breastfeeding, we could not adjust for these confounding factors. Reliable data on socioeconomic status were also missing, since it is difficult to determine such status among young women of childbearing age. We did, however, have information on maternal smoking, which strongly correlates with socioeconomic status in Finland.[22]

The clinical pictures of LRTIs such as bronchiolitis, wheezing bronchitis and pneumonia may overlap. Therefore, it is challenging to differentiate between diagnoses of wheezing bronchitis and bronchiolitis, especially in children less than 3 years of age. In previous studies these have often been analyzed together.[14,16] In our study, 6% of all children were hospitalized because of bronchiolitis/bronchitis by 7 years of age; about half of them by 12 months of age. This is in accordance with previous literature, where 2-3% of all children were hospitalized because of bronchiolitis during their 1st year of life.[10] In another population-based birth cohort studied in England, it was estimated that 21% of hospitalized infants had experienced more than one admission because of bronchiolitis during the 1st year of life.[23] The true incidence of pneumonia could not be analyzed here due to the lack of data on cases of pneumonia diagnosed and treated in general practice. The annual incidence of pneumonia in children of less than 5 years of age has been reported to range from 0.2-0.33% to 3.5-4% and approximately half of the children with pneumonia at this age group are treated in hospital.[17] This is in accordance with our hospital admission rates due to pneumonia.

Our results on the association between MP and LP birth and an increased incidence of hospital admissions for LRTIs are in line with previous findings.[5–9] A Canadian retrospective health record linkage study of a total of 35 733 infants including 2,051 LP (33-36 weeks) births revealed increased risk of acute bronchiolitis/bronchitis (OR 1.64, 95% CI 1.13-2.39) and pneumonia (OR 1.17, 95%CI 1.05-1.30) in the first 3 years of life in LP infants compared with term infants.[24] In a recent Spanish prospective observational study including 2468 hospital admissions for respiratory conditions, MP children (32-36 weeks) under the age of 14 years needed more medical support and more frequent intensive care, and wheezy MP children needed longer hospital stays than full-term children.[25] Additionally, in our study, MP and LP children had longer hospital stays due to bronchiolitis/bronchitis than term children. Previous studies on bronchiolitis due to RSV infection distinctly show an increased risk of hospital admission in MP and LP versus term children.[26,27] In our register study we were not able to obtain data on bronchiolitis confirmed by positive RSV test, but the distribution of the ICD 10 diagnoses supports the previous findings.

Susceptibility to LRTIs during early infancy in children born MP and LP might be a consequence of incomplete transfer of maternal antibodies as a result of premature birth and an immature neonatal immune system. Final maturation of the immune system occurs during the first six months of life.[28] Premature birth also interrupts lung development, since alveoli are not completely mature until 36 weeks of GA.[2] This causes inadequate maintenance of functional residual capacity, decreased compliance, and smaller airway diameters compared to term infants. Together with an infection early in the course of immune maturation causing a greater inflammatory response, these features make MP and LP infants susceptible to more severe symptoms of LRTIs.[2,3]

TABLE 4 Risk factor analysis for hospital admissions for bronchiolitis/ bronchitis (n = 60 588) and pneumonia (n = 25 575) by the age of 7 years in 1991-2008 (N = 1 018 256)

		Bronchiolitis/bronchitis (n = 60 588)	Pneumonia (n = 25 575)
	n	OR (95%CI)	OR (95%CI)
Gestational age			
Term ≥37 wk	965 203	1.00	1.00
Very preterm <32 wk	6329	**3.33 (3.09-3.59)**	**2.59 (2.32–2.89)**
Moderately preterm 32^{+0}-33^{+6} wk	6796	**1.89 (1.75–2.03)**	**1.49 (1.32–1.67)**
Late preterm 34^{+0}-36^{+6} wk	39 928	**1.51 (1.45–1.56)**	**1.25 (1.18–1.33)**
Mothers' age	1 018 256	**0.98 (0.98–0.98)**	**0.99 (0.99–1.00)**
Smoking			
No	841 835	1.00	1.00
Yes	153 067	**1.47 (1.44–1.50)**	**1.10 (1.07–1.14)**
First delivery			
No	598 536	1.00	1.00
Yes	419 720	**1.74 (1.14–1.21)**	0.96 (0.92-1.00)
Number of fetuses			
1	988 965	1.00	1.00
2	28 605	**0.91 (0.87-0.95)**	0.92 (0.85–0.98)
3-4	786	0.76 (0.62–0.92)	0.72 (0.57–0.91)
Birth hospital			
University (level III)	325 560	1.00	1.00
Central (level II)	466 569	**0.95 (0.94–0.97)**	**0.94 (0.91–0.96)**
Other[a]	225 992	**0.88 (0.86–0.90)**	0.97 (0.94–1.01)
Mode of delivery			
Vaginal	853 362	1.00	1.00
Cesarean section	164 076	**1.15 (1.13–1.18)**	**1.08 (1.04–1.12)**
Sex			
Boy	519 025	**1.61 (1.58–1.64)**	**1.13 (1.10-1.16)**
Girl	499 231	1.00	1.00
Gestational weight			
AGA	965 260	1.00	1.00
SGA	21 809	**1.09 (1.03-1.15)**	1.08 (1.00-1.17)
LGA	31 133	0.99 (0.94-1.04)	0.96 (0.90-1.03)
Admission to neonatal unit			
No	929 068	1.00	1.00
Yes	89 184	**1.24 (1.20-1.29)**	**1.21 (1.15-1.27)**
Ventilator therapy			
No	1 008 727	1.00	1.00
Yes	9529	**1.27 (1.18-1.36)**	**1.32 (1.19-1.46)**
Antibiotic therapy			
No	981 906	1.00	1.00
Yes	36 350	**1.15 (1.09-1.20)**	1.04 (0.97-1.12)

Multivariable Generalized Linear Mixed Models were used, with results given as the odds ratios (OR) and 95% confidence intervals (CI). Statistically significant results (P < 0.001) are bolded. Categories with missing values are not shown.

AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

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

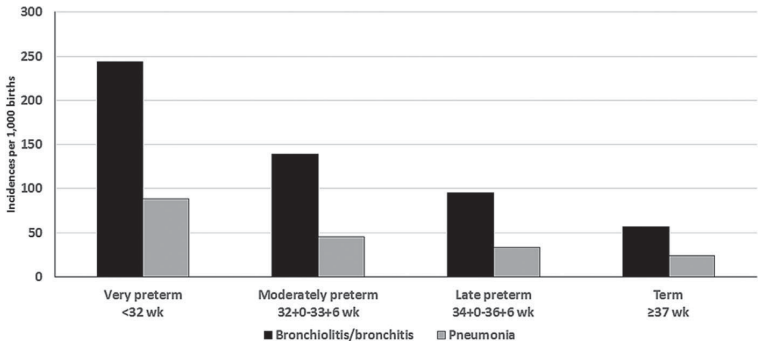

FIGURE 1 Incidences of hospital admissions for lower respiratory tract infections per 1000 births by 7 years of age in relation to gestational age group at birth; birth years 1991-2008 (*N* = 1 018 256)

Supporting previous work,[8,10,29,30] we found an association between maternal smoking during pregnancy and bronchiolitis/bronchitis and pneumonia of the offspring. Data on daily maternal smoking during pregnancy are relatively well covered in the Finnish MBR.[22] We could not establish postnatal exposure to smoking, which is a known risk factor of wheezing in early childhood[29] and LRTIs in pre-school children.[30] Avoidance of smoking during and after pregnancy is one means to improve the respiratory health of children.

In our study, birth by cesarean section was associated with increased risk of hospital admission because of bronchiolitis/bronchitis and pneumonia. This is in line with the results of a recent Danish national register-based cohort study showing that children delivered by elective cesarean section had an increased risk of LRTIs.[11] Differences in early microbial exposure related to the mode of delivery might be of importance in immunomodulation. In an elective cesarean section, the membranes are usually intact, which is in contrast to the situation in acute cesarean section or vaginal delivery.[11,31] Following strict indications for delivery via cesarean section might have a beneficial influence on the long-term respiratory outcome of neonates.

Male sex appeared to increase the risk of hospital admission for both bronchiolitis/bronchitis and pneumonia. Our results are consistent with those of previous studies showing associations between male sex and increased risk of childhood wheezing[8,32] and RSV hospitalization[33] and pneumonia.[4]

In line with the previous results SGA children seemed to carry a greater risk of bronchiolitis/bronchitis.[6,7,10,34] Past epidemiological studies have reported the link between low birth weight and childhood wheezing disorders, although some results have been inconsistent.[34]

Admission to a neonatal unit also seemed to be associated with increased risk of LRTIs. These infants are usually those suffering from early neonatal respiratory morbidity or infection.

In our study, ventilator therapy during the neonatal period predicted LRTIs. Very preterm children need ventilator support after birth more often and have long-term respiratory problems such as bronchopulmonary dysplasia, which is a known risk factor of bronchiolitis and recurrent wheezing in early childhood.[35] Avoiding ventilator treatment and using less invasive respiratory management practices, thus minimising ventilator induced lung injury, might also improve the long-term respiratory outcome for more mature neonates.

Our finding that antibiotic therapy during the first week of life predicted the risk of hospital admission for bronchiolitis/bronchitis is in line with the results of the Swedish birth-cohort study, in which the treatment with broad-spectrum antibiotics during the 1st week of life increased the risk of recurrent wheezing at preschool age.[36] However, the association between wheezing and early antibiotic treatment is controversial.[37] The first weeks of life probably represent the most important time window for changes in the intestinal microbiota caused by antibiotics.[31] Perinatal infection itself may also modify immune programming.[31] Cautious use of antibiotics during the neonatal period is recommended.

Interestingly, in our study, first-born children had an increased risk of bronchiolitis/bronchitis. This may be partially explained by the previous finding that first-born children at birth have reduced anti-inflammatory profile in T-cells and possibly the enhanced risk of developing later immune-related diseases.[38] Being first-born has elsewhere been found to be protective as regards childhood wheezing.[39] Twins seemed to have a decreased risk of bronchiolitis/bronchitis. Supporting this finding, the protective effect of twin birth against RSV hospitalization in preterm children has been described.[33] Previous results suggest that the presence of older siblings and day-care attendance increase the risk of RSV infection hospitalization[33] and transient wheezing in early childhood.[8,32]

Lower maternal age and birth in a level-II hospital seemed to decrease the risk of hospital admission for LRTI. This might be related to a previous finding on the association with higher maternal age and neonatal risks[40] and the fact that deliveries associated with higher risk are treated in level-II hospitals.

5 | CONCLUSIONS

Children born MP and LP appear to be admitted to hospital for LRTIs more often than term controls but less frequently than VP children by 7 years of age. Preterm children had longer hospital stays due to

bronchiolitis/bronchitis. These results suggest that MP or LP births have a significant impact on the use of health-care services. Interventions to affect the underlying risk factors such as maternal smoking, birth by caesarean section, neonatal ventilator therapy and early antibiotic therapy should be considered.

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PUBLICATION III

Asthma and atopic dermatitis after early-, late-, and post-term birth

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ORIGINAL ARTICLE: ASTHMA

WILEY PEDIATRIC PULMONOLOGY

Asthma and atopic dermatitis after early-, late-, and post-term birth

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Abstract

Objective: To assess the incidence and risk factors of asthma and atopic dermatitis by seven years of age after early-term (ET) (37^{+0}-38^{+6} weeks), full-term (FT) (39^{+0}-40^{+6} weeks), late-term (LT) (41^{+0}-41^{+6} weeks), and especially post-term (PT) (≥42 weeks) birth.

Methods: Altogether, 965 203 infants born between 1991 and 2008 in Finland were investigated in ET, FT, LT, and PT groups. Data on asthma medication reimbursement and hospital visits for atopic dermatitis were retrieved from national health databases.

Results: The frequencies of asthma medication reimbursement in the ET, FT, LT, and PT groups were 4.5%, 3.7%, 3.3%, and 3.2%, respectively. Hospital visits due to atopic dermatitis were most common after PT birth. Compared with FT births, ET births were associated with an increased risk of asthma (adjusted odds ratio (aOR), 95% confidence interval (CI) 1.20, 1.17-1.23), while LT (aOR, 95%CI 0.91, 0.89-0.93) births and PT (aOR, 95%CI 0.87, 0.83-0.92) births decreased this risk. PT birth (aOR, 95%CI 1.06, 1.01-1.10) predicted atopic dermatitis. From a population point of view, the most relevant risk factors for asthma were male sex, ET birth, smoking during pregnancy and birth by elective cesarean section, and for atopic dermatitis male sex, first delivery, birth in a level II hospital and birth by cesarean section.

Abbreviations: AGA, appropriate for gestational age; CI, confidence interval; CS, cesarean section; ET, early term; FT, full term; GA, gestational age; HDR, Hospital Discharge Register; ICD, International Classification of Diseases; LGA, large for gestational age; LT, late term; MBR, Medical Birth Register; OR, odds ratio; PAR, population attributable risk; PROM, premature rupture of membranes; PT, post term; SD, standard deviation; SGA, small for gestational age.

Conclusions: Early-term birth was a predictor of asthma, and PT birth was associated with atopic dermatitis. Counseling against smoking and following strict indications for planned ET deliveries and cesarean sections may be means to reduce the risk of later asthma.

KEYWORDS
cesarean section, hospital admission, reimbursement, risk factor, tobacco smoke exposure

1 | INTRODUCTION

Children born prematurely appear to carry an increased risk of asthma and/or asthma-like symptoms in childhood,[1–3] whereas their risk of atopic dermatitis has been found to be decreased[3–5] compared with children born at a later gestational age (GA).

Because of the reported health risks of the mother and infant after elective deliveries prior to 39 weeks of GA, sub-grouping the traditional "term birth" into early-term (ET, 37^{+0}-38^{+6} weeks), full-term (FT, 39^{+0}-40^{+6} weeks), late-term (LT, 41^{+0}-41^{+6}weeks), and post-term (PT, ≥42 weeks) birth has been recommended.[6] Although milder and less common than in the most premature groups, the health problems of ET, LT, and PT infants may result in a substantial burden to society owing to the high number of infants.[7-9]

Early-term birth has been associated with an increased risk of childhood asthma,[1,7,8,10] whereas birth at ≥41 weeks' GA[10] and PT birth[11] have been associated with a decreased risk compared with FT birth. An increased risk of atopic dermatitis by school age has been suggested in children born PT,[4] but further studies on this risk in GA subgroups are warranted.

In our previous study on 1 018 302 children born in Finland between 1991 and 2008, the risk of receiving reimbursement for asthma medication by seven years of age was higher in moderately and late-preterm children compared with term controls, whereas the risk of hospitalization due to atopic dermatitis increased with GA.[3] In the present study, we evaluated further the incidence and risk factors of asthma and atopic dermatitis by seven years of age in term subgroups of the same population, with a special emphasis on PT children.

2 | MATERIALS AND METHODS

The study population was derived from the cohort of all live-births (*N* = 1 039 263) in Finland in 1991-2008, described in detail elsewhere.[3,12] Data on GA were missing in 5520 infants. A subgroup of infants born at ≥37 weeks of GA (*N* = 978 224) was chosen, excluding those with major congenital anomalies (*N* = 12 123) and those who died before one year of age (*N* = 898). Selection was based on data from the Medical Birth Register (MBR), the Register of Congenital Malformations and the Cause of Death Register. The final study population included 965 203 (98.7% of all) infants who were analyzed in ET (*N* = 181 667), FT (*N* = 546 845), LT (*N* = 189 373), and PT (*N* = 47 318) groups. The cases were followed-up to seven years of age or up to the year 2009.

Perinatal and neonatal data were obtained from the MBR. Pregnancy- and delivery-related diagnoses of the mothers were collected from the Hospital Discharge Register (HDR). Details of data collection have been presented earlier.[12] Gestational age was based on early pregnancy ultrasonography, and corrected according to menstrual anamnesis in cases of discrepancy of 5-7 days or more between evaluations. Cesarean sections (CS) were classified as elective (decided upon and undertaken before labor) or emergency (undertaken according to maternal or fetal indications during labor) procedures. The collected parameters are listed in Table 1.

In Finland, a child with asthma diagnosed according to national current care guidelines[13] is entitled to receive reimbursement (currently 65%) for asthma medication costs. In small children, the diagnostic criteria of asthma include three to four episodes of wheezing bronchitis within one year. Data on asthma medication reimbursement were retrieved from the Social Insurance Institution database and data on inpatient (the whole study period) and outpatient (since 1998) visits to all public hospitals because of asthma and atopic dermatitis were gathered from the HDR. The International Classification of Disease 9th Revision (ICD-9) was used in 1991-1995 and 10th Revision (ICD-10) thereafter to detect diagnoses of asthma (J45, J46), atopic dermatitis (L20.0) and dermatitis due to ingested food (L27.2). The two latter were combined in analyses of atopic dermatitis. Register data were linked by means of a unique anonymized identification code.

The regional Ethics Committee approved the study. The registering organizations (the National Institute for Health and Welfare, the Social Insurance Institution and Statistics Finland) gave permission to use sensitive health data for research.

2.1 | Statistical methods

Differences between GA groups in categorical variables were tested by Pearson's chi-square test or Fisher's exact test and those in continuous variables by analysis of variance, Mann-Whitney *U*-test or Kruskal-Wallis test. To account for the number of deliveries of one mother, risk factors for asthma medication reimbursement and hospital visits due to atopic dermatitis were sought by Generalized Linear Mixed Model with an *lmer* function. The outcome variables were analyzed as

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 7 years of age (*N* = 965 203)

	Early-term 37^{+0}-38^{+6} wk (*n* = 181 667)	Full-term 39^{+0}-40^{+6} wk (*n* = 546 845)	Late-term 41^{+0}-41^{+6} wk (*n* = 189 373)	Post-term ≥42 wk (*n* = 47 318)
Mother				
Age, years, Mean (SD)	29.7 (5.4)	29.2 (5.3)	28.9 (5.2)	28.9 (5.3)
40 years or more, *n* (%)	6978 (3.8)	15 987 (2.9)	4604 (2.4)	1149 (2.4)
Smoking, *n* (%)	28 215 (15.5)	79 713 (14.6)	28 414 (15.0)	7752 (16.4)
First delivery, *n* (%)	71 578 (39.4)	214 262 (39.2)	81 677 (43.1)	25 057 (53.0)
Previous deliveries, Md (IQR)	1 (0-2)	1 (0-2)	1 (0-1)	1 (0-1)
Number of fetuses at birth, *n* (%)				
1	168 239 (92.6)	543 815 (99.4)	189 325 (100)	47 316 (100)
2 or more	13 428 (7.4)	3030 (0.6)	48 (0.0)	2 (0.0)
Birth hospital, *n* (%)				
University (level III)	59 972 (33.0)	167 964 (30.7)	55 942 (29.5)	15 592 (33.0)
Central (level II)	81 413 (44.8)	252 010 (46.1)	89 406 (47.2)	22 123 (46.8)
Other[a]	40 260 (22.2)	126 798 (23.2)	44 003 (23.2)	9593 (20.3)
Mode of delivery, *n* (%)				
Vaginal	139 104 (76.6)	473 812 (86.6)	169 151 (89.3)	38 875 (82.2)
Elective CS	26 168 (14.4)	39 932 (7.3)	3178 (1.7)	1092 (2.3)
Emergency CS	16, 259 (8.9)	32 642 (6.0)	16 04 (8.9)	7316 (15.5)
Newborn				
Boys, *n* (%)	96 029 (52.9)	275 714 (50,4)	94 257 (49.8)	24 211 (51.2)
Birth weight, g, Md (IQR)	3275 (2970-3590)	3600 (3310-3900)	3775 (3490-4080)	3850 (3560-4150)
Gestational weight, *n* (%)				
SGA	6346 (3.5)	8056 (1.5)	1958 (1.0)	302 (0.6)
AGA	167 611 (92.3)	523 946 (95.8)	182 891 (96.6)	45 522 (96.2)
LGA	7710 (4.2)	14 843 (2.7)	4524 (2.4)	1494 (3.2)
Apgar 1 min, Md (IQR)	9 (9-9)	9 (9-9)	9 (8-9)	9 (8-9)
Less than 4	1573 (0.9)	3609 (0.7)	1691 (0.9)	618 (1.3)
Resuscitation at birth, *n* (%)	655 (0.4)	1385 (0.3)	716 (0.4)	318 (0.7)
Admission to neonatal unit, *n* (%)	18 386 (10.1)	26 681 (4.9)	10 067 (5.3)	3231 (6.8)
Ventilator therapy, *n* (%)	827 (0.5)	1163 (0.2)	575 (0.3)	228 (0.5)
Antibiotic therapy in the first week of life, *n* (%)	4810 (2.6)	11 464 (2.1)	5626 (3.0)	1949 (4.1)

Statistical differences were tested by Pearson's chi-square test, Fisher's exact test, or the Kruskal-Wallis test. All *P*-values were <0.001.
AGA, appropriate for gestational age; CS, cesarean section; ET, early-term; FT, full-term; IQR, interquartile range; LGA, large for gestational age; LT, late-term; Md, median;
PT, post-term; SD, standard deviation; SGA, small for gestational age.
[a]Regional hospital, private hospital, health center, and home birth.

dichotomic variables. All explanatory variables were modeled as a fixed variable and the number of deliveries per mother was added as random effect. Results were presented as odds ratios (OR) with 95% confidence intervals (CI). Values of *P* less than 0.05 (two-tailed) were considered statistically significant. Variables with good validity in the registers were selected as independent variables, including maternal (age, smoking during pregnancy, primiparity, place of birth, and mode of delivery) and newborn (sex, gestational weight, ventilator or antibiotic therapy) characteristics. Categorization of variables is presented in Table 1. As a surrogate for severe atopic tendency, need of hospital visits due to atopic dermatitis by seven years of age was included in the multivariate model for asthma medication. The Generalized Linear Mixed Model analyses were performed with the Statistical Package R version 3.3.0 package lme4 (www.r-projcet.org) and the remaining analyses by using IBM SPSS Statistics version 23.0 software (IBM SPSS, Chicago, Illinois).

To study the relevance of the risk factors from public health and clinical point of view, we calculated population attributed risks (PAR, %) for the variables included in the multivariate models assessing the risk factors of asthma medication reimbursement and hospital visits

due to atopic dermatitis (yes/no). PAR provides the proportion of incidence of disease in the population that is due to exposure. This is the incidence of a disease that would be eliminated in the population if the exposure were removed. PAR was calculated as (f [OR − 1]) / (1 + f [OR − 1]), where f is the frequency of the risk factor in the population and OR is the OR for disease due to that exposure.

3 | RESULTS

Background characteristics are presented in Table 1. Birth by CS, admission to a neonatal unit and ventilator therapy were most common in the ET group. The frequency of elective CS was highest in the ET and lowest in the LT group. Emergency CS was most common in the PT group. Post-term infants were most often first-born and exposed to maternal smoking during pregnancy and to postnatal antibiotic therapy.

In mothers aged 40 years or more, smoking during pregnancy was less common (1894 (10.7%) vs 142 200 (15.0%), $P < 0.001$) and CS more common (4328 (24.5%) vs 139 163 (14.7%), $P < 0.001$) than in younger mothers.

In all, 36 210 (3.8%) children received asthma medication reimbursement. Hospital visits by seven years of age were reported in 46 636 (4.8%) children as a result of asthma and in 49 795 (5.2%) children as a result of atopic dermatitis. The frequencies of asthma medication reimbursement and hospital visits due to asthma were highest in the ET group, and hospital visits due to atopic dermatitis were most common in the PT group (Table 2).

The results of risk factor analyses regarding asthma medication reimbursement in the whole study population are presented in Table 3. Both in the uni- and multivariate analysis, ET birth was associated with an increased risk, and LT and PT births with decreased risks of asthma medication reimbursement, compared with FT birth. In the latter, the OR (95%) CI was 1.20 (1.17-1.23) in the ET group, 0.91 (0.89-0.93) in the LT group and 0.87 (0.83-0.92) in the PT group. According to PAR analyses, the most relevant risk factors of asthma from a population point of view were male sex, hospital visits due to atopic dermatitis (as a surrogate for atopic tendency), tobacco smoke exposure during pregnancy, ET birth, and birth by elective CS (Table 3). Maternal age of 40 years or more, being first-born or born in a level-II hospital were associated with a decreased risk of asthma.

The results of risk factor analyses regarding hospital visits due to atopic dermatitis in the whole study population are presented in Table 3. PT birth was associated with an increased risk (OR 1.10 (1.06-1.15) for hospital visits due to atopic dermatitis. According to PAR analyses, male sex, first delivery, birth in a level II hospital and birth by emergency CS were the most relevant risk factors for atopic dermatitis, whereas smoking during pregnancy and place of birth other than a level-III or level-II hospital seemed to decrease this risk (Table 3).

In the subgroup analysis among PT children (Table 4), no association was found between birth by CS and asthma medication reimbursement. Ventilator therapy seemed to increase the risk of asthma medication reimbursement. Birth by emergency CS emerged as a risk factor for hospital visits due to atopic dermatitis, whereas birth by elective CS did not (Table 4). Otherwise the results of the risk factor analyses in the PT group resembled those performed in the whole study population.

4 | DISCUSSION

In this large national register study on children born at ≥37 weeks of GA, we found a decreasing trend with GA in the frequency of asthma medication reimbursement and need of hospital visits due to asthma by seven years of age. Even after controling for several confounding factors, ET birth was associated with an increased risk of asthma,

TABLE 2 Reimbursement for asthma medication and hospital visits due to asthma and atopic dermatitis in infants born at ≥37 weeks of gestation in 1991-2008 and followed-up to 7 years of age (N = 965 203)

	Early-term 37^{+0}-38^{+6} wk (n = 181 667)	Full-term 39^{+0}-40^{+6} wk (n = 546 845)	Late-term 41^{+0}-41^{+6} wk (n = 189 373)	Post-term ≥42 wk (n = 47 318)	P
Reimbursement for asthma medication, n (%)	8166 (4.5)	20,180 (3.7)	6330 (3.3)	1534 (3.2)	<0.001
Age at 1st reimbursement, Md (IQR) in years	2.7 (1.6-4.3)	2.9 (1.8-4.5)	3.0 (1.8-4.6)	3.0 (1.8-4.5)	<0.001
Hospital visits due to asthma, n (%)	10 351 (5.7)	25 937 (4.7)	8372 (4.4)	1976 (4.2)	<0.001
Number of visits, Md (IQR)	4 (2-7)	3 (2-7)	3 (2-6)	3 (1-6)	0.001
Hospital visits due to atopic dermatitis, n (%)	9359 (5.2)	28 032 (5.1)	9836 (5.2)	2568 (5.4)	0.034
Number of visits, Md (IQR)	2 (1-5)	2 (1-5)	2 (1-5)	2 (1-5)	0.030
Age at 1st visit, Md (IQR) in years	1.1 (0.6-2.4)	1.1 (0.6-2.4)	1.1 (0.6-2.4)	1.0 (0.6-2.3)	<0.001

Statistical differences were tested by Pearson's chi-square test, Fisher's exact test, or the Kruskall-Wallis test.
IQR, interquartile range; ET, early-term; FT, full-term; LT, late-term; Md, median; PT, post-term.

TABLE 3 Risk factor analysis regarding asthma medication reimbursement (n = 36 210) and hospital visits due to atopic dermatitis (n = 49 795) by the age of 7 years in the whole study population in 1991-2008 (N = 965 203)

	Dependent variables							
	Asthma medication reimbursement n = 36 210/N = 965 203				Hospital visits due to atopic dermatitis n = 49 795/N = 965 203			
Independent variables	n	OR	95%CI	PAR (%)[a]	n	OR	95%CI	PAR (%)
Univariate analysis								
Gestational age group								
Early-term	8166	**1.23**	**1.20-1.26**		9359	1.06	0.98-1.03	
Full- term	20 180	1.00			28 032	1.00		
Late-term	6330	**0.91**	**0.88-0.93**		9836	1.02	1.00-1.05	
Post-term	1534	**0.89**	**0.85-0.93**		2568	**1.10**	**1.06-1.15**	
Multivariate analysis[b]								
Gestational age group								
Early-term	8166	**1.20**	**1.17-1.23**	3.63	9359	0.99	0.96-1.01	−0.19
Full-term	20 180	1.00			28 032	1.00		
Late-term	6330	**0.91**	**0.89-0.93**	−1.80	9836	1.02	0.99-1.04	0.39
Post-term	1534	**0.87**	**0.83-0.92**	−0.64	2568	**1.06**	**1.01-1.10**	0.29
Mother's age								
Less than 40 years	35 374	1.00			48 319	1.00		
40 years or more	836	**0.69**	**0.63-0.76**	−0.93	1476	1.02	0.95-1.09	0.06
Smoking								
No	29 229	1.00			42 297	1.00		
Yes	6193	**1.23**	**1.20-1.27**	3.32	6363	**0.85**	**0.82-0.87**	−2.29
First delivery								
No	22 283	1.00			29 841	1.00		
Yes	13 927	**0.95**	**0.92-0.98**	−2.08	19 954	**1.61**	**1.56-1.66**	19.9
Birth hospital								
University (level III)	11 904	1.00			15 384	1.00		
Central (level II)	15 512	**0.86**	**0.84-0.88**	−6.90	24 257	**1.08**	**1.06-1.10**	3.56
Other[c]	8792	1.02	0.99-1.05	0.46	10 146	**0.90**	**0.88-0.93**	−2.34
Mode of delivery								
Vaginal	30 184	1.00			41 700	1.00		
Elective CS	3106	**1.14**	**1.10-1.18**	1.01	3835	**1.08**	**1.05-1.12**	0.51
Emergency CS	2892	**1.06**	**1.01-1.10**	0.45	4225	**1.14**	**1.10-1.18**	1.05
Sex								
Girl	13 057	1.00			21 760	1.00		
Boy	23 153	**1.71**	**1.67-1.74**	26.5	28 035	**1.26**	**1.24-1.28**	11.7
Gestational weight								
SGA	683	1.04	0.97-1.12	0.07	796	**0.91**	**0.85-0.98**	−0.16
AGA	34 382	1.00			47 437	1.00		
LGA	1145	1.03	0.97-1.09	0.09	1562	1.04	0.99-1.09	0.12
Ventilator therapy								
No	36 067	1.00			49 631	1.00		
Yes	143	**1.24**	**1.07-1.43**	0.14	164	0.90	0.79-1.03	−0.03

(Continues)

TABLE 3 (Continued)

	Dependent variables							
	Asthma medication reimbursement *n* = 36 210/*N* = 965 203				Hospital visits due to atopic dermatitis *n* = 49 795/*N* = 965 203			
Independent variables	***n***	**OR**	**95%CI**	**PAR (%)[a]**	***n***	**OR**	**95%CI**	**PAR (%)**
Antibiotic therapy								
No	35 162	1.00			48 182	1.00		
Yes	1048	**1.09**	**1.02-1.16**	0.47	1613	**1.30**	**1.24-1.37**	0.74
Hospital visits due to atopic dermatitis					-		-	-
No	29 892	1.00			-	-	-	-
Yes	6318	**4.23**	**4.11-4.35**	14.3	-	-	-	-

Binomial linear mixed models with *lmer* function were used. The number of deliveries per mother was added as random effect.
CI, confidence interval; CS, cesarean section; AGA, appropriate for gestational age; LGA, large for gestational age; OR, odds ratio; PAR, population attributed risk; SGA, small for gestational age.
Statistically significant odds ratios and confidence intervals are bolded.
[a]PAR was calculated as (f [OR − 1]) / (1 + f [OR − 1]), where f is the frequency of the risk factor in the population and OR is the OR for disease due to that exposure.
[b]In multivariate analysis, all variables were entered simultaneously into the model.
[c]Regional hospital, private hospital, health center, home birth.

whereas LT and PT births appeared to decrease this risk. In contrast, PT birth emerged as a risk factor as regards hospital visits due to atopic dermatitis. From a population point of view, the most relevant risk factors of asthma were male sex, atopic tendency, tobacco smoke exposure during pregnancy, ET birth and elective CS, and those of atopic dermatitis male sex, first delivery, birth in a level II hospital, and birth by emergency CS.

Our finding of an increased risk of asthma in ET children is in line with previous reports.[1,7,8,10] In a large Swedish cohort of 1 100 826 children and young people (6-19 years old), ET children had an increased risk of inhaled corticosteroid use, evaluated by registered drug retrievals, compared with those born at 39-41 weeks of gestation.[1] Some other investigators have analyzed data based on parental reports[7] or questionnaires.[8] A hospital-based Finnish register study on 44 173 women delivering during a 10-year period revealed a negative association between asthma medication reimbursement and GA at birth of the offspring. The burden of asthma in children was particularly associated with deliveries at 37-38 weeks of gestation.[10] It may be that both spontaneous and iatrogenic preterm and ET deliveries have common causes and that there are similar exposures to postnatal treatments, such as those needed for neonatal respiratory problems.[14] The effect of smaller airway size at birth on the risk of asthma in preterm and ET infants seems to be less likely, because small-for-GA birth weight was not a significant predictor in multivariate analysis in our study.

According to our hypothesis, PT birth was associated with a decreased risk of childhood asthma, despite the increased frequency of neonatal respiratory problems defined as need of ventilator therapy in the PT group. Similar findings among LT[10] and PT[10,11,15] children have been reported previously. This seems to represent part of a continuum found in our previous study, where the risk of asthma decreased with increasing GA from very preterm birth to term,[3] possibly due to continuous intrauterine maturation of the airways.

In line with previous results,[4] post-maturity emerged as a predictor of atopic dermatitis. However, the PAR of PT birth for atopic dermatitis was low. The possible roles of maturation of the mucosal and skin barriers, and immunotolerance, are of interest.[4,5]

Supporting our findings, exposure to maternal prenatal smoking has been reported to increase the risk of wheezing or asthma among children aged six years or more.[16] Exposure to tobacco smoke has an effect on fetal lung development. It may alter the expression of susceptibility genes associated with respiratory diseases, predispose the mother to preterm delivery,[17] and increase the risk of early pulmonary problems of the infant. In our study, maternal smoking during pregnancy was associated with a decreased risk of atopic dermatitis in offspring. Tobacco smoke exposure during pregnancy might preclude sensitization through an immunosuppressive effect.[18] It was not possible to establish the degree of postnatal exposure to smoking in our population.

A meta-analysis has shown a 20% increase in asthma risk in childhood after birth via elective and emergency CS.[19] In one study, the risk of later asthma has been increased especially after elective CS,[20] in another after emergency CS.[21] Background factors related to the association between birth by CS and later asthma might be an increased risk of neonatal respiratory problems and effects on gut microbiota and the Th1/Th2 balance.[21] Lack of microbial exposure during labor results in delayed and altered colonization of the infant gut. In deliveries by elective CS, the membranes are usually intact, and the probability of colonization with vaginal bacteria is even smaller than in emergency CS. The maternal and fetal conditions leading to emergency CS might partly explain the association between CS and the risk of asthma.[21] Different levels of adaptive stress at the time of birth as well as altered epigenetic regulation might be further mechanisms connecting CS and development of the immune system.[22]

The association of the mode of delivery with the risk of atopic dermatitis is controversial. Some investigators have found no association,[23] whereas others have.[24] In our study, emergency CS in

TABLE 4 Multivariate risk factor analysis regarding asthma medication reimbursement (n = 1534) and hospital visits due to atopic dermatitis (n = 2568) by the age of 7 years among post-term children in 1991-2008 (N = 47 318)

	Dependent variables					
	Asthma medication reimbursement n = 1534/N = 47 318			Hospital visits due to atopic dermatitis n = 2568/N = 47 318		
Independent variables	***n***	**OR**	**95%CI**	***n***	**OR**	**95%CI**
Mother's age						
Less than 40 years	1515	1.00		2511	1.00	
40 years or more	19	**0.38**	**0.19-0.73**	57	0.92	0.65-1.30
Smoking						
No	1207	1.00		2146	1.00	
Yes	297	**1.29**	**1.13-1.47**	373	**0.88**	**0.78-0.98**
First delivery						
No	741	1.00		1163	1.00	
Yes	793	0.90	0.81-1.01	1405	**1.81**	**1.55-2.11**
Birth hospital						
University (level III)	538	1.00		844	1.00	
Central (level II)	675	**0.87**	**0.77-0.98**	1218	1.03	0.94-1.12
Other[a]	321	0.97	0.84-1.12	506	0.97	0.87-1.09
Mode of delivery						
Vaginal	1241	1.00		2046	1.00	
Elective CS	36	1.03	0.73-1.45	57	1.02	0.78-1.33
Emergency CS	256	1.06	0.92-1.22	463	**1.19**	**1.07-1.33**
Sex						
Girl	543	1.00		1099	1.00	
Boy	991	**1.72**	**1.55-1.92**	1469	**1.28**	**1.18-1.39**
Gestational weight						
SGA	9	0.87	0.45-1.71	14	0.85	0.50-1.44
AGA	1476	1.00		2488	1.00	
LGA	49	1.04	0.77-1.39	66	0.78	0.61-1.01
Ventilator therapy						
No	1520	1.00		2556	1.00	
Yes	14	**1.78**	**1.00-3.18**	12	0.75	0.42-1.34
Antibiotic therapy						
No	1454	1.00		2428	1.00	
Yes	80	1.12	0.88-1.44	140	**1.32**	**1.10-1.59**
Hospital visits due to atopic dermatitis						
No	1233	1.00		-	-	-
Yes	301	**4.59**	**4.02-5.25**	-	-	-

In multivariate analysis, all variables were entered simultaneously into the model. Binomial linear mixed models with *lmer* function were used. The number of deliveries per mother was added as random effect.

Statistically significant ($P < 0.05$) *odds ratios and confidence intervals are bolded.*

CI, confidence interval; CS, cesarean section; AGA, appropriate for gestational age; LGA, large for gestational age; OR, odds ratio; SGA, small for gestational age.

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

particular emerged as a risk factor of atopic dermatitis in the PT group, supporting the role of mediators other than the effect on the microbiota between CS and the occurrence of atopic dermatitis. The smaller number of infants in the PT group may account for some differences between this group and others.

Higher maternal age has been associated with compromised neonatal outcome[25,26] and, supporting our results, a higher rate of CS.[26] Interestingly, in our study maternal age of 40 years or more was associated with a decreased risk of asthma. Smoking during pregnancy was less common and delivery by CS more frequent among these older

mothers, but the protective effect remained after controlling for these factors in the analyses. A negative association has been suggested between the number of siblings and atopic asthma or dermatitis.[27] In our analyses adjusted for atopic tendency, first-born status emerged protective as regards asthma medication reimbursement. This may be associated with fewer infection contacts compared with those with more siblings. Supporting previous results,[28] first-born children presented with a greater risk of atopic dermatitis. A reduced anti-inflammatory profile in T-cells has been found in first-born children at birth, possibly contributing to the later development of immune-mediated diseases by increasing overall immune reactivity.[29]

In line with the results of another study, male sex increased the risk of asthma[30] as well as the risk of atopic dermatitis. Children born SGA seemed to carry less risk of atopic dermatitis. An association between anthropometric parameters at birth and later atopic tendency has been suggested, but the findings concerning atopic dermatitis have been inconsistent.[31]

In a Finnish register study, very premature infants treated in or transferred to level-II hospitals from level-III hospitals presented with a similar occurrence of asthma at five years of age.[32] We found a decreased risk of asthma in children born in level-II hospitals. More risk-associated deliveries are treated in level-III hospitals. The risk of hospital visits due to atopic dermatitis was higher in infants born in level-II facilities, but lower in other places of birth compared with level-III hospitals, despite adjustment for several perinatal and neonatal factors. The reason for this association is not clear.

Antibiotic therapy during pregnancy[33] and exposure to broad-spectrum antibiotics during the first week of life[30] have been described as risk factors of childhood asthma. The comparability of our results with those reported previously is limited by the fact that we had access to data on antibiotic treatment during the first week of life but not on maternal antibiotic therapy or later antibiotic courses given to the infant. We found an association, between antibiotic therapy and both asthma medication reimbursement and atopic dermatitis, suggesting long-lasting effects of neonatal antibiotic exposure. However, this risk factor was not very relevant from a population point of view, having a PAR below one per cent. Antibiotics may be more often prescribed to infants who are admitted to a neonatal ward and to those whose mothers have signs of other infections. Suggested mechanisms mediating the effects of antibiotics include changes in the gut microbiota and alteration of the immunological balance towards the Th2 model of allergic asthma.[34]

Differences in recording practices in different hospitals and regions are a common limitation in register studies. However, the Finnish health information system is based on national registers of high quality and with good coverage.[35–37] The study population was substantial. In Finland, asthma diagnoses given by a pediatrician are required for all children to qualify for medication reimbursement.[13] The Social Insurance Institution database is held as a valid source of prevalence data.[38] The overall prevalence of asthma medication reimbursement and hospital visits due to asthma by seven years of age in our study cohort corresponds to the expected rate in Finland.[13] No data were obtained on ethnic background, parental asthma or atopy, indications for CS, psychosocial factors, breastfeeding or environmental conditions. Reliable data on socioeconomic status were also missing, since it is difficult to determine such a status for young women of childbearing age. We had, however, information on maternal smoking, which strongly correlates with socioeconomic status in Finland.[39] Because of our study design, children born in the latest years of the study period had shorter follow-up times than those born in earlier years. The youngest were less than one year of age at the time of first hospital visit due to asthma. Due to difficulties in ascertaining the diagnosis of asthma in infants, we decided to use asthma medication reimbursement, a parameter based on national criteria, as the main outcome measure in the risk factor analyses. The median age at first reimbursement for asthma medication was three years or less in all GA groups. Hospital visits due to atopic dermatitis were used as a surrogate for severe atopic tendency in the risk-factor analyses for asthma. Mild atopic dermatitis is usually treated in the primary health care system. In our study, cases with atopic dermatitis were identified through hospital visits only, thus representing severe disease.

5 | CONCLUSIONS

Early-term birth was associated with an increased risk of asthma by seven years of age compared with full-term birth. Late- and post-term births appeared to be associated with a decreased risk of asthma. Counseling against smoking during pregnancy and strict indications for elective CS might be important tools in preventing later asthma in offspring. Post-term birth and especially emergency CS were associated with an increased risk of atopic dermatitis, referring to the importance of optimal timing of delivery after due date.

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CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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PUBLICATION IV

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

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