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Respiratory Morbidity, Lung Function, and Health-related Quality of Life in the 30-year Follow-up

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ABSTRACT:

Lower respiratory tract infections (LRTI´s) in childhood have been associated with respiratory morbidity and lung function disorders in adulthood, but so far the prospective data about the adulthood outcome of children with early childhood LRTI´s is scarce.

In 1981-1982, 83 bronchiolitis and 44 pneumonia patients who were hospitalized at less than 2 years of age were enrolled in the study. Viral etiology of LRTI was determined from nasopharyngeal secretion (NPS) samples during hospitalization. Blood eosinophils were measured at hospital admission and on convalescence. In 2010, 48 former bronchiolitis patients, 22 former pneumonia patients, and 138 population controls participated in the clinical study between the ages of 28-31 years. Saint George's Respiratory Questionnaire (SGRQ) was used as a health-related quality of life (HRQoL) assessment tool. Participants underwent two-week peak expiratory flow (PEF) monitoring, spirometry with bronchodilatation test (BD), and skin prick testing. Asthma was defined as doctor-diagnosed or self-reported to determine the certainty of the diagnosis.

Asthma prevalence between the ages of 28-31 years was 31-35% in the bronchiolitis group, 9-23% in the pneumonia group, and 11-14% in the control group, with a significant difference between the bronchiolitis and control groups. Asthma prevalence after respiratory syncytial virus (RSV) LRTI was increased, if wheezing was present during LRTI. Forced vital capacity (FVC%), forced expiratory volume in one second (FEV1%), and FEV1/FVC-ratio% were all reduced in bronchiolitis and FEV1% in pneumonia patients, all before and after BD. These findings demonstrated irreversible airway obstruction in adulthood. Eosinophilia outside the infection in early childhood predicted asthma in adulthood, whereas low eosinophil count during bronchiolitis protected from asthma. Parental history of asthma and eosinophilia during bronchiolitis were significant predictors for impaired lung function in adulthood. SGRQ scores were higher in former bronchiolitis and pneumonia patients compared to controls, indicating lower HRQoL in adulthood.

The current study demonstrates that increased risk for asthma continues up to the age of 28-31 years after early childhood bronchiolitis and after wheezing RSV LRTI. Irreversible airway obstruction is present in adulthood after bronchiolitis. Repeated wheezing and eosinophilia outside the infection predict asthma, whereas eosinopenia during infection protects from asthma in adulthood. Family history of asthma and eosinophilia during bronchiolitis predict lung function impairment in adulthood. Decreased HRQoL is present between the ages of 28-31 years after bronchiolitis and pneumonia.

National Library of Medicine Classification: QW 168.P2; WA 30; WC 202; WF 102; WF 140; WF 141; WF 553; WF 600

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TIIVISTELMÄ:

Lapsuusiän alahengitystieinfektiot (AHI) on yhdistetty hengityselinsairauksiin ja keuhkojen toimintahäiriöihin aikuisiällä, mutta toistaiseksi prospektiivinen tutkimusnäyttö varhaislapsuudessa alahengitystieinfektioon sairastuneiden ennusteesta aikuisuudessa on vähäistä.

Tutkimukseen otettiin mukaan 83 bronkioliittiin ja 44 keuhkokuumeeseen alle 2-vuotiaana sairastunutta lasta, jotka otettiin sairaalahoitoon vuosina 1981–82. AHI:n aiheuttajaviruksia tutkittiin nenänielun imulimanäytteestä sairaalaan otettaessa. Veren eosinofiilit määritettiin AHI:n aikana ja sen jälkeen. Vuonna 2010 48 entistä bronkioliittipotilasta, 22 keuhkokuumepotilasta ja 138 väestöverrokkia kutsuttiin kliiniseen seurantatutkimukseen 28–31 vuoden iässä. Saint Georgen sairaalan Keuhkosairauksia Koskevaa Kyselylomaketta käytettiin elämänlaatumittarina. Tutkimuksen yhteydessä toteutettiin tutkittaville 2 viikon PEF-seuranta, spirometiatutkimus bronkodilataatiokokeella sekä ihopistokokeet. Astma määritettiin lääkärin diagnosoimaksi tai itse raportoiduksi riippuen määritelmän tiukkuudesta.

Astman vallitsevuus 28–31 vuoden iässä oli bronkioliittiryhmässä 31–35%, keuhkokuumeryhmässä 9–23% ja verrokeilla 11–15%, ollen bronkioliittiryhmässä merkittävästi verrokkeja korkeampi. RSV:n aiheuttaman AHI:n jälkeen astman prevalenssi oli verrokkeja korkeampi, jos infektion aikana oli todettu hengityksen vinkunaa. Uloshengityksen nopea vitaalikapasiteetti (FVC%), uloshengityksen sekuntikapasiteetti (FEV1%) ja FEV1/FVC%-suhde olivat kaikki matalammat bronkioliitin jälkeen ja FEV1% keuhkokuumeen jälkeen sekä ennen että jälkeen bronkodilataatiokokeen, paljastaen palautumattoman hengitysteiden ahtautumisen aikuisiällä. Eosinofilia infektion jälkeen ennusti astmaa 28–31 vuoden iässä, kun taas matala eosinofiilitaso infektion aikana näytti suojaavan astmalta. Vanhempien astma ja eosinofilia AHI:n aikana ennustivat keuhkojen toimintamuutoksia aikuisuudessa. Korkeat SGRQ pisteet osoittivat bronkioliitti- ja keuhkokuumeryhmissä matalampaa elämänlaatua aikuisuudessa verrattuna kontrolliryhmään.

Tutkimuksemme osoittaa, että astmariski on kohonnut 28–31-vuotiaana varhaislapsuuden bronkioliitin jälkeen sekä vinkuvan RSV AHI:n jälkeen. Bronkioliitin jälkeen palautumattomaan hengitysteiden ahtautumiseen sopivat muutokset voidaan todeta aikuisiässä. Eosinofilia infektion jälkeen ennustaa astmaa, kun taas matalat eosinofiilit infektion aikana olivat suojaava tekijä. Vanhempien astma ja eosinofilia bronkioliitin aikana ennustivat keuhkojen toimintahäiriötä aikuisuudessa. Bronkioliitti ja keuhkokuumepotilailla on verrokkeja matalampi elämänlaatu 28–31-vuotiaana.

Luokitus: QW 168.P2; WA 30; WC 202; WF 102; WF 140; WF 141; WF 553; WF 600
Yleinen Suomalainen asiasanasto: Astma; Bronkioliitti; Elämänlaatu; Keuhkoahtaumatauti; Keuhkokuume; Riskitekijät; RS-virus; Seurantatutkimus; Spirometria

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Kuopio, October 2015

Katri Backman

List of the original publications

This dissertation is based on the following original publications:

I Backman K, Piippo-Savolainen E, Ollikainen H, Koskela H, Korppi M. Irreversible airway obstruction in adulthood after bronchiolitis in infancy: evidence from a 30-year follow-up study. *Respir Med 108: 218-223, 2014.*

II Backman K, Piippo-Savolainen E, Ollikainen H, Koskela H, Korppi M. Increased asthma risk and impaired quality of life after bronchiolitis or pneumonia in infancy. *Pediatr Pulmonol 49: 318-325, 2014.*

III Backman K, Piippo-Savolainen E, Ollikainen H, Koskela H, Korppi M. Adults face increased asthma risk after infant RSV bronchiolitis and reduced respiratory health-related quality of life after RSV pneumonia. *Acta Paediatr 103: 850-855, 2014.*

IV Backman K, Nuolivirta K, Ollikainen H, Korppi M, Piippo-Savolainen E. Low eosinophils during bronchiolitis in infancy are associated with lower risk of adulthood asthma. *Pediatr Allergy Immunol 26: 668-673, 2015.*

Contents

Abbreviations

AR	Airway responsiveness
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
CAP	Community acquired pneumonia
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
ERS	European Respiratory Society
EVW	Episodic viral wheeze
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
FVS	Flow volume spirometry
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQoL	Health-related quality of life
HRV	Human rhinovirus
ICS	Inhaled Chorticosteroid
IgE	Immunogobulin E
IL	Interleukin
ITQOL	Infant Toddler Quality of Life Questionnaire
IUGR	Intra uterine growth retardation
LLN	Lower limit of normality
LRTI	Lower respiratory tract infection
MTW	Multiple trigger wheeze
PEF	Peak expiratory flow
Post-BD	Post-bronchodilator
Pre-BD	Pre-bronchodilator
RSV	Respiratory syncytial virus
SD	Standard deviation

TH	T-helper
WHO	World Health Organization

1 Introduction

Bronchiolitis is an acute, viral, lower respiratory tract infection that presents in early childhood (Nagakumar & Doull 2012, Oymar et al. 2014, Zorc & Hall 2010, Tapiainen et al. 2015). It is a common disease with symptoms varying from mild rhinorrhea and wheezing, treated at home, to severe breathing difficulties that require hospital care (Oymar et al. 2014, Ralston et al. 2014, Mecklin et al. 2014). Bronchiolitis is usually considered as the first wheezing episode in young children (Jartti et al. 2009). However wheezing bronchitis is a common symptom also in older children and these conditions have a significant overlap (Brand et al. 2008).

Lower respiratory tract infections (LRTI) like bronchiolitis and pneumonia in early childhood have been previously associated with increased respiratory morbidity like asthma (Piippo-Savolainen & Korppi 2008, Stern et al. 2008, Chan et al. 2015) and chronic obstructive pulmonary disease (COPD) (de Marco et al. 2011) in adulthood.

Wheezing is commonly associated with early childhood viral LRTI. About 30% of all children experience wheezing during the first years of their lives (Martinez et al. 1995, Brand et al. 2014, Henderson et al. 2008). It is also a heterogenous condition, and a majority of children grow out of the wheezing tendency as they get older (Martinez et al. 1995, Henderson et al. 2008). However, in others, wheezing at an early age may be the first sign of persistent respiratory morbidity. These children continue to wheeze persistently and eventually may develop asthma later in life (Martinez et al. 1995, Henderson et al. 2008, Piippo-Savolainen et al. 2004, Goksor et al. 2006, Sigurs et al. 2010). During the first years of life, the prevalence of wheezing is very high after hospitalization for severe bronchiolitis (Korppi et al. 1993, Kuikka et al. 1994). However, the tendency for wheezing and the asthma prevalence decline at school age down to 15-40%, before increasing again in early adulthood (Piippo-Savolainen et al. 2004, Goksor et al. 2006, Sigurs et al. 2010, Sigurs et al. 2000, Sigurs et al. 2005, Korppi et al. 1994, Kotaniemi-Syrjanen et al. 2002, Hyvarinen et al. 2005).

Respiratory syncytial virus (RSV) is the most common causative virus associated with lower respiratory tract infections like bronchiolitis and pneumonia in young children (Jartti et al. 2004, Miller et al. 2013, Stockman et al. 2012, Garcia et al. 2010). However, the more recently discovered human rhinovirus (HRV) comprises a considerable proportion of bronchiolitis cases (Miller et al. 2013, Midulla et al. 2010, Miron et al. 2010, Mansbach et al. 2012) and has also been associated with pneumonia in childhood (Cilla et al. 2008). Viral etiology of initial LRTI in early childhood seems to be a determinant for the subsequent outcome in later childhood and even in adulthood. RSV etiology of bronchiolitis has been associated with increased risk for asthma in childhood, with decreasing tendency in relation to increasing age (Regnier & Huels 2013). However, HRV etiology of initial bronchiolitis is associated with an even greater risk for asthma compared to RSV, probably due to associations with atopy and heredity for asthma (Kotaniemi-Syrjanen et al. 2003, Carroll et al. 2012, Jartti & Korppi 2011, Turunen et al. 2014).

Because of the heterogenity of early childhood wheezing disorders, it has been a challenge to distinguish those children who are about to develop chronic respiratory disease and to target possible preventive actions. Huge efforts have been made to identify risk factors that could predict the risk for the development of chronic respiratory morbidity in wheezing children (Piippo-Savolainen et al. 2006, Castro-Rodriguez et al. 2000, Kurukulaaratchy et al. 2003, Hafkamp-de Groen et al. 2013).

Immunoglobulin E (IgE) -mediated atopy (Martinez et al. 1995, Piippo-Savolainen et al. 2006, Kusel et al. 2007, Kusel et al. 2012, Jackson et al. 2012) and blood eosinophilia (Kotaniemi-Syrjanen et al. 2002, Midulla et al. 2014, Ehlenfield et al. 2000) have been demonstrated to be important risk factors for the subsequent development of asthma in children with early childhood wheezing. Eosinopenia, whether during infection or persistently,

seems to protect from the development of asthma (Karakoc et al. 2002, Martinez et al. 1998). Other factors associated with the development of asthma after early childhood wheezing have included the following: family history of asthma (Goksor et al. 2006, Sigurs et al. 2010, Piippo-Savolainen et al. 2006), maternal smoking during pregnancy (Goksor et al. 2007) or passive smoking in infancy (Goksor et al. 2007), and the recurrence of wheezing symptoms in early childhood (Piippo-Savolainen et al. 2006).

In line with increased clinical respiratory morbidity, impaired lung function has also been described to be present in childhood after early childhood bronchiolitis (Sigurs et al. 2005, Kotaniemi-Syrjanen et al. 2008, Hyvarinen et al. 2007) and pneumonia (Castro-Rodriguez et al. 1999). In previous studies, lung function tests have consistently demonstrated signs of irreversible obstruction at early adult age after early childhood bronchiolitis (Piippo-Savolainen et al. 2004, Sigurs et al. 2010, Sigurs et al. 2005, Goksor et al. 2008). However, there is an ongoing debate whether this lung function reduction is caused by viral LRTI or is merely a sign of premorbid lung function impairment, which has been described to associate with increased susceptibility to early LRTI´s (Martinez et al. 1988, Martinez et al. 1991, Tager et al. 1993, Young et al. 2000, Dezateux et al. 1999, Murray et al. 2002).

In addition to lung function impairment, decreased quality of life has also been described 9 months and 3 years after bronchiolitis (Rolfsjord et al. 2015, Bont et al. 2004) and after pneumonia in the short-term (Shoham et al. 2005). However, studies in this field are scarce, and there are no previous studies on HRQoL after early childhood LRTIs including follow-ups to adolescence or adulthood.

In conclusion, children with early childhood LRTIs form a heterogenous group with different outcomes in later life. Despite the active research activity in the field during the last decades, more efforts are needed to clarify the risk factors and the long-term outcome of these children, preferably in a prospective long-term setting.

We have followed up with a group of study subjects who were hospitalized for bronchiolitis or pneumonia before the age of 2 years in 1981-1982 (Piippo-Savolainen et al. 2004, Korppi et al. 1993, Kuikka et al. 1994, Korppi et al. 1994, Korppi et al. 1986). This study is the longest on-going prospective study about the long-term effects of early childhood LRTIs. Our aim was to evaluate the outcome of children with the history of early childhood LRTI in terms of asthma prevalence, health-related quality of life, and lung function in adulthood, with the special focus on RSV etiology of the initial LRTI in infancy.

2 Review of the Literature

2.1 BRONCHIOLITIS AND PNEUMONIA IN EARLY CHILDHOOD

2.1.1 Bronchiolitis and wheezing in early childhood

Bronchiolitis is an acute, viral, lower respiratory tract infection that presents in early childhood (Nagakumar & Doull 2012, Oymar et al. 2014, Zorc & Hall 2010, Tapiainen et al. 2015). It is a self-limited disease, characterized by acute inflammation of small airways that leads to edema, mucus production, and necrosis of airway epithelium (Nagakumar & Doull 2012, Ralston et al. 2014). There is no uniform definition of diagnostic criteria for bronchiolitis, but the most common clinical features and findings include rhinitis, breathing difficulties, cough, poor feeding, irritability, wheezing and/or crepitations on auscultation, and even apnoea in young babies (Oymar et al. 2014, Ralston et al. 2014, Mecklin et al. 2014). The severity of the disease varies from mild respiratory symptoms that are treated at home to severe respiratory distress that requires hospital care and even respiratory support.

Bronchiolitis is a disease with a high disease burden, since about 30-40% of children develop bronchiolitis before the age of 2 years (Zorc & Hall 2010, Ralston et al. 2014). One out of ten bronchiolitis patients are admitted to the hospital because of the disease (Nagakumar & Doull 2012, Smyth & Openshaw 2006). However the need for hospitalization is more common in young age groups (Murray et al. 2014, Deshpande & Northern 2003), since over 90% of the hospitalized cases are under 12 months, and over 60% are under 6 months old (Deshpande & Northern 2003, Scottish Intercollegiate Guideline Network 2012).

Bronchiolitis is usually defined as the first wheezing episode in childhood (Jartti et al. 2009). Several studies, and also current care guidelines, have used the age limit of 24 months for the diagnosis (Ralston et al. 2014, Scottish Intercollegiate Guideline Network 2012). However, recent European studies have applied the age limit of 12 months (Zorc & Hall 2010, Mecklin et al. 2014, Smyth & Openshaw 2006, Henderson et al. 2005), and this age limit is also in clinical use in Finland.

There is a significant heterogenity in the definition of acute bronchiolitis in terms of age but also in terms of symptoms. This is crucial when we try to understand the differences in outcome studies of early childhood bronchiolitis. Mostly in the United Kingdom and Australia, the definition of acute bronchiolitis includes evidence of coryza, cough, airway obstruction, and crepitations on auscultation with or without wheezing (Elphick et al. 2007, Everard 2006). In North America and many other countries, the term “acute bronchiolitis” includes the evidence of audible wheezing (Elphick et al. 2007, Everard 2006).

Evidently, RSV is the predominant virus associated with LRTIs, especially bronchiolitis and pneumonia, in children under 1 year of age (Jartti et al. 2004, Miller et al. 2013, Stockman et al. 2012, Garcia et al. 2010). Depending on the ages of enrolled patients, study design, and definition of bronchiolitis, RSV has comprised 40-80% of bronchiolitis cases needing hospitalization (Jartti et al. 2004, Miller et al. 2013, Midulla et al. 2010, Miron et al. 2010, Mansbach et al. 2012, Calvo et al. 2010). The primary infection occurs in young children, and re-infections are common at any age (Miller et al. 2013, Calvo et al. 2010, Bezerra et al. 2011). RSV etiology of bronchiolitis has also been associated with more severe disease compared to other viruses (Miller et al. 2013, Garcia et al. 2010, Calvo et al. 2010, Bezerra et al. 2011, Hervas et al. 2012). In temperate climates, RSV occurs as annual outbreaks usually between late autumn and early spring (Jartti et al. 2004, Hervas et al. 2012, Hall et al. 2013).

Human rhinoviruses are the most common respiratory pathogens that cause upper respiratory infections in all age groups (Jartti et al. 2012). However, increasing evidence

suggests that rhonoviruses also comprise 10-30 % of bronchiolitis cases needing hospitalization (Miller et al. 2013, Midulla et al. 2010, Miron et al. 2010, Mansbach et al. 2012). In previous studies, children diagnosed with HRV bronchiolitis have been older and more likely atopic compared to children diagnosed with RSV bronchiolitis (Miller et al. 2013, Korppi et al. 2004).

Human metapneumovirus has been found in 2-8% of bronchiolitis patients and human bocavirus in 5-8% (Jartti et al. 2004, Miller et al. 2013, Midulla et al. 2010, Miron et al. 2010, Calvo et al. 2010, Bezerra et al. 2011, Soderlund-Venermo et al. 2009, Jartti et al. 2002, Schuster & Williams 2013). Metapneumovirus and bocavirus occur in older children compared to RSV (Calvo et al. 2010, Schuster & Williams 2013). In a Spanish study, half of the patients under 2 years old with bocavirus bronchiolitis were under 12 months old, and half of the metapneumovirus bronchiolitis patients were under 6 months old, while half of the children with RSV bronchiolitis were under 3 months old (Calvo et al. 2010). Co-infections of viruses in different combinations are also common (Calvo et al. 2010, Bezerra et al. 2011). Other viruses detected in bronchiolitis patients have been adenovirus, coronaviruses, influenza A and B viruses, and parainfluenzaviruses, especially type 3.

2.1.2 Community acquired pneumonia in early childhood

Pneumonia is an infection of lung tissue that can be caused by numerous viruses and bacteria (Stein & Marostica 2007). Community acquired pneumonia (CAP) can be defined as the presence of signs and symtoms of pneumonia in a previously healthy child due to an infection that has been acquired outside the hospital (Harris et al. 2011).

The most common clinical symptoms and findings of pneumonia are tachypnoea, fever, and cough (Stein & Marostica 2007, Don et al. 2010). Clinical signs and symptoms of viral and bacterial pneumonia are highly variable and overlap (Ruuskanen et al. 2011, Cevey-Macherel et al. 2009). Fever higher than 38·5°C, tachypnea, and chest recessions are suggestive of bacterial pneumonia. In comparison, young age, wheezing, fever less than 38·5°C, and striking chest recessions are suggestive of a viral cause (Harris et al. 2011, Ruuskanen et al. 2011).

Pneumonia can be diagnosed on a clinical basis (Harris et al. 2011). In addition to indicative symptoms of pneumonia, fine end-inspiratory cracles on auscultation can be present. Currently, the gold standard of pneumonia diagnosis is the presence of lung infiltration on a chest radiograph, even though in clinical practice the diagnosis can be made without imaging (Don et al. 2010). Interstitial infiltrates apparent on a chest radiograph are generally believed to suggest a viral cause of pneumonia, and alveolar infiltrates indicate a bacterial cause; but, these findings overlap (Ruuskanen et al. 2011).

The most common pathogen in CAP is *Streptococcus pneumoniae* (Juven et al. 2000), even though the introduction of pneumococcal vaccines has dramatically decreased pneumococcal pneumonia in those countries where the vaccine has been universally introduced (Weil-Olivier et al. 2012). *Chlamydophila pneumoniae* and Mycoplasma pneumoniae are common pathogens in older children (Juven et al. 2000, Don et al. 2005). Viral pneumonia is the most common in children under 2 years of age, whereas at school age bacterial etiology predominates (Ruuskanen et al. 2011, Juven et al. 2000, Pavia 2013). Mixed viral-viral and viral-bacterial infections are common (Cevey-Macherel et al. 2009, Juven et al. 2000, Don et al. 2005).

In a Spanish study, the total prevalence of viral infection was 67% in chidren under 3 years of age with CAP. RSV was found in 20%, rhinovirus in 14%, bocavirus in 14%, metapneumovirus in 12%, and parainfluenza viruses in 11% of children with CAP. Other agents detected were influenza, corona, and adenoviruses (Cilla et al. 2008).

RSV is the most common virus that causes CAP in children (Cilla et al. 2008, Juven et al. 2000, Pavia 2013, Heiskanen-Kosma et al. 1998, Korppi 2002), and it is also the most common virus found in viral-bacterial mixed infections in children (Heiskanen-Kosma et al. 1998). RSV accounts for almost 10% of all pneumonias in children at less than 2 years of age

(Deshpande & Northern 2003). The proportion of RSV etiology increses during RSV epidemic, accounting for 25-30% of pneumonias in children at less than 1 year of age (Deshpande & Northern 2003). The differential diagnosis of RSV bronchiolitis and pneumonia is challenging due to similar clinical symptoms being presented. So, it has also been suggested that RSV pneumonia is part of the same clinical entity than bronchiolitis (Piippo-Savolainen 2006).

2.2 WHEEZING, ASTHMA AND COPD

2.2.1 Wheezing phenotypes in preschool children

Wheezing can be described as a high-pitched sound with a musical quality emitting from the chest during expiration (Elphick et al. 2001). A wheezing breathing sound is a result of the narrowing of the intrathoracic airways and expiratory flow limitation that can be a result of exposure to multiple triggers such as tobacco smoke, allergens or exercise (Brand et al. 2008).

Definitions of wheezing used in children aged less than 6 years are very heterogenous (Brand et al. 2008). The term bronchiolitis is usually used for the first wheezing episode in the youngest age group (Jartti et al. 2009, Brand et al. 2008), although the age limit of the definition varies (Zorc & Hall 2010, Ralston et al. 2014, Scottish Intercollegiate Guideline Network 2012). However, wheezing is also a common symptom in older children (Brand et al. 2008, Saglani 2013). Terms like "wheezing bronchitis", "wheezy bronchitis, "virus-associated wheezing", "viral-induced wheezing" and "asthmatic bronchitis" have been used to describe wheezing in children (Tapiainen et al. 2015, Saglani 2013, Wennergren 2003). Thus, wheezing in children under three years of age covers two clinical conditions: wheezing bronchitis and bronchiolitis (Tapiainen et al. 2015). However, in previous literature, both of these conditions are often include in the same trials (Tapiainen et al. 2015). Thus, bronchiolitis and wheezing bronchitis have a significant overlap (Brand et al. 2008).

Wheezing during childhood is a common condition since approximately 30% of all children experience wheezing before the age of three years (Martinez et al. 1995, Brand et al. 2014, Henderson et al. 2008). A majority wheezing children become asymptomatic by the age of 8 years (Martinez et al. 1995, Henderson et al. 2008), while others continue to wheeze and are prone to develop chronic asthma. So, early childhood wheezers form a heterogenous group of children with different types of risk factors, triggers, and severity of wheezing as well as different kinds of sequelae from childhood to old age. Several attempts have been made to classify these wheezing children in order to identify the different phenotypes of wheezing that might predict outcomes in childhood and even in adulthood.

In the 1990´s, the Tucson Children´s Respiratory Study introduced a classification for wheezing children that was based on the onset and duration of wheezing symptoms (Martinez et al. 1995). The majority of children (60%) who experienced wheezing during the first three years of life did not exhibit wheezing at the age of six. These children were classified as early transient wheezers. These transient wheezers form a group of children who have wheezing symtoms at a very early age during viral infections but no longer later in life (Martinez et al. 1995, Taussig et al. 2003). In the Tucson study, these children were more likely to have mothers who smoked and lower levels of lung function (i.e., maximal expiratory flow at functional residual capacity, VMax FRC) as infants compared to those children who never wheezed. However, these children did not present factors associated with allergic diathesis, such as family history of asthma, high IgE levels, atopic dermatitis, or rhinitis apart from colds (Martinez et al. 1995, Taussig et al. 2003).

Children who experienced wheezing at the age of 6 years were classified as non-atopic or atopic wheezers. Those children, who were classified as non-atopic wheezers, still experienced wheezing at the age of 6 years, but they did not have any atopic disease. Atopic wheezers were divided into two groups: early atopic wheezers who had early symptoms that

continued at the age of 6 years and late atopic wheezers who did not have symtoms at early age but experienced wheezing at the age of six years. Both groups were equally sensitized to aeroallergens at the age of 6 years. However, early atopic wheezers had the lowest lung function levels of all groups at the ages of 6 and 11 years and highest IgE levels at the same age, respectively (Taussig et al. 2003).

The Tucson classification of wheezing phenotypes has been criticized to be of less importance in a clinical practice due to its retrospective view. In 2008, the European Respiratory Society (ERS) introduced a new classification of wheezing phenotypes that were based on the temporal pattern of wheezing: Episodic (viral) wheeze (EVW) and multiple trigger wheeze (MTW) (Brand et al. 2008). EVW is defined as discrete wheezing episodes that occur usually during viral respiratory infections. MTW wheeze, however, is defined as wheezing that shows discrete exacerbations but also with symptoms between these episodes (Brand et al. 2008).

This guideline was widely accepted into clinical use, but it was also criticized because it does not take the severity or frequency of wheezing episodes into account. In 2014, a consensus group published a new report that summarized new evidence and proposed some modifications. The report agreed that the severity and frequency of wheezing symptoms are stronger predictors of long term outcome than distinction of EVW and MTW (Brand et al. 2014).

Asthma often has its origins in childhood (Stern et al. 2008, Wenzel 2012), with half of the adults who have asthma experiencing their first symptoms during childhood (Simpson & Sheikh 2010). In children, however, the diagnosis of asthma can be difficult due to a high prevalence of wheezing in young age groups. Previous classification of different wheezing phenotypes has attempted to recognize those wheezing children who will develop asthma in the future. However, because of significant overlap of phenotypes and shifting from one class to another, the development of chronic asthma is still hard to predict in clinical practice.

2.2.2 Characteristics of Asthma

According to the Global Initiative for Asthma (GINA) 2014 report, asthma is a heterogenous disease, usually characterized by chronic airway inflammation (Global Initiative for Asthma 2014). It is diagnosed based on the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity. In addition to asthma presumptive symtoms the diagnosis of asthma in over 6-years-old children and adults requires evidence of variable expiratory airflow limitation. Airway hyperreactivity to different stimuli, *e.g.*, allergens, exercise, or viral respiratory infections is often associated with asthma (Global Initiative for Asthma 2014).

Asthma is one of the most common chronic diseases in the world and is recognized as a major public health problem throughout the world (Masoli et al. 2004). In the cross-sectional World Health Survey, implemented by the WHO, the global prevalence of asthma was approximately 4% (To et al. 2012). However, the prevalence of asthma varied as much as 21-fold amongst the 70 countries studied (To et al. 2012). In Finnish studies, the prevalence of asthma has been 7% among school schildren (Hugg et al. 2008), 3% in 16 year old adolescents, and 5% in 32 year old adults (Huurre et al. 2004). In studies also including older adults, the prevalence of physician-diagnosed asthma in Finland has been 8-9% (Pallasaho et al. 2011, Laatikainen et al. 2011).

Asthma is diagnosed based on respiratory symptoms suggestive for asthma as well as based on documented findings of variable airflow limitation (Global Initiative for Asthma 2014). Characteristic changes in flow-volume spirometry (FVS) are considered as the most reliable indicators of variable airflow limitation. Increase in FEV1 by 200ml and 12% in adults, or 12% in children from the baseline after bronchodilator administration is considered the diagnostic for asthma (Global Initiative for Asthma 2014). In addition, the average daily diurnal variability of 10% in adults and 13% in children in peak expiratory flow (PEF) values during the two-week PEF follow-up are considered diagnostics for astma (Global Initiative for Asthma

2014). In Finnish current care guidelines PEF daily diurnal variability of 20% or increase by 15% from the baseline after bronchodilator administration are considered diagnostic for asthma (Asthma: Current Care Guidelines 2012). A variable airflow limitation may also be present in exercise test or in bronchial challenge test. Other possible diagnostic finding in FVS is a significant increase in FEV1 after treatment with anti-inflammatory medication (Global Initiative for Asthma 2014).

Asthma is a phenotypically heterogeneous disorder that results from a combination of various genetic and environmental factors (Wenzel 2012, Bel 2004). Due to this heterogeneity, patients with asthma can be divided into different phenotypes,(Wenzel 2012, Bel 2004, de Nijs et al. 2013).

The best-described asthma phenotype is allergic asthma, which often begins during childhood (Global Initiative for Asthma 2014, Bel 2004, de Nijs et al. 2013). Although the majority of children with wheezing during their preschool years have a favorable outcome, some of these children show ongoing airway inflammation and eventually develop asthma that may persist up to adulthood (Stern et al. 2008, Bel 2004, de Nijs et al. 2013). Early-onset allergic asthma is characterized by T-helper 2 (TH2) -type immunological responses, increased immunoglobulin E (IgE) production and allergic diseases like atopic eczema or allergic rhinitis (Wenzel 2012, Bel 2004, de Nijs et al. 2013). However, low levels of IgE and a lack of responsiveness to corticosteroids in some children with asthma suggest that not all early-onset asthma is associated with allergies (Wenzel 2012). Some children with early-onset asthma have a remission during puberty, but develop symptoms again in early adulthood (Stern et al. 2008, Bel 2004).

There is also a population of patients who develop their first asthma symptoms in adulthood (Wenzel 2012, de Nijs et al. 2013). In contrast to early-onset asthma, adult-onset asthma is less commonly associated with allergies (Wenzel 2012, Tuomisto et al. 2015). The prognosis of adult-onset asthma is not as favorable as cases of early-onset asthma (Tuomisto et al. 2015). Phenotypes such as late-onset eosinophilic, exercise-induced, obesity-related and neutrophilic have been suggested (Wenzel 2012, Tuomisto et al. 2015). Increasing evidence suggests that even though asthma is a single clinical diagnosis, the term "asthma" instead describes a group of clinical symptoms with variable expiratory airflow limitation (Wenzel 2012).

2.2.3 COPD

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality in the world, although the defined prevalence varies depending on the population studied, differences in study methods and the prevalence of risk factors such as tobacco smoke (Global Initiative for Chronic Obstructive Lung Disease 2014, Celli et al. 2004, Zeng et al. 2012). Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a common preventable and treatable disease. It is characterized by persistent airflow limitation and is usually progressive (Global Initiative for Chronic Obstructive Lung Disease 2014, Celli et al. 2004). COPD is further characterized by chronic inflammatory responses in the airways and the lung that are caused by inhaled noxious particles or gases, usually tobacco smoke (Global Initiative for Chronic Obstructive Lung Disease 2014, Celli et al. 2004).

Diagnosis of COPD is based on typical clinical symptoms, which are dyspnea, chronic cough and sputum production in patients who have a history of exposure to COPD risk factors (Global Initiative for Chronic Obstructive Lung Disease 2014, Chronic obstructive pulmonary disease: National Clinical Guideline Centre 2014). In addition to these symptoms, COPD diagnosis requires the presence of persistent airflow limitation, confirmed by spirometry (Global Initiative for Chronic Obstructive Lung Disease 2014, Chronic obstructive pulmonary disease: National Clinical Guideline Centre 2014). According to GOLD standards, spirometric criterion for persistent airflow limitation, and therefore COPD, is a fixed ratio of post-

bronchodilator FEV1/FVC below 0.70 (Global Initiative for Chronic Obstructive Lung Disease 2014). However, using this fixed cut-off limit can lead to an underdiagnosis of young adults and an overdiagnosis of older people (Swanney et al. 2008, Pellegrino et al. 2005). Therfore, American Thoracic Society (ATS) and ERS have proposed that classification should be based on a FEV1/FVC ratio below the lower limit of normality (LLN), i.e., more than 1.64 standard deviations (SD) below the predicted level (5th percentile), for the specific age group, sex and height (Pellegrino et al. 2005).

Tobacco smoking has long been recognized as the single most important risk factor for COPD (Global Initiative for Chronic Obstructive Lung Disease 2014, Zeng et al. 2012, Landau 2008). However, recent data have demonstrated that non-smokers comprise a substantial proportion of individuals with COPD (Zeng et al. 2012, Lamprecht et al. 2011). In addition to tobacco smoke, genetic susceptibility and exposure to other inhaled particles have been shown to increase the risk for COPD (Global Initiative for Chronic Obstructive Lung Disease 2014, Zeng et al. 2012).

Asthma has also been recognized as a risk factor for development of COPD (Global Initiative for Chronic Obstructive Lung Disease 2014, Lamprecht et al. 2011). A classical sign of asthma is evidence of variable airflow limitation in the spirometry test (Global Initiative for Asthma 2014). However, after 40 years of age, persistent airflow limitation, which is characteristic of COPD, becomes more common in the population with respiratory symptoms (Global Initiative for Asthma 2014, Global Initiative for Chronic Obstructive Lung Disease 2014). Asthma and COPD, therefore, have a significant overlap, and a high proportion of adult patients who have a chronic respiratory disease present symptoms and findings from both diseases (Global Initiative for Asthma 2014, Global Initiative for Chronic Obstructive Lung Disease 2014).

It has also been established that early childhood respiratory infections, like bronchiolitis and pneumonia, are associated with an increased risk for COPD later in life (de Marco et al. 2011, Barker et al. 1991). In addition, any other factor that hampers lung growth during gestation or childhood can lead to impaired lung function in adulthood and increase the risk for COPD in the future (de Marco et al. 2011, Global Initiative for Chronic Obstructive Lung Disease 2014, Barker et al. 1991).

2.3 COHORT STUDIES EXPLORING ASTHMA DEVELOPMENT AFTER EARLY CHILDHOOD LRTI AND WHEEZING

The link between early childhood respiratory infections and later respiratory morbidity has been an issue of interest during recent decades, and an association has been found between LRTIs in early childhood and later respiratory problems, such as asthma or COPD in adulthood (de Marco et al. 2011, Piippo-Savolainen et al. 2004, Svanes et al. 2010, Goksor et al. 2015).

2.3.1 Birth cohort studies

Over 130 birth cohort studies focusing on the development of asthma and allergies have been initiated over the past 30 years (Bousquet et al. 2014). Most of these have not continued follow-ups beyond childhood ages. In this thesis, we present prospective birth cohort studies that have continued from childhood to adolescence or adulthood and have also focused on early lung function and early respiratory infections and their association with later outcome.

The Tucson Children's Respiratory Study

This prospective, long-term birth cohort study was started in the beginning of the 1980´s. The purpose of the study was to determine the risk factors for acute lower respiratory tract illnesses in early childhood and for chronic obstructive airway diseases in later life. A total of 1246

newborns were enrolled into the study, and 176 infants underwent lung function testing and maximal flow at functional residual capacity (V'maxFRC) soon after birth (Martinez et al. 1995, Martinez et al. 1988). Lung function testing was repeated at the ages of 6, 11, 16, and 22 years (Taussig et al. 2003, Stern et al. 2007, Morgan et al. 2005). During the first three years of life, a careful collection of data on respiratory symptoms and respiratory infections was collected. Serum IgE levels were measured at birth and at the ages of 9 months and 6 years. The latest follow-up of the subjects was published at the age of 22 years (Stern et al. 2008). The Tucson birth cohort is thus far the longest published prospective birth cohort study focused on the sequelae of early respiratory illnesses (Stern et al. 2008, Taussig et al. 2003, Stern et al. 2007).

One of the main objectives of the study has been to explore how lung function in infancy is associated with morbidity and lung function later in life. The Tucson study demonstrated that low V'maxFRC in infancy is associated with an increased risk of LRTI in infancy (Martinez et al. 1991). In addition, infant lung function correlated with all measurements of airway function at ages 11–22 years. This demonstrates that lung function trajectories are determined early in life (Stern et al. 2007).

In the Tucson birth cohort, 33% of all children experienced wheezing during LRTI before the age of three years, and almost 50% of all children had experienced wheezing at some stage of their lives before the age of 6 years (Martinez et al. 1995). For the first time, the Tucson birth cohort demonstrated the fact that had been suspected for a long time on a clinical basis: about 60% of children who experience wheezing along with respiratory infection before the age of 3 years grow out of this tendency by the age of 6 years (Martinez et al. 1995). Later it was demonstrated that the majority of these transient wheezers remain asymptomatic at the ages of 11, 16, and 22 years of age (Stern et al. 2008, Taussig et al. 2003, Morgan et al. 2005). However, age at the time of the initial LRTI is an importat predictive factor, since the younger the child has wheezing, the more unlikely will be the tendency for wheezing to continue later. More than 80% of children who wheeze during the first year of life do not wheeze later in life, whereas 60% of those wheezing during the second year and 30% to 40% of those wheezing during the third year do not wheeze in later life (Taussig et al. 2003). Even though in the majority of children wheezing is a benign symptom, 40% of children with wheezing before the age of 3 years continue to wheeze later in childhood as well (Martinez et al. 1995, Taussig et al. 2003). In the Tucson birth cohort, 46 % of children with persistent wheezing had been given a diagnosis of asthma by the age of six years (Martinez et al. 1995). So, in a proportion of children, early wheezing is a sign of developing asthma (Martinez et al. 1995). The Tucson birth cohort demonstrated that the wheezing patterns established at the age of 6 persist up to the age of 16 and 22 years (Stern et al. 2008, Morgan et al. 2005). In over 70% of cases with current asthma at the age of 22 years, the first wheezing episode had happened before the age of 6 years (Stern et al. 2008). The results of the Tucson birth cohort study documented, at least to the age of 22, that adulthood asthma, including asthma with early adulthood onset, has its origin in early childhood (Stern et al. 2008).

The Melbourne Asthma Study

The Melbourne Asthma study followed 484 study subjects from a 1957 birth cohort up to the age of 50 years (Phelan et al. 2002, Tai et al. 2014). Children with a past history of wheezing were recruited at the age of 7 years and an early childhood history was collected retrospectively. The original study group was divided into 5 groups: no wheezing history control, mild wheezy bronchitis (less that 5 episodes), wheezy bronchitis (5 or more episodes), asthma (wheezing not related to respiratory tract infections) and severe asthma (persistent symptoms, FEV1/FVC-ratio 50% or less) (Phelan et al. 2002, Grad & Morgan 2012). The subjects were subsequently reviewed at ages of 10, 14, 21, 28, 35, 42 and 50 years (Phelan et al. 2002, Tai et al. 2014). During the course of the study, it became evident that children with wheezy bronchitis had a very favorable outcome, whereas only a small proportion of those with

persistent symptoms, i.e., asthma or severe asthma, achieved remission of symptoms. Approximately 60% of children with wheezy or mild wheezy bronchitis were symptom free at the age of 42 years, whereas only 30% of study subjects with asthma and 10% with severe asthma had a remission of symptoms (Horak et al. 2003). There were not significant changes in the asthma remission rates at the age of 50 years compared to age 42 years; 64% of those with wheezy or mild wheezy bronchitis, 47% of those with persistent asthma and 15% of those with severe asthma in childhood were symptom free, while the rest were diagnosed as having asthma (Tai et al. 2014). A majority of the study subjects in the wheezy bronchitis group reached remission before the age of 10 years (Tai et al. 2014). Severe childhood asthma, female sex and childhood hay fever were predictors of asthma at the age of 50 years (Tai et al. 2014).

At the beginning of the study, subjects with wheezy bronchitis had a comparable FEV1 and FEV1/FVC-ratio to controls. However the FEV1 and FEV1/FVC-ratio were lower in children with asthma. Lung function was established by the age of 10, and the differences between groups did not increase significantly even though symptoms persisted up to the age of 50 years (Tai et al. 2014). Despite the ongoing symptoms in asthma groups, no further decline in the FEV1/FVC ratio was seen at the age of 50 years (Tai et al. 2014).

Perth infant asthma follow-up (PIAF)

The Australian Perth birth cohort of 253 babies has been followed up from birth up to the age of 18 years (Young et al. 1991, Turner et al. 2002, Mullane et al. 2013). Lung function test (V'maxFRC) and bronchial hyperreactivity were studied at the ages of 1, 6 and 12 months (Young et al. 1991, Turner et al. 2009). Study subjects were followed up annually by questionnaires up to the age of 6 years (Turner et al. 2002). At 11 years of age, children underwent an assessment that included spirometry, airway responsiveness to histamine, and skin prick testing (Turner et al. 2002). Lung function testing was repeated at the age of 18 years (Mullane et al. 2013). This study has mainly concentrated on evaluating the impact of early lung function on future morbidity. Half of the 160 children who completed the early childhood follow-up had wheezing during the first 2 years of their lives (Young et al. 2000). Maternal antenatal smoking was associated with wheezing during the first year of life and the persistence of wheezing up to the age of 2 years (Young et al. 2000). Maternal asthma was associated only with wheezing during the first year of life (Young et al. 2000). The Perth birth cohort demonstrated the association between increased bronchial hyperreactivity at the age of 12 months and childhood asthma at the age of 11 years (Turner et al. 2009). Among the 116 subjects assessed at both 12 months and 11 years, asthma was present in 27% of children with increased bronchial hyperreactivity at both ages and 0% in those who did not have increased bronchial hyperreactivity at either age (Turner et al. 2009). Bronchial hyperreactivity that persisted from infancy to childhood was associated with male gender, early respiratory illness, and maternal smoking and asthma (Turner et al. 2009). Low lung function soon after birth was associated with wheezing in infancy (Young et al. 2000), at the age of 4 years (Turner et al. 2002) and the age of 18 years (Mullane et al. 2013).

Copenhagen Prospective Studies on Asthma in Childhood (COPSAC)

COPSAC is a prospective birth cohort of 411 children who were enrolled during the first month of life (Bisgaard 2004). All children were born to mothers with asthma. Lung function testing was completed in 403 neonates and again by age 7 in 317 children (Bisgaard et al. 2012). It was demonstrated that lung function abnormalities increase the risk of bronchiolitis in young children (Chawes et al. 2012) and asthma in older children (Bisgaard et al. 2012). The harmful effect of environmental tobacco smoke exposure to lung function development in childhood was again demonstrated (Bisgaard et al. 2012). The COPSAC group recenty demonstrated that asthma at the age of 7 was associated with the number of respiratory infections, but not the specific viral trigger (Bonnelykke et al. 2015). In addition duration of wheezy episodes in early

childhood was found to be independent of the microbial trigger (Carlsson et al. 2015). These findings have underlined the importance of host factors in the development of asthma in wheezing children instead of specific viral triggers (Bonnelykke et al. 2015, Carlsson et al. 2015).

The Environment and Childhood Asthma birth cohort study (ECA)
This Norwegian birth cohort study was established in 1992 in Norway. This study included 3754 children, of whom 802 had lung function measured at birth and at 10 and 16 years. Data has been obtained so far at the 2, 10, and 16 year investigations (Lodrup Carlsen et al. 1997, Lodrup Carlsen et al. 1999, Lodrup Carlsen et al. 2006, Hovland et al. 2013, Lodrup Carlsen et al. 2014). The risk factors for impaired lung function early in life were studied. It was found that maternal smoking during pregnancy was associated with low lung function in newborn babies (Lodrup Carlsen et al. 1997). In addition, it was demonstrated that low lung function, measured soon after birth, is a risk factor for LRTIs in infancy and obstructive airway disease later in childhood (Lodrup Carlsen et al. 1999). The natural course of early childhood wheezing until adolescence was studied, and children with recurrent bronchial obstruction before the age of 2 years were demonstrated to have reduced lung function and more frequent bronchial hyperreactivity at 16 years compared with those with no wheezing or asthma (Hovland et al. 2013). In addition, only one third of the children with recurrent bronchial obstruction by 2 years of age were found to be free from asthma medication, asthma symptoms, or bronchial hyperreactivity by 16 years of age (Hovland et al. 2013).

Children, Allergy, Milieu, Stockholm, Epidemiological Survey (Bamse)
The Bamse cohort was collected between 1994 and 1996 in Stockholm, Sweden. Four thousand eighty nine children were enrolled soon after birth, and the cohort has been followed-up by repeated questionnaires from early childhood up to the age of 16 years. Questionnaires were administered at 1, 2, 4, 8, 12, and 16 years of age. At the ages of 4 and 8 years, children were also invited to a clinical examination (Hallberg et al. 2010, Ballardini et al. 2012, Ekstrom et al. 2015). FVS was conducted at the ages of 8 and 16 years. At the age of 8 years, 9% of the cohort were classified as having transient asthma (symtoms only before the age of 4 years), 3% had late-onset asthma (symtoms only after 4 years of age) and 4% had persistent asthma (symtoms at 4 years and 8 years of age) (Hallberg et al. 2010). Children with persistent asthma had significantly reduced lung function at the age of 8 years and had more atopic diseases like eczema or rhinitis. At the age of 16 years, all asthma groups had a lower FEV_1 and FEV_1/FVC-ratio compared to controls with no wheezing history (Hallberg et al. 2015). The lowest lung function values were seen for the early persistent asthma group (Hallberg et al. 2015). Early childhood factors such as maternal body mass index, maternal smoking, gender, and exposure to air pollution and their association with respiratory morbidity up to the age of 16 were studied (Ekstrom et al. 2015, Lannero et al. 2006, Melen et al. 2004, Gruzieva et al. 2013).

2.3.2 Prospective studies on viral LRTI

There are number of post-bronchiolitis cohort studies currently taking place in the world. However, only four prospective post-bronchiolitis studies, started in the 1980's and 1990´s including two in Sweden and two in Finland, have continued beyond puberty (Sigurs et al. 2010, Goksor et al. 2015, Ruotsalainen et al. 2013, Ruotsalainen et al. 2010a). Thus far, two of the cohorts have been followed up to between the ages of 15-18 years (Sigurs et al. 2010, Ruotsalainen et al. 2013), and two cohorts have been followed up to between the ages of 25-29 years (Goksor et al. 2015, Ruotsalainen et al. 2013). In these studies, bronchiolitis in infancy has been unanimously associated with increased risk of asthma up to adult age (Sigurs et al. 2010, Goksor et al. 2015, Ruotsalainen et al. 2013, Ruotsalainen et al. 2010a).

1980's Finnish bronchiolitis and pneumonia study

The follow-up of the 1980's Finnish bronhiolitis and pneumonia study (Kuopio, Finland) has continued for 30 years and has included several clinical follow-ups. It is thus far the longest active post-bronchiolitis study in the world.

During admission to hospital in 1981-1982, viral or *Mycoplasma pneumoniae* etiology was found in 71/127 bronchiolitis and pneumonia patients under 2 years of age. RSV was responsible for 51/127 admissions (Korppi et al. 1986). At the age of 1-2 years, subsequent wheezing was present in 76% of bronchiolitis patients and in 9% of pneumonia patients (Korppi et al. 1993). At the age if 2-3 years, the respective figures were 58% in bronchiolitis patients and 16% in pneumonia patients (Korppi et al. 1993). Atopic eczema and elevated IgE-levels during admission to hospital were more common in children with bronchiolitis compared to pneumonia patients (Korppi et al. 1993).

At the age of 4.5-6 years, the prevalence of asthma was 25% in former bronchiolitis patients, and the results confirmed that children with atopy were at a greater risk for developing asthma later in childhood than non-atopics (Kuikka et al. 1994).

At the 8-10 year follow-up, asthma risk was increased after bronchiolitis in infancy; asthma was present in 15% of bronhiolitis patients, 7% of pneumonia patients, and 2% of controls (Korppi et al. 1994). Bronchial hyperreactivity in the methacoline inhalation challenge and bronchial obstruction in spirometry were significantly more common in bronchiolitis and pneumonia patients compared to controls.

In the posted questionnaire between the ages of 13-16 years, the prevalence of asthma was 14% in the original bronchiolitis patents and 12% in the pneumonia patients. By the less strict asthma criteria, the prevalence of asthma was 23% and 15% in the two groups, respectively (Hyvarinen et al. 2005).

In the 20-year follow-up of the cohort, current physician-diagnosed asthma was present in 30% of the bronchiolitis patients, in 15% of the pneumonia patients, and in 11% of the controls (Piippo-Savolainen et al. 2004). Bronchiolitis patients had asthma significantly more often than controls. By less strict asthma criteria, the corresponding figures were 41% in bronchiolitis patients, 24% in pneumonia patients, and 11% in controls. In lung function testing, lung function abnormalities were present in former bronchiolitis patients more often compared to controls (Piippo-Savolainen et al. 2004).

In the latest follow-up conducted as a postal questionnaire study at the age of 26-29 years, doctor-diagnosed asthma was present in 20% and self-reported asthma was present in 41% of former bronchiolitis patients. Asthma prevalence was significantly higher by both definitions compared to controls (Ruotsalainen et al. 2010a).

Swedish post-bronchiolitis study

One hundred and one children, aged less than 2 years and hospitalized for bronchiolitis in 1984-1985, were enrolled in the study ((Wennergren et al. 1992). At re-investigation, when the children were 3-6 years old, 53% were free from asthmatic symptoms, 33% had mild asthma, and 8% and 6% had moderate and severe asthma, respectively (Wennergren et al. 1992). At the age of 10 years, 20% had mild asthma, 8% and 2% had moderate and severe asthma, respectively, and the majority of the study subjects were symptom-free (Wennergren et al. 1997). The histamine challenge test was initiated at the age of 10 years, and bronchial hyperreactivity correlated with the clinical disease. However, no association was seen between the RSV etiology of the disease and asthma. This cohort has been reinvestigated between the ages of 17-20 years (Goksor et al. 2006) and between the ages of 25-28 years (Goksor et al. 2015). Between the ages of 17-20, 43% of the subjects had asthma, and 27% were classified as having mild asthma and and 16% had moderate or severe asthma, respectively. The risk of having asthma was 4 times higher in the bronchiolitis cohort compared to controls. Between the ages of 25-28 years, current doctor-diagnosed asthma was present in 37% of the study subjects, and 50%

of these had moderate or severe asthma compared to 7% asthma prevalence in controls (Goksor et al. 2015).

Swedish post-RSV bronchiolitis study

A Swedish RSV bronchiolitis cohort was collected in 1989-90 (Sigurs et al. 1995). Forty seven children hospitalized for bronchiolitis before the age of one year, and 93 controls attended the follow-up studies at the ages of 1 and 3 years. Allergen specific IgE for foods and inhalant allergens was measured at the second follow-up. Later, the study subjects were invited to follow-up at the ages of 7, 13, and 18 years (Sigurs et al. 2010, Sigurs et al. 2000, Sigurs et al. 2005). FVS with the bronchodilatation test and the dry air challenge test were performed at the ages of 13 and 18 years.

At the age of 3 years, 23% of study subjects in the RSV group had asthma compared to 1% in controls. (Sigurs et al. 1995) In addition, 40% had experienced wheezing during the preceding year compared to 9% in controls. RSV bronchiolitis was a risk factor for asthma even without a family history of asthma. However, the combination of asthma heredity and bronchiolitis further increased asthma risk significantly. Atopy was also significantly more common in RSV bronchiolitis patients compared to controls.

At the age of 7, the prevalence of current asthma was 23% in RSV bronchiolitis patients and 2% in controls (Sigurs et al. 2000). Prevalence of current asthma/recurrent wheezing was also increased at the ages of 13 (43%) and 18 (39%) years compared to controls with respective figures of 8% and 9% (Sigurs et al. 2010, Sigurs et al. 2005). Allergy has been significantly more common after RSV bronchiolitis compared to controls in every follow-up of this cohort, but this finding has not been confirmed in other studies. FVS before and after bronchodilatation was conducted at the ages of 13 and 18 years, and the main finding was a mild bronchial obstruction before and after the bronchodilatation test (Sigurs et al. 2010, Sigurs et al. 2005).

1990's Finnish viral wheezing study

For this study, 100 children hospitalized for bronchiolitis in 1992-93 were recruited at the age of less than 2 years (Reijonen & Korppi 1998). Seven viruses were studied by antigen detection from the nasopharyngeal aspirates (NPA), and later PCR was used for detection of rhinoviruses. Five clinical follow-up visits were organized during the first 3 years after the hospitalization, and later this cohort has been re-investigated at the mean ages of 7, 12, and 16.5 years (Kotaniemi-Syrjanen et al. 2002, Ruotsalainen et al. 2013, Reijonen & Korppi 1998, Reijonen et al. 2000, Hyvarinen et al. 2005). At the ages of 1 and 3 years, 49% and 52%, respectively, of wheezing children had experienced more than 2 wheezing episodes and were diagnosed as having asthma (Reijonen & Korppi 1998). At 7 and 11 years of age, 40% of study the subjects had asthma (Kotaniemi-Syrjanen et al. 2002, Hyvarinen et al. 2005)).

At the latest follow-up between the ages of 15-18 years, 30% of the study subjects had doctor-diagnosed asthma and 64% had self-reported asthma, which was significantly more compared to 5% and 11% in population-based controls, respectively (Ruotsalainen et al. 2013). Self-reported asthma was more common in former rhinovirus bronchiolitis patients compared to RSV bronchiolitis patients.

2.3.3 Pneumonia and asthma

Studies investigating the association with early childhood pneumonia and asthma are scarce compared to studies about bronchiolitis, wheezing, or asthma. In the Tucson birth cohort, pneumonia before 3 years of age was associated with a 3-fold risk of asthma at the age of 6 and 11 years compared to children with no respiratory infections in early childhood (Castro-Rodriguez et al. 1999). In the recent follow-up of the same cohort, pneumonia was associated with increased asthma risk at the age of 26 (Chan et al. 2015). However, the results of the

previous follow-up of the current cohort at the age of 18-20 years are controversial since asthma prevalence after early childhood pneumonia was not increased compared to controls (Piippo-Savolainen et al. 2004).

Table 1. Prevalence of recurrent wheezing or asthma after hospitalization for bronchiolitis in four prospective post-bronhiolitis cohorts, followed-up to adulthood.

Age	Asthma prevalence after hospitalization for bronchiolitis			
	Finnish post-bronchiolitis study	**Swedish post-bronchiolitis study**	**Swedish post-RSV bronchiolitis study**	**Finnish viral wheezing study**
1-2#	76%[1]			49%[15]
2-3#	58%[1]		63%[11]	52%[16]
3-6	25%[2]	47%[7]		
7-10	15%[3]	30%[8]	23%[12]	40%[17]
11-16	14%[4]		43%[13]	40%[18]
17-20	30%[5]	43%[9]	39%[14]	30% (15-18 yrs)[19]
25-29	20%[6]	37%[10]		

#Recurrent wheezing

References: [1]Korppi 1993, [2]Kuikka 1994, [3]Korppi 1994, [4]Hyvärinen 2005, [5]Piippo-Savolainen 2004, [6]Ruotsalainen 2010, [7]Wennergren 1992, [8]Wennergren 1997, [9]Goksör 2006, [10]Goksör 2014, [11]Sigurs 1995, [12]Sigurs 2000, [13]Sigurs 2005, [14]Sigurs 2010, [15]Reijonen 1998, [16]Reijonen 2000, [17]Kotaniemi-Syrjänen 2002, [18]Hyvärinen 2005, [19]Ruotsalainen 2013

2.3.4 Summary

Early childhood wheezing, usually associated with viral LRTI, is very common, and approximately 30% of children experience wheezing before the age of 3 years (Martinez et al. 1995). Birth cohorts that continued through to adulthood have demonstrated that the outcome of early childhood wheezing and asthma is determined during the childhood years. Children with persistent or severe wheezing continue to have persistent symptoms or relapse in adolescence or adulthood (Stern et al. 2008, Phelan et al. 2002, Tai et al. 2014, Hovland et al. 2013). However, early childhood intermittent wheezing during respiratory infections has a more favorable outcome, since approximately 60% of these children achieve remission later in life (Stern et al. 2008, Martinez et al. 1995, Tai et al. 2014).

The prevalence of asthma after hospitalization for early childhood LRTI in different ages is summarized in Table 1. At the age of 2-3 years, the prevalence of repeated wheezing after hospitalization for bronchiolitis has been 52-63% in post-bronchiolitis studies (Korppi et al. 1993, Sigurs et al. 1995, Reijonen et al. 2000) (Table 1). However, the asthma prevalence declines at school age, being 15-40% at the age of 7-10 years (Sigurs et al. 2000, Korppi et al. 1994, Kotaniemi-Syrjanen et al. 2002, Wennergren et al. 1997) (Table 1). In adolescence, the prevalence of asthma increases again, and between the ages of 17-20 years, the prevalence of athma rises to 30-43% (Piippo-Savolainen et al. 2004, Goksor et al. 2006, Sigurs et al. 2010). Later in adulthood, the prevalence of asthma seems to obtain a steady state between 20-37% (Goksor et al. 2015, Ruotsalainen et al. 2010a). Increased risk for asthma after early childhood pneumonia has been

demonstrated up to the age of 11 years (Castro-Rodriguez et al. 1999), but in adulthood the outcome in regards to asthma is controversial (Chan et al. 2015, Piippo-Savolainen et al. 2004).

2.4 FACTORS ASSOCIATED WITH THE DEVELOPMENT OF ASTHMA AFTER EARLY CHILDHOOD WHEEZING

The development of asthma in wheezing children is complex and not fully understood. A number of factors contribute to an individual´s risk to develop asthma. These can be classified as host factors including genetic features, obesity and sex, and environmental factors including allergens, respiratory infections, microbial effects, medication, exposure to tobacco smoke, and air pollution (Global Initiative for Asthma 2014). The development of asthma probably requires multiple exposures that can in genetically predisposed individuals interact and result in the development of asthma (Turner & Devereux 2007).

2.4.1 Virus or the host factors: Do viral LRTIs cause asthma?

As mentioned earlier, RSV is undoubtedly the most important virus causing LRTI in young children (Jartti et al. 2004, Miller et al. 2013, Stockman et al. 2012, Garcia et al. 2010). RSV LRTI has been found to be a risk factor for wheezing as well as asthma in childhood in several studies (Henderson et al. 2005, Sigurs 2002, Martinez 2003, Escobar et al. 2013, Fjaerli et al. 2005, Schauer et al. 2002, Singleton et al. 2003, James et al. 2013). In the Tucson birth cohort, children with RSV LRTI in infancy were 3 to 5 times more likely to wheeze at the age of 6 years compared to those with no LRTI (Taussig et al. 2003, Stein et al. 1999). However, this association decreased with age and turned insignificant by the age of 13 years (Taussig et al. 2003, Stein et al. 1999). In a recent systematic review and meta-analysis, it was demonstrated that RSV hospitalizations were associated with a significantly increased risk of wheezing and asthma in childhood (odds ratio: 3.84; 95%CI: 3.23–4.58) (Regnier & Huels 2013). However, as presented in the Tucson birth cohort, the association between RSV hospitalization and asthma decreased with age at the follow-up (Regnier & Huels 2013). In adulthood this association has been more controversial; some studies demonstrate increased risk for asthma in adulthood (Sigurs et al. 2010), while others do not (Korppi et al. 2004).

There is strong epidemiological evidence that RSV increases wheezing symptoms and prevalence of asthma during childhood. However, these studies have not described the mechanism for this association. It has been demonstrated that RSV causes cytopathic effects in the airway epithelium of the growing lung, leading to extensive damage of the airway epithelium (Rossi & Colin 2015, Piedimonte 2001, Jafri et al. 2004, You et al. 2006, Becnel et al. 2005). In addition, experimental studies based on animal models have demonstrated that RSV is able to induce neurogenic inflammation that results in long-term airway hyperreactivity, a characteristic of asthma (Rossi & Colin 2015, Piedimonte 2001, Jafri et al. 2004). It has been suggested RSV could act as a direct inducer of childhood wheezing and asthma by these mechanisms (Rossi & Colin 2015). However, there are enoumous gaps in our knowledge about the causality of these associations.

Viruses other than RSV have been described to associate with an even greater risk of asthma compared to RSV-induced wheezing (Kotaniemi-Syrjanen et al. 2003, Ruotsalainen et al. 2013, Reijonen et al. 2000, Piippo-Savolainen et al. 2007, Mikalsen et al. 2012). In a 7-year follow-up of a Finnish viral wheezing cohort, it was for the first time demonstrated that rhinovirus etiology of bronchiolitis is associated with a 10-fold increase in the risk of asthma compared to those hospitalized for RSV bronchiolitis (Kotaniemi-Syrjanen et al. 2003). Later, several studies have confirmed this finding, and evidently rhinovirus-induced wheezing in early childhood is a risk factor for future asthma (Kotaniemi-Syrjanen et al. 2003, Jartti & Korppi

2011, Jartti & Korppi 2011, Jackson et al. 2008, Lehtinen et al. 2007); also, this association seems to continue at least up to the ages of 15-18 years (Ruotsalainen et al. 2013). More specifically, it was demonstrated in the 1990's Finnish viral wheezing study that risk for asthma is increased between the ages of 15-18 years after the RSV and rhinovirus bronchiolitis when compared with population-based controls with no history of bronchiolitis (Table 2). However, when comparing the bronchiolitis groups, those with history of rhinovirus bronchiolitis had a higher risk for asthma compared to RSV bronchiolitis patients (Ruotsalainen et al. 2013).

HRVs induce limited cytotoxicity in airway epithelium (Rossi & Colin 2015). However, release of pro-inflammatory mediators during HRV infection can lead to recurrent or persistent bronchial hyperreactivity, especially in the presence of other predisposing factors (Rossi & Colin 2015, Schneider et al. 2012, Hong et al. 2014). In epidemiological studies, the susceptibility to rhinovirus-induced wheezing in infancy has been linked to a predisposition to other conditions, such as atopy, eosinophilic activity and maternal asthma (Kotaniemi-Syrjanen et al. 2003, Carroll et al. 2012, Jartti & Korppi 2011, Turunen et al. 2014). It has been concluded that there may be a subgroup of infants with early-life respiratory allergy who are prone to wheeze during rhinovirus infections.

It has been suggested that host factors in children with early LRTI might explain the differences in the outcomes of long-term studies better than the type of virus (Elphick et al. 2007, Everard 2006). More specifically, increased risk for respiratory symptoms and atopy has been reported in those children who present only wheezing symptoms during RSV LRTI (Elphick et al. 2007). Children who present bronchiolitis as characterised by widespread crepitations with or without wheeze do not differ from controls in regards to atopy and respiratory symptoms (Elphick et al. 2007). Due to these findings, it has been concluded that host factors rather than viral factors influence the phenotype of the initial illness and that the same host factors influence later outcomes (Elphick et al. 2007). A large Danish twin study studied the causation and the direction of causation between RSV hospitalization and asthma between 3-5 years of age (Thomsen et al. 2009). Asthma risk was significantly increased in the study subjects with a history of RSV bronchiolitis hospitalization. However the researchers were only able to demonstrate the causal relationship between asthma and RSV, whereas the causal link between RSV infection and asthma was rejected (Thomsen et al. 2009). However, in a prospective multicenter study, it was demonstrated that preventing RSV LRTI in premature infants with an anti-RSV monoclonal antibody, palivizumab, reduces subsequent recurrent wheezing in childhood. This suggests an independent role of RSV as an inducer of childhood wheezing (Simoes et al. 2007). This finding was especially seen in children who did not have an atopic predisposition and it was concluded that the predisposition to recurrent wheezing by is an atopy-independent mechanism (Simoes et al. 2010).

It has been suggested that the association between early childhood viral LRTIs and subsequent asthma are more in favor of the hypothesis that the association between viral infection and asthma is due to shared predisposition rather than to a causal effect of virus (Thomsen et al. 2009, Kuehni et al. 2009). Thus, wheezing during LRTI, especially during rhinovirus infection, might merely reveal children who are already predisposed to asthma on the basis of host risk factors, such as abnormal lung function or immune response. However, there is growing evidence, based primarily on animal studies, that viruses are cabable of altering immune responses, especially in young children. This produces airway hyperreactivity and induces long-term wheezing and the development of asthma (Rossi & Colin 2015, Piedimonte 2001, Jafri et al. 2004, You et al. 2006, Becnel et al. 2005). Despite the increasing epidemiological and experimental data supporting an important role for viruses in the pathogenesis of wheezing and asthma, the underlying mechanism of this effect remains mainly unexplained (Rossi & Colin 2015).

2.4.2 Atopy and allergy

Evidently, atopy increases the risk for persistent wheezing and asthma in later childhood in children who present early childhood wheezing illness (Martinez et al. 1995, Kusel et al. 2007, Kusel et al. 2012, Jackson et al. 2012). In children, the stepwise increase of symptoms called the "atopic march" starts with allergic sensitization and is often accompanied by eczema in the first year of life. These children are prone to develop allergic rhinitis and asthma in later life (Lambrecht & Hammad 2014). As seen in Table 1, atopy in early childhood is associated with current asthma up to between the ages of 18-20 years compared to non-atopic early wheezers (Piippo-Savolainen et al. 2006). However, early atopy seems to lose its significance as a predictor for asthma by the age of 27, as seen in Swedish and Finnish post-bronchiolitis cohorts (Goksor et al. 2015, Ruotsalainen et al. 2010a). Instead, current allergy was significantly associated with asthma in adulthood in these studies (Goksor et al. 2015, Ruotsalainen et al. 2010a).

In a Swedish RSV bronchiolitis cohort, the risk for allergic rhinitis and allergic sensitization was significantly increased after the early RSV bronchiolitis up to the age of 18 years compared to controls with no history of RSV LRTI (Sigurs et al. 2010, Sigurs et al. 2005). Thus, RSV might have provoked the development of atopy. However, as the study subjects were recruited at the time of the hospitalization, it was not possible to determine the underlying susceptibility for atopic diseases of the study subjects before RSV infection.

The interaction between viral infections and atopy is clearly complex, and there is not a consensus about the causality between these conditions. Both viral infections and allergic inflammation can damage airway epithelium, and it has been proposed that the viral and atopy-associated inflammation may interact synergistically, eventually leading to persistent respiratory morbidity (Kusel et al. 2007, Siegle et al. 2010). To support the idea of synergistic interaction between atopy and LRTIs, it has been demonstrated that at the age of 5 years the highest risk for persistent wheezing after RSV or rhinovirus LRTI is present in those children who present atopy by the age of 2 years (Kusel et al. 2007, Kusel et al. 2012).

Taken together, the interaction between atopy, early childhood LRTIs, and subsequent persistent wheezing in later life is evident. While the causal relationship between these conditions remains unclear, there is growing evidence that pre-existing immunological status of the child matters when evaluating the outcome of early childhood LRTIs.

2.4.3 Altered immunology

It has been proposed that the delay in the maturation of the immune system plays an important role in the development of asthma (Lemanske 2002). After birth, a conversion from a predominant TH2 -type immunity shifts to a balance between T-helper 1 -type and TH2-type responses. In atopic children, this maturation is delayed, which allows TH2-type responses to persist. TH2-type responses stimulate the production of cytokines that regulate the allergen-specific synthesis of IgE regulated by interleukin (IL)-4, the recruitment of eosinophils regulated by IL-5, the recruitment and growth of mast cells regulated by IL-9, and airway hyperreactivity that is characteristic for asthma (Kim et al. 2010). In contrast, TH1-type responses are characterized by an enhanced production of IL-2 and interferon gamma (IFN-γ). The delayed production of IFN-γ may predispose young children to environmental factors like aeroallergens or viruses that again may enhance adverse effects to the developing lungs (Lemanske 2002).

To support the idea of allergic hypothesis it was demonstrated in the 6-years follow-up of the Tucson cohort that serum IgE levels were significantly higher at the age of 9 months in those who were about to continue wheezing at the age of 6 years compared to non-wheezers (Martinez et al. 1995). IgE-mediated specific allergic sensitization in childhood has also been recognized as a risk factor for asthma in childhood (Hyvarinen et al. 2005, Stoltz et al. 2013, Simpson et al. 2010). However, this association between early sensitization and asthma

seems to lose its significance in adulthood (Ruotsalainen et al. 2010a, Piippo-Savolainen et al. 2007b).

2.4.4 Eosinophilic inflammation

Eosinophils are granulocytes that develop in bone marrow, and are then released into the blood and subsequently migrate to peripheral tissues, usually to the thymus or gastrointestinal tract (Rosenberg et al. 2013). The activation of TH2-lymphocytes and chemokines in the eotaxin family leads to inflammation that stimulates the activation of eosinophils, which then migrate to the sites of inflammation (Lambrecht & Hammad 2014, Rosenberg et al. 2013). It has been established that eosinophil dysregulation contributes to the development of allergic diseases and asthma (Rosenberg et al. 2013, Phipps et al. 2007). However, eosinophils also have beneficial roles in host defense. In recent years, it has been it has been demonstrated in animal models that eosinophils promote viral clearance during viral respiratory infections and may thus limit virus-induced lung dysfunction (Phipps et al. 2007, Percopo et al. 2014). These interactions between eosinophils and viruses have not yet been fully studied.

Recruitment of eosinophils to lung tissue is part of the pathophysiology of asthma. Most current evidence suggests that subepithelial fibrosis in the airways, which is a characteristic of allergic asthma, is mediated by eosinophilic inflammation (Lambrecht & Hammad 2014, Rosenberg et al. 2013, Zagai et al. 2004). Eosinophils contain several cytotoxic substances, such as eosinophil cationic protein (ECP), that can promote inflammation and cause tissue damage to the lungs (Zagai et al. 2004). High blood eosinophils during early viral infection have been recognized as a risk factor for asthma in childhood (Kotaniemi-Syrjanen et al. 2002, Midulla et al. 2014, Ehlenfield et al. 2000). This association has been demonstrated up to the ages of 15-18 years (Ruotsalainen et al. 2013) but not thereafter (Ruotsalainen et al. 2010a) (Table 2). Decrease in eosinophils seems to be the normal response to viral infection in infants during lower respiratory infection (Ehlenfield et al. 2000, Rosenberg et al. 2009). In line with this, children who are to become persistent wheezers have no eosinopenic reaction during LRTI (Karakoc et al. 2002, Martinez et al. 1998). In addition, persistently low blood eosinophil count in the population-based study has been recognized to associate with decreased risk for asthma up to the age of 13 years (Karakoc et al. 2002). Later it was demonstrated in the 20-year follow-up of the present cohort that blood eosinophils were significantly lower on admission for bronchiolitis than on convalescence if the study subjects did not have doctor-diagnosed asthma or lung function deficiency between the age of 18-20 years (Piippo-Savolainen et al. 2007a). This association, suggesting an eosinopenic response to infection, was more evident in former RSV positive than RSV negative bronchiolitis patients (Piippo-Savolainen et al. 2007a). Also, a French study presented that the absence of eosinophilia alone predicted 91% of remissions of wheezing in infants (Just et al. 2008).

The allergic pathway including TH2-derived IgE production, IgE-mediated allergic sensitization, and eosinophilia is clearly important in the development of asthma. However, the causal relationship and underlying host-factors related to these findings in early childhood wheezers remain to be solved.

2.4.5 Heredity

It has been known for a long time that the development of asthma after early childhood wheezing has a genetic component. This association has been demonstrated in epidemiological studies as increased risk of asthma in those with a family history and in particular with a maternal history of asthma (Martinez et al. 1995). In a 7-year follow-up of a Swedish RSV-bronchiolitis cohort, it was demonstrated that those children with both a family history of asthma and bronchiolitis had higher rates of asthma (38%) compared to those with a family history of asthma or bronchiolitis alone (Sigurs et al. 2000). Family history of asthma increases the risk for asthma up to early adulthood (Stern et al. 2008, Goksor et al. 2006, Sigurs et al. 2010,

Piippo-Savolainen et al. 2006, Goksor et al. 2015) (Table 1). However, in a Swedish RSV bronhiolitis cohort, family history of asthma lost its significance as a risk factor for asthma in early adulthood (Sigurs et al. 2010). Parental atopy has not been a risk factor for future asthma in any of the long-term post-bronchiolitis studies (Sigurs et al. 2010, Piippo-Savolainen et al. 2006, Goksor et al. 2015). However, in birth cohorts, family history of atopy has been described to be one of the most important risk factors for childhood persistent asthma (Nordlund et al. 2014).

Asthma has a significant genetic contribution; heritability estimates vary between 35% and 95% (Ober & Yao 2011). Many studies have demonstrated associations with single nucleotide polymorphisms (SNPs) at chromosome 17q21 and childhood onset asthma (Ober & Yao 2011). It has been described that 17q21 variants enhance the association between early respiratory infections and early-onset asthma. Risk genotypes also increase the association between infection and childhood asthma that remits in adulthood (Smit et al. 2010). 17q21 variants also have a role in the development of HRV wheezing illnesses during early childhood. The increased risk for asthma among children with at-risk genotypes has been present in those children who had HRV wheezing illnesses in early life but not in those with RSV wheezing illnesses (Caliskan et al. 2013). So, there may be other underlying risk factors that increase the risk for both rhinovirus infection and asthma. It is also possible that rhinovirus infection acts as one in genetically susceptible children.

2.4.6 Gender

Wheezing in early life is more common in boys than in girls (Taussig et al. 2003, Melen et al. 2004). In addition, the incidence of asthma is higher in boys up to adolescence (Taussig et al. 2003). However, during adolescence the reversal of sex distribution is seen, and by the age of 22-23 years asthma becomes more common in females (Stern et al. 2008, Anderson et al. 1992). The female gender also predicts the persistence of wheezing symptoms from childhood to adulthood (Sears et al. 2003).

2.4.7 Parental smoking

The relationship between maternal smoking during pregnancy or passive smoking in infancy and later asthma in children has been established in numerous studies (Martinez et al. 1995, Sigurs et al. 2010, Goksor et al. 2007, Tager et al. 1993, Lannero et al. 2006, Nordlund et al. 2014, Burke et al. 2012). In a recent review and meta-analysis, it was concluded that pre- or postnatal passive smoke exposure was associated with a 30% to 70% increase in the risk of wheezing and a 21% to 85% increase in asthma before the age of 2 years (Burke et al. 2012). In the same review, the strongest significant association was found between prenatal maternal smoking and incidence of asthma in children aged less than 2 years. The effect of prenatal maternal smoking became progressively weaker in relation to asthma incidence with increasing age. However, it remained significantly associated with asthma onset between the ages of 5 and 18 years (Burke et al. 2012).

In a Swedish post-bronchiolitis cohort, it was demonstrated that both pre- and post-natal smoke exposure are risk factors for asthma in adulthood and also in a high risk post-bronchiolitis population (Table 2) (Goksor et al. 2007). However, in this same cohort, maternal smoking during pregnancy and passive smoking in infancy lost their association with asthma between the ages of 25-28 years (Goksor et al. 2015).

Table 2. Early factors associated with asthma in adolescence and adulthood in hospitalized bronchiolitis patients.

Risk factor	Age (yrs) at the time of asthma diagnosis	OR (95%CI)[1]	Reference
Wheezing history			
Recurrent wheezing < 2 years	18-20	5.35 (1.03 – 27.82)	Piippo-Savolainen 2006
	26-29	NS.[2]	Ruotsalainen 2010
Inheritance			
Parental asthma	18-20	16.11 (1.66 – 156.46)	Piippo-Savolainen 2006
	13	4.7 (1.6 – 13.9)[3]	Sigurs 2005
	27	4.0 (1.3–12.5) [4]	Goksör 2014
Host factors			
Female gender	27	3.2 (1.1–9.3)[5]	Goksör 2014
Atopy < 2 years	18-20	4.43 (1.29 – 15.2)	Piippo-Savolainen 2006
	26-29	NS. [2]	Ruotsalainen 2010
Sensitization to pollens < 3 years[6]	13.5 - 16	7.99 (1.09 – 58.52)[7]	Piippo-Savolainen 2008
Eosinophilia (>0.45x10E9/l)[8]	15-18	21.30 (1.06 – 426.42)	Ruotsalainen 2009
	26-29	NS. [2]	Ruotsalainen 2010
Environmental factors			
Maternal smoking during pregnancy	17-20	3.5 (1.1 – 11.3)[9]	Goksör 2007
Passive smoking in infancy	17-20	3.4 (1.2 – 10.1)[9]	Goksör 2007
RSV etiology	15-18	11.63 (1.71) [10]	Ruotsalainen 2012
	18-20	1.40 (0.36 – 5.35)[11]	Korppi 2004
	26-29 [12]	11.4 (2.95 – 44.05)	Ruotsalainen 2010
Non-RSV etiology	15-18	11.49 (3.88 – 34.00)[10]	Ruotsalainen 2012
	18-20[13]	8.34 (1.18 – 58.69)[14]	Piippo-Savolainen 2007

[1]Odds ratio and 95% Confidence interval, [2] NS, Not significant, OR or p-value not available, [3]Adjusted with history of RSV bronchiolitis, parental asthma and atopy, [4]Multivariate analysis with female gender, maternal smoking during pregnancy, RSV infection at first admission, furry pets at home in infancy, start of wheezing before the age of 6 months and intense obstructive disease as a young child included, [5]Adjusted with current allergy and active smoking, [6]Serum allergen-specific immunoglobulin (IgE) >0.35kU/l, [7]Adjusted with RSV etiology of bronchiolitis, and parental asthma, [8]Adjusted with sex and age, [9]Multivariate analysis with family atopy and female gender included in analysis, [10]Adjusted with age, sex, smoking, allergic rhinitis, asthma in parents, asthma in siblings, [11]Adjusted with atopy at the age if 18-20 years, [12]Compared to population controls, [13]Compared to RSV bronchiolitis patients, [14]Adjusted with sex, age on admission, current smoking and atopy

2.4.8 Frequency of wheezing symptoms

Recurrent wheezing symptoms after early childhood bronchiolitis are common (Korppi et al. 1993, Reijonen et al. 2000). It has previously been demonstrated that afterhospitalized bronchiolitis more than 2 wheezing episodes during the first 2 years of life increased the likelihood of asthma in adolescence and adulthood (Hyvarinen et al. 2005, Piippo-Savolainen et al. 2006). In more recent studies, school-age asthma was associated with the frequency of wheezing episodes (Pescatore et al. 2014, Bacharier et al. 2012) or the frequency of troublesome respiratory symptoms (Bonnelykke et al. 2015) in children less than 3 years of age.

2.4.9 Early lung function

Several studies have demonstrated the association between diminished infantile lung function and subsequent tendency for wheezing in early childhood (Martinez et al. 1991, Young et al. 2000, Dezateux et al. 1999, Murray et al. 2002). In a similar manner, decreased lung function soon after birth is associated with an increased risk for asthma in childhood (Bisgaard et al. 2012, Lodrup Carlsen et al. 2014), adolescence (Lodrup Carlsen et al. 2014) and adulthood (Mullane et al. 2013). In addition, bronchial hyperreactivity at the age of 12 months has also been associated with an increased risk for asthma in childhood (Turner et al. 2009). These findings suggest that lung function deficits found in asthma patients are at least partly congenital (Guerra & Martinez 2009).

2.4.10 Predicting the persistence of wheezing symptoms

The recurrence of wheezing symtoms in early childhood predicts asthma in later life. In the present cohort, recurrent symptoms were a significant risk factor for later asthma still between the ages of 18-20 years after bronchiolitis but not after that (Piippo-Savolainen et al. 2006, Ruotsalainen et al. 2010a) (Table 1). However, not all children who have wheezing before the age of 3 years develop persistent symptoms and eventually asthma. In fact, the majority of them are asymptomatic by the age of 6 years and can be classified as transient wheezers (Martinez et al. 1995). It is difficult to distinguish transient wheezers and those with more persistent type of wheezing in early childhood. Therefore, predicting the persistence of wheezing symptoms and the development of later asthma in children with early childhood wheezing symptoms has been a challenge.

In 2000, the Tucson group presented the asthma predictive index (API), which predicts asthma up to the age of 13 years in young children with recurrent wheezing (Castro-Rodriguez et al. 2000) (Table 3). A stringent index includes frequent wheezing during the first 3 years of life and either one of the major risk factors, parental history of asthma or eczema in child, or two of three minor risk factors, which are the presence of eosinophilia, wheezing without colds, and allergic rhinitis in child (Table 2). The lenient index requires any wheezing during the first 3 years of life plus the same combination of risk factors as the stringent index (Castro-Rodriguez et al. 2000). A positive stringent API score by the age of 3 years is associated with a 77% chance of active asthma between the ages of 6–13 years (Castro-Rodriguez et al. 2000). However, children with a negative API score at the age of 3 years have less than a 3% chance of developing active asthma during their school years and can be classified as transient wheezers (Castro-Rodriguez 2011). Modification of API (mAPI) has been proposed (Guilbert et al. 2004b, Guilbert et al. 2004a) and tested recently in the Childhood Origins of Asthma (COAST) cohort (Chang et al. 2013). Regarding mAPI, sensitization to at least one aeroallergen was proposed as an additional major criterion and allergic sensitization to milk, egg, or peanuts as a minor criterion instead of allergic rhinitis (Chang et al. 2013). However, it has been argued that the determination of sensitization is expensive and unreliable, since allergens vary in different populations (Castro-Rodriguez 2011).

The Isle of Wight score, described in 2003, identified risk factors to predict the persistence of wheezing in early childhood wheezers (Kurukulaaratchy et al. 2003). The score

has four criteria, including family history of asthma, recurrent chest infections in the second year of life, atopic sensitization at 4 years of age, and the absence of recurrent nasal symptoms in the first year of life.

The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) risk score was developed in 2009 to predict asthma up to the age of 8 years (Caudri et al. 2009) and updated later (Hafkamp-de Groen et al. 2013). In addition to atopic characteristics that are also described in other asthma predictive scores, it also includes male sex, preterm birth, and parental education.

In 2008, the Korppi group presented a modified asthma predictive index for children hospitalized for bronchiolitis based on findings of the Finnish and Swedish post-bronchiolitis cohorts (Piippo-Savolainen & Korppi 2008) (Table 3). As in the Tucson API, the risk factors were classified as major or minor factors. This is so far the only predictive algorithm that takes viral etiology of wheezing illness into account. However, this index has not been validated, and its predictive value is not known.

Of these indices, API is probably the most well known and the easiest to use in a clinical setting. The asthma predictive index of the Korppi group includes factors that are known to be risk factors for adult asthma in hospitalized bronchiolitis patents. However, all these indices share low sensitivity but fairly good negative predictive value to identify children with probable transient wheezing (Castro-Rodriguez 2011). Parental history of asthma and features of atopic disease in children seem to be common features in predicting the future risk for asthma. However, these indices predict asthma only up to the school age, since follow-up up to the adult age is not included in any of these indices.

As a conclusion, it seems that in long-term follow-up studies, the early risk factors for asthma seem to lose their significance in adulthood. In a 27-year follow-up of Finnish post-bronchiolitis cohort, significant early life risk factors could not be identified (Ruotsalainen et al. 2010a), and in a Swedish follow-up at the same age, only female gender and parental asthma predicted the persistence of asthma up to adulthood (Goksor et al. 2015). This may be due to numerous disease modifying factors and new risk factors that weaken and modify the effect of early risk factors in the development of adulthood asthma (Ruotsalainen et al. 2010a).

Table 3. Asthma predictive indices in children with early childhood wheezing

Asthma predictive index (API)[1]	
≥3 wheezing episodes before the age of 3 years and one major or two minor criteria required for positive index	
Major Criteria	
Physician diagnosis of parental asthma	
Physician diagnosis of atopic dermatitis in child	
Minor Criteria	
Physician diagnosis of allergic rhinitis	
Wheezing apart from colds	
Eosinophilia (≥4%)	

Isle of Wight score[2]	
Wheeze ever before the age of 4 years required. Scoring 4 risk factors was associated with symptom persistence in 83% up to the age of 10 years.	
Criteria	
Recurrent chest infections at 2 yrs	
Family history of asthma	
Atopic SPT at 4 yrs	
Nasal symptoms at 1 yr	

PIAMA risk score[3]	
Wheeze ever before the age of 4 years required. Risk of asthma when total score 0-7 <5%, 8-15 6%-22%, 16-23 25%-60%, maximum 23 points.	
Risk score	
Male sex	2
Medium/low parental education	1
Parental asthma	4
preterm delivery <37 weeks	1
Wheezing frequency	
1-3 times/y	4
4 times/y	7
Wheezing/dyspnea apart from colds	2
Doctor's diagnosis of eczema	6

Asthma predictive index for children hospitalized for bronchiolitis[4]	
Hospitalization for bronchiolitis in infancy and one major or two minor criteria required for positive index	
Major Criteria	
Physician diagnosis of parental asthma	
Physician diagnosis of atopic dermatitis or food allergy in child	
Parental, especially maternal, smoking	
Minor Criteria	
Sensitization to inhaled allergens	
Wheezing induced by other viruses than RSV	
Blood eosinophilia or lack of eosinopenic response during viral infection	

[1]Castro-Rodriguez 2000, [2]Kurukulaaratchy 2003, [3]Hafkamp 2013, [4]Piippo-Savolainen 2008

2.5 LUNG FUNCTION AFTER EARLY CHILDHOOD WHEEZING

2.5.1 Early childhood lung function and LRTI´s

Several retrospective studies and post-bronchiolitis studies have demonstrated the association between early childhood respiratory infections, lung function reduction, and respiratory morbidity in adulthood (de Marco et al. 2011, Piippo-Savolainen et al. 2004, Sigurs et al. 2010, Goksor et al. 2008, Barker et al. 1991). However, these studies have been unable to answer the question of whether or not the impairment of lung function is a consequence of respiratory infections in early childhood.

The Tucson birth cohort study was the first study to attempt to answer this question. In this cohort, lung function was measured in early childhood before any respiratory infections. It became evident that infants who have respiratory illnesses with wheezing during the first year of life have lower levels of lung function before any lower respiratory illness develops than non-symptomatic infants (Martinez et al. 1995, Martinez et al. 1988). Later, several birth cohorts have verified this finding (Tager et al. 1993, Dezateux et al. 1999, Murray et al. 2002, Young et al. 1991). In addition, it has been demonstrated that bronchial hyperreactivity in early infancy is a specific finding that also predicts increased hyperreactivity and is strongly associated with asthma later in childhood (Turner et al. 2009). In line with this, neonatal bronchial hyperreactivity has been demonstrated to increase the risk of acute severe bronchiolitis (Chawes et al. 2012). According to these results it seems that neonatal bronchial hyperreactivity is a pre-existing state, predisposing infants to later development of both acute viral bronchiolitis and childhood asthma (Bisgaard et al. 2012, Chawes et al. 2012). According to their results, it may be justified to conclude that the association between early airway impairment and subsequent development of LRTIs during the first years of life has been established (Martinez 2002).

Even though most children who have wheezing during respiratory infections in early childhood grow out of this tendency, transient wheezers have also been described to have impaired lung function before any respiratory infections. In the Tucson birth cohort study, the level of lung function did not seem to improve with inceasing age, and lung function impairment was still present at the age of 6 years (Martinez et al. 1995) and even at the age of 22 years (Stern et al. 2007). So, it seems evident that, at least partly, early childhood wheezing reflects congenitally small airways and predisposes children to wheezing during respiratory illness at early age (Martinez et al. 1995) and to lung function impairment up to adult age (Stern et al. 2007). Due to these findings, it has been speculated that even transient early wheezers may have increased risk for COPD as they get older (Taussig et al. 2003). However, the Australian birth cohort study was not able to confirm these findings, since low lung function soon after birth associated only with persistent wheezing phenotype at the age of 18 years (Mullane et al. 2013).

Despite these convincing results, lung function at birth is not the only determinant of later respiratory morbidity. A Danish birth cohort study demonstrated that 14% of children with asthma by age 7 already had a significant airflow deficit as neonates (Bisgaard et al. 2012). However, this deficit progressed significantly during early childhood, and it was concluded that approximately 40% of the airflow deficit associated with asthma at the age of seven is present at birth, whereas 60% develops with clinical disease (Bisgaard et al. 2012). Environmental tobacco exposure also hampered lung function development in childhood (Bisgaard et al. 2012). As a conclusion, it seems that even if part of the lung function is determined before birth or very soon after that, the lung development can be influenced by various factors also in later life.

2.5.2 Risk factors for early lung function impairment

There are numerous factors that may hamper lung growth during pregnancy or during the rapid growth of the lungs in early childhood. These factors may prevent the lungs to acquire the full pulmonary potential, and can alone or together with later environmental factors predispose subjects to respiratory morbidity such as asthma and even COPD in the future (Postma et al. 2015, Stocks et al. 2013).

Intrauterine growth retardation (Canoy et al. 2007) and preterm delivery (Kotecha et al. 2013) result in decreased alveolar number and surface area and, as a result, reduced lung function at birth and later in life.

Maternal smoking during pregnancy is evidently the most important preventable factor associated with lung function impairment in utero (Martinez et al. 1988, Tager et al. 1993, Landau 2008, Lodrup Carlsen et al. 1997, Bisgaard et al. 2009, Murray et al. 1992). Significant suppression of alveolarization, functional residual capacity, and tidal flow volume have been demonstrated in children with prenatal smoke exposure (Rehan et al. 2009). In addition, the inverse dose-response relationship of smoked cigarettes during pregnancy and tidal flow-volume ratios in healthy newborn babies was demonstrated in a Norwegian birth cohort (Lodrup Carlsen et al. 1997). It was demonstrated later in the same cohort that low lung function measured at birth as well as maternal daily smoking during pregnancy are independent risk factors for developing obstructive airway disease within the first 2 years of life (Lodrup Carlsen et al. 1999). In addition to lung function impairment at birth, maternal smoking during pregnancy has been associated with poor lung function up to early adulthood (Stern et al. 2007).

Decreased airway conductance, determined from plethysmographic measurements of lung volume and airway resistance, has been described to be present in early infancy in relation to familial asthma (Dezateux et al. 1999). Parental asthma is also a risk factor for bronchial hyperreactivity to histamine in small babies, suggesting a significant role of heredity with regards bronchial hyperreactivity at early age (Martinez et al. 1988, Young et al. 1991).

2.5.3 Viral infections and the lungs

It has been established in epidemiological studies that early childhood LRTI leads to impaired lung function later in life (de Marco et al. 2011, Piippo-Savolainen et al. 2004, Sigurs et al. 2010, Goksor et al. 2008, Barker et al. 1991). However, it has been proposed that low lung function after LRTI might instead result from adverse events during the prenatal period (Martinez et al. 1995, Martinez et al. 1988, Tager et al. 1993, Dezateux et al. 1999, Murray et al. 2002, Young et al. 1991, Rossi & Colin 2015). However, experimental studies based on animal models have demonstrated that respiratory viruses can also directly damage developing lungs at an early age (Rossi & Colin 2015).

During RSV infection, viral antigen recognition induces the production of a variety of pro-inflammatory mediators, such as tumor necrosis factor alfa, eotaxins, interleukins and chemokines. These activate the innate and adaptive immune responses to limit viral infection (McNamara et al. 2004, McNamara et al. 2005, McNamara et al. 2004). Pro-inflammatory mediators induce monocyte and polymorphonuclear cell influx in the airways to enhance the cytopathic effect of RSV and to misdirect the immune response (Rossi & Colin 2015, Bem et al. 2011). It has also been demonstrated that RSV infection causes neurogenic inflammatory reactions that activate cholinergic and excitatory noncholinergic, nonadrenergic neural pathways, resulting in a predisposition for airway obstruction and airway hyperreactivity (Rossi & Colin 2015, Jafri et al. 2004, You et al. 2006).

In the absence of other contributing factors, primary RSV infection does not usually lead to marked eosinophilia in the lungs (Becnel et al. 2005, Bem et al. 2011, Johnson et al. 2007). However, early allergic sensitization or very early primary infection can lead to aberrant immune responses following RSV infection that have long lasting affects on the lungs (Becnel et

al. 2005, Johnson et al. 2007). More specifically, it has been demonstrated that bronchial hyperreactivity, increased eosinophil and lymphocyte cell numbers, enhanced mucus production and signs of airway remodeling, including subepithelial fibrosis, were present in young mice after RSV infection when combined with allergic sensitization prior to infection (Becnel et al. 2005). Subsequent work demonstrated the relationship between early-life viral infections and allergen sensitization in the development of a TH2-biased immune response and allergic inflammation in the lungs (You et al. 2006, Siegle et al. 2010). Based on these findings, it has been suggested that allergic inflammation can potentiate the effect of RSV infection on the developing lung, leading to the development of chronic asthma (You et al. 2006, Becnel et al. 2005). In addition, the timing of the primary RSV infection seems to be a crucial factor in determining the outcome of reinfection later in life (Culley et al. 2002, Dakhama et al. 2005). Developing immune systems in neonates tend to display prolonged TH2-biased immune responses to RSV instead of more immunologically mature TH1-responses (Culley et al. 2002). It has been demonstrated that infected neonatal mice results in the production of severe inflammatory responses, lung eosinophilia, mucus and bronchial hyperreactivity during RSV reinfection. In contrast, later primary infection protects against the development of these altered airway responses during the reinfection (Culley et al. 2002, Dakhama et al. 2005).

A similar association has also been found between age at the time of the HRV infection and outcome after the infection (Schneider et al. 2012, Hong et al. 2014). HRV infection in neonatal mice, unlike infection in mature mice, induced TH2-biased immune responses, airway hyperresponsiveness and mucous metaplasia (Schneider et al. 2012, Hong et al. 2014). Thus, it seems that TH2-biased immune responses early in life can provide a favorable environment for asthma development, particularly when maintained by appropriate stimuli like viral infections (Schneider et al. 2012, Hong et al. 2014).

2.5.4 Lung function after early childhood LRTI

Impaired lung function (Sigurs et al. 2005, Hyvarinen et al. 2007) and increased bronchial responsiveness (Kotaniemi-Syrjanen et al. 2008, Wennergren et al. 1997) in childhood have been demonstrated to be present after early childhood bronchiolitis. In addition, it has been demonstrated that after bronchiolitis in infancy, lung function may remain reduced until early adulthood (Piippo-Savolainen et al. 2004, Sigurs et al. 2010, Goksor et al. 2008). In a Swedish post-RSV bronchiolitis cohort, a reduced FEV1/FVC ratio was present before and after bronchodilatation at the ages of 13 and 18 years despite the increased reactivity in airways (Sigurs et al. 2010, Sigurs et al. 2005). In line with a RSV bronchiolitis cohort, 17-20 year follow-up of Swedish post-bronchiolitis cohort revealed that FEV1/FVC and MEF50 were reduced before and after bronchodilatation. As a conclusion, findings from these two cohorts indicated signs of irreversible airway obstruction after bronchiolitis (Sigurs et al. 2010, Goksor et al. 2008). It was also demonstrated in a Swedish post-bronhiolitis cohort that lung function reduction is present in symptom-free study subjects who had lower levels of lung function compared to symptom-free controls, which corroborates the results of the 22-year follow-up of the Tucson birth cohort study (Goksor et al. 2008, Stern et al. 2007).

Factors associated with lung function impairment or bronchial hyperreactivity after early childhood wheezing have included female gender (Kotaniemi-Syrjanen et al. 2008, Goksor et al. 2008), prenatal smoke exposure (Goksor et al. 2007, Hyvarinen et al. 2007), parental smoking (Piippo-Savolainen et al. 2006), and early atopy (Hyvarinen et al. 2007). Rhinovirus etiology of bronchiolitis, however, has been associated with increased bronchial responsiveness in a Finnish viral bronchiolitis cohort (Kotaniemi-Syrjanen et al. 2008). However, the later follow-up of the same cohort at the age of 11 years revealed a more restrictive type of lung function impairment after RSV bronchiolitis (Hyvarinen et al. 2007).

Lung function after early childhood pneumonia has not been studied with the intensity of post-bronchiolitis lung function. However, in the Tucson birth cohort study,

radiologically confirmed pneumonia at less than 3 years of age was associated with reduced lung function at the age of 6 and 11 years compared to those with no respiratory infections at early age (Castro-Rodriguez et al. 1999). Pneumonia patients also had similar premorbid changes in lung function than bronchiolitis patients (Taussig et al. 2003). In addition, a recent systematic review concluded that restrictive pulmonary disease is the most common sequela after pneumonia in early childhood (Edmond et al. 2012). However, two historical birth cohorts found more obstructive patterns of lung function reduction with reduced FVC and FEV1 in late adulthood in those with history of early childhood pneumonia (Barker et al. 1991, Shaheen et al. 1998). In addition, in a recent follow-up of the Tucson cohort, reduced FEV1/FVC was demonstrated at the age of 26 years in those with a history of early childhood pneumonia (Chan et al. 2015). These findings suggest that pneumonia and bronchiolitis may share the same predisposing factors and that these diseases are in the same spectrum of viral respiratory infections (Taussig et al. 2003).

It is still unclear whether early childhood LRTIs such as bronchiolitis and pneumonia cause further impairment of lung function in young children. In the Australian birth cohort study, reduced lung function was present before and after bronchiolitis at the age of 11 years, and the level of reduction was comparable (Turner et al. 2002). It was concluded that the mechanism for wheeze and reduced lung function after bronchiolitis appears to be related to state of premorbid lung function, not to bronchiolitis (Turner et al. 2002). However, there is clear evidence that RSV causes damage to airways that leads to bronchial hyperreactivity, peribronchial and perivascular inflammation, and subepithelial fibrosis several months after initial infection in mice (Jafri et al. 2004, You et al. 2006).

It has been established that impaired lung function occurs after early childhood LRTI. Results of several birth cohort studies suggest that impaired lung function is associated with premorbid low infantile lung function rather than the consequence of viral infection. However, recent data have demonstrated that viral infections cause direct damage to the lungs that can result in long-term consequences for bronchial hypereactivity and airway remodelling. These findings suggest that both theories may be true.

2.6 HEALTH-RELATED QUALITY OF LIFE AFTER EARLY CHILDHOOD LRTI

2.6.1 Health-related quality of life, wheezing and asthma

The WHO defines 'quality of life' as an individual´s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns (The World Health Organization Quality of Life Instruments 1997). The emphasis in medicine has changed from acute diseases to prevention and control of chronic conditions. As a result, the measurement of health-related quality of life is becoming an increasingly important method to assess health outcome measurement in medical studies (Eiser & Morse 2001, Rutishauser et al. 1998). Various questionnaires have been developed to measure quality of life in children and adolescents with asthma and asthma-related symptoms (Rutishauser et al. 1998, Rutishauser et al. 2001) and adults with asthma or COPD (Wilson et al. 2012, Weldam et al. 2013).

Asthma and wheezing have been associated with reduced health-related quality of life (HRQoL) in childhood (Covaciu et al. 2013, Beattie & Lewis-Jones 2006, Oostenbrink et al. 2006, Cui et al. 2015) and adulthood (Adams et al. 2001). At the 8-year follow-up of the Swedish Bamse birth cohort, HRQoL was assessed by parents completing the standard HRQoL instrument EQ-5D. They found that allergic diseases such as asthma, rhinitis, atopic eczema, and food hypersensitivity were all associated with reduced HRQoL at the age of 8 years. Study subjects with asthma had the lowest HRQoL scores (Covaciu et al. 2013). Asthma-like symptoms during the first year of life have also been associated with impaired HRQoL at the

age of 12 months. In addition, wheezing attacks during the past 12 months have also been associated with reduced HRQoL in adolescents (Mohangoo et al. 2007, Mohangoo et al. 2012).

2.6.2 Health-related quality of life after LRTI

There are not many studies about the association between early bronchiolitis or pneumonia and subsequent HRQoL after these diseases. A recent Norwegian study enrolled 209 infants that had been hospitalized for bronchiolitis and 206 controls at a mean age of 4 months (Rolfsjord et al. 2015). Quality of life was studied with Infant Toddler Quality of Life Questionnaire (ITQOL) 9 months later. Infants with a history of bronchiolitis had lower quality of life scores compared to controls in the overall health and general health domains of the questionnaire (Rolfsjord et al. 2015). A very similar pattern of HRQoL impairment was found in another study that also used ITQOL 2-6 months after RSV bronchiolitis (Spuijbroek et al. 2011). In addition to these studies, impaired HRQoL attributed to post-bronchiolitis wheezing has been described in children 3 years after hospitalization for RSV bronchiolitis (Bont et al. 2004). However, there are no previous studies on quality of life after early childhood bronchiolitis, including follow-ups longer than three years.

In the child population, CAP has been described to affect HRQoL in the short term (Shoham et al. 2005). In the adult population, the recovery of respiratory symptoms after CAP is fast, but the recovery of general HRQoL to premorbid levels has been described to take 6-18 months (El Moussaoui et al. 2006). There are no studies that would had provided information about the long-term outcome of early childhood pneumonia with regards to HRQoL.

3 Aims of the study

The aim of the present study was to evaluate respiratory morbidity, health-related quality of life, and lung function in adulthood in study subjects who were hospitalized for bronchiolitis or pneumonia at ages less than 2 years. The connection of RSV etiology of LRTI in infancy with these outcomes was studied. In addition early childhood risk or protective factors for asthma and lung function reduction in adulthood were investigated.

The specific aims of the study were as follows:

Evaluate if the prevalence of asthma is increased in adulthood after bronchiolitis or pneumonia in early childhood when compared to population controls;

Study if reduced lung function and irreversible bronchial obstruction are present between the ages of 28-31 years after bronchiolitis or pneumonia in early childhood;

Describe the respiratory health-related quality of life in adulthood after bronchiolitis or pneumonia in early childhood;

Examine the impact of RSV etiology on the adulthood outcome of ealy childhood LRTI hospitalization;

Clarify the role of early-childhood risk or protective factors for asthma and lung function reduction in adults 30 years after bronchiolitis in infancy;

Examine the role of blood eosinophil count during early childhood bronchiolitis or outside the infection as a determinant for subsequent respiratory morbidity in adulthood.

4 Subjects and Methods

4.1 STUDY DESING AND ENROLLMENT OF STUDY SUBJECTS IN 1981-1982

4.1.1 Enrollment of study subjects

Between 1 September 1981 and 31 August 1982, 130 children who were hospitalized for LRTI in Kuopio University Hospital Department of Pediatrics at the age of less than 2 years were enrolled in the study (Korppi et al. 1986). Three children were excluded before the analysis due to inappropriate collection of early childhood data. Among the 127 recruited children (77 boys and 50 girls) with LRTI, 83 of them had bronchiolitis and 44 had pneumonia.Most (75%) of the children with diagnosed bronchiolitis were wheezing for the first time. Bronchiolitis was diagnosed based on the auscultatory findings of prolonged expiratory phase and expiratory wheezing. Chest radiographs were obtained in all cases, and pneumonia was diagnosed in study subjects who presented viral LRTI without wheezing but had an interstitial infiltration on chest radiograph. None of the pneumonia patients had large alveolar infiltrates that are characteristic for *Streptococcus pneumoniae* pneumonia. Those study subjects who presented an interstitial infiltration on the chest radiograph and had expiratory breathing difficulties (n=46) were included in bronchiolitis group (Korppi et al. 1986).

4.1.2 Viral etiology

The viral etiology of LRTI was determined with antigen assays from nasopharyngeal aspirates (NPA) and with abtibody assays from paired serum samples for 7 respiratory viruses, including RSV, parainfluenza 1, 2 or 3 viruses, adenovirus, and influenza A and B viruses (Korppi et al. 1986). The RSV antigen or antibody test was positive in 51/127 (40%) children (Korppi et al. 1986). In addition, 30 children who were RSV negative (and negative for the other six studied viruses) were hospitalized during the severe nationwide RSV epidemic between 1 October and 31 December 1981. Thus, 81/127 (64%) of the children either had a confirmed RSV infection or a highly probable RSV infection due to the susceptible age, typical clinical presentation, and community epidemic.

4.2 COLLECTION OF DATA UNTIL THE AGE OF 2-3 YEARS

4.2.1 Follow-up visits in early childhood

After the index LRTI episode, 4 prospective follow-up studies were conducted to collect the early childhood data: one on convalescence, 4-6 weeks after hospitalization, 2 between the ages 1-2, and one between the ages of 2.5-3 years (Figure 1). Collected data included doctor-diagnosed asthma and allergy in mothers and fathers, parental smoking history, and the presence of doctor-diagnosed atopic dermatitis in children at less than 2 years of age. The number of wheezing episodes was registered separately for the age periods of 0-1 years and 1-2 years. Doctor-diagnosed, repeated wheezing was defined by more than 2 wheezing episodes during the year preceding the control visit.

Serum allergen-specific IgE (RAST, Pharmacia Diagnostica, Uppsala, Sweden) was measured in 67 children between 1.5-2 years of age and in 76 children between 2.5-3 years of age (Piippo-Savolainen et al. 2007b). The studied allergens were birch, timothy grass and mugwort pollens, house dust mite *Dermatophagoides pteronyssinus*, spores of *Cladosporium herbarum,* and dander of cat and dog. Total serum IgE was studied at the age of 6-12 months and

at the age of 18-24 months. Atopy in infancy was originally defined as the presence of doctor-diagnosed atopic eczema and/or high total serum IgE (>60kU/l) at the age of less than 2 years (Reijonen & Korppi 1998, Piippo-Savolainen et al. 2007a, Saarinen et al. 1982). Atopic sensitization was defined as the presence of specific IgE to any allergen at the detection level >0.35 kU/l.

Blood eosinophils were counted on admission and on convalescence 4-6 weeks after admission to hospital. The cut-off limit was >0.45x10E9/l for high blood eosinophil count and <0.25x10E9/l for low blood eosinophil count (Reijonen & Korppi 1998, Piippo-Savolainen et al. 2007a).

4.3 FOLLOW-UP IN CHILDHOOD, ADOLESCENCE, AND EARLY ADULTHOOD

4.3.1 Study subjects

Between the ages of 4.5-6 years, when pneumonia cases were not invited, 68/83 former bronchiolitis patients attended the clinical study. Between the ages of 8-9.5 years, 91 study subjects (62/83 from bronchiolitis and 29/44 from pneumonia group) were clinically examined. At the age of 13.5-16 years, 98/127 (77%) former bronchiolitis and pneumonia patients attended the questionnaire study. In 2000, 54/83 former bronchiolitis and 34/44 pneumonia patients attended the clinical follow-up study (Figure 1). On each follow-up visit, allergy and asthma were carefully screened. Skin prick tests (SPT) were performed betwen the ages of 8-10 years and 18-20 years including the most common inhaled allergens (Piippo-Savolainen et al. 2004, Korppi et al. 1994). Flow volume spirometry (FVS) was conducted at the age periods of 8-10 years and 18-20 years (Piippo-Savolainen et al. 2004, Korppi et al. 1994).

The control group was not originally enrolled in the study. However, at the age periods of 8-10, 18-20, and 26-29 years, controls were recruited from an atopy prevention study (Figure 1) (Piippo-Savolainen et al. 2004, Korppi et al. 1994, Ruotsalainen et al. 2010a, Poysa et al. 1988). At the 26-29 years follow-up, population-based controls were recruited for the first time (Ruotsalainen et al. 2010a).

4.4 FOLLOW-UP STUDY IN 2010

4.4.1 Study subjects

In 2010, at the age period of 28-31 years, a written questionnaire and an invitation to the clinical study was sent to 122 of the 127 study subjects. The current addresses of the five other study subjects were unavailable. Sixty (72%) of the 83 subjects from the bronchiolitis and 24 (55%) of the 44 subjects from the pneumonia group returned the questionnaire. Forty-eight (58%) and 22 (50%) study subjects, respectively, attended the clinical study.

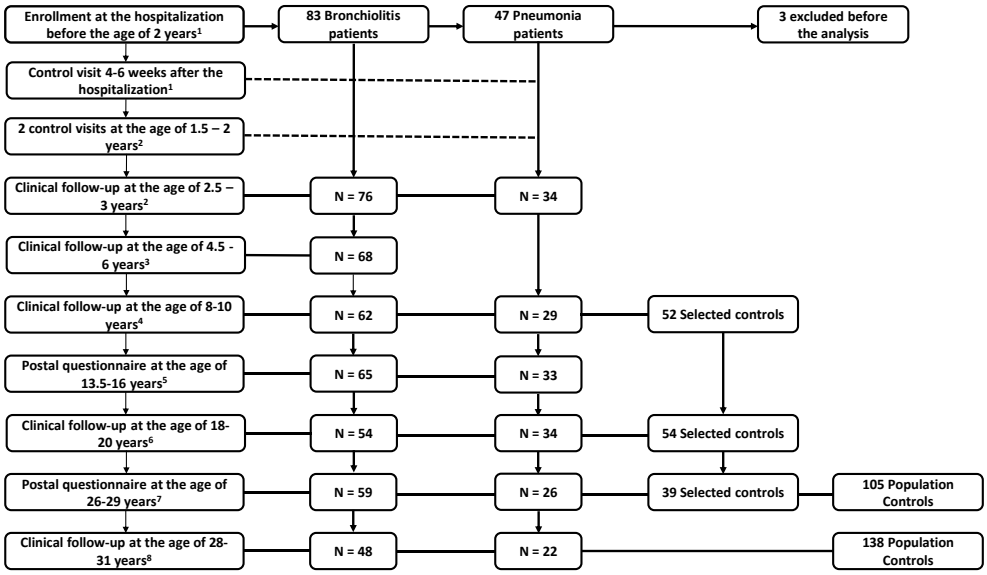
The RSV LRTI group consisted of 43 clinically examined study subjects, including 27 former bronchiolitis and 16 former pneumonia patients. Out of them, 24 subjects had confirmed RSV infection during LRTI in infancy, and 19 had highly probable RSV infection (*i.e.*, hospitalized during the epidemic with identical clinical pictures as the confirmed RSV cases) in infancy.

4.4.2 Controls

For the 2010 follow-up, 488 population-based control subjects were enrolled at a 4:1 ratio for the 122 cases from the Population Register Centre in Finland. Controls were born in the primary area near the Kuopio University Hospital, and they were matched for sex and birth month. Four control subjects who had been treated in the hospital for lower airway infection at less than 24 months of age were excluded. In total, 166 (34%) control subjects returned the

completed questionnaire, and 138 (28%) attended the clinical study. For 43 RSV positive study subjects, a control group of 86 (2 controls for each study subject) was constructed by using sex and birth date as the selection criteria.

Figure 1. Flow chart showing the follow-up of the *1980's Finnish post-bronchiolitis and pneumonia study* from early childhood up to the age of 28-31 years.



References: [1]Korppi 1986, [2]Korppi 1993, [3]Kuikka 1994, [4]Korppi 1994, [5]Hyvärinen 2005, [6]Piippo-Savolainen 2004, [7]Ruotsalainen 2010, [8]Backman 2014

4.4.3 Questionnaire data

The questionnaire comprised of questions on asthma-presumptive symptoms such as wheezing, repeated night cough, or prolonged day cough apart from infection during the preceding 12 months. In addition, the questionnaire also included inquiries about the presence of previous doctor-diagnosed asthma and the regular use of inhaled corticosteroids (ICS) or on-demand use of bronchodilators during the preceding 12 months. The occurrence of presumptively allergic nasal, eye, and skin symptoms were charted for the preceding 12 months.

Current and previous smoking status was determined. Study subjects were considered to be current daily smokers if they smoked at the time of the study and had smoked at least one cigarette per day for one year. Pack-years were calculated for current and earlier smokers if they had smoked daily at least for one year using the following equation: the number of cigarettes smoked daily multiplied by smoking years and divided by 20 (Forey et al. 2011).

4.4.4 Respiratory health-related quality of life

The participants completed the St. George's Respiratory Questionnaire (SGRQ), a widely used self-administered questionnaire designed to measure health impairment and respiratory health-related quality of life in adults with asthma or COPD (Jones et al. 1991, Jones et al. 1992).

Three different component scores can be calculated from the SGRQ: the symptom component (the level of respiratory symptoms based on their frequency and severity), the

activity component (the activities that cause breathlessness or the activities in which participation is limited due to breathlessness), and the impact component (social or psychological disturbances resulting from airway disease). The total score summarizes the influence of the disease on the overall respiratory health-related quality of life of the participant. The scores are expressed as a percentage of complete impairment; thus, the score 100 represents the worst possible respiratory health status, and the score 0 represents the best possible respiratory health status (Jones et al. 1991, Jones et al. 1992).

4.4.5 Clinical study

The clinical study consisted of an interview, physical examination, exhaled Nitric Oxide (FeNO) measurement, lung function test with bronchodilatation, SPTs for common inhaled allergens, and two-week home peak expiratory flow (PEF) monitoring.

4.4.6 Exhaled nitric oxide measurement

Orally exhaled nitric oxide (F_{ENO}) was measured with a NIOX MINO Airway Inflammation Monitor (Aerocrine AB, Solna, Sweden) according to the ATS and ERS standards (American Thoracic Society & European Respiratory Society 2005). At minimum, two measurements were required, and inhalations were repeated until two values were obtained within 10% of each other. Acceptable F_{ENO} was obtained from all but one of the study subjects and from all controls.

4.4.7 Flow volume spirometry and the definition of irreversible airway obstruction

Baseline lung function was measured with a Medikro SpiroStar USB spirometer (Medikro, Kuopio, Finland) using Spiro 2000, Software version 2.2. FVS was performed, and the results were reported according to ATS (American Thoracic Society) and ERS (European Respiratory Society) standards (Miller et al. 2005). At a minimum, 3 technically acceptable measurements were required, and if needed the measurements were repeated up to 8 times. The measured indices were forced vital capacity (FVC) and forced expiratory volume in one second (FEV1). FVC and FEV1 were presented as percentages of the means of age- and sex-specific, height-related reference values (FVC% and FEV1%) (Viljanen et al. 1982). FEV1/FVC was counted based on FVC and FEV1 results and is presented as age- and sex-specific, height-related (% of predicted) values (FEV1/FVC%). In addition to baseline FVS measurement (pre-BD values), FVS was also performed 15 minutes after inhalation of 400μg salbutamol (Ventoline Evohaler 0.1mg/dos, GlaxoSmithKline) (post-BD values) (Miller et al. 2005).

Irreversible airway obstruction was defined in categorized analysis as post-BD FEV1/FVC% below 88% of the predicted value (FEV1/FVC%<88%) according to the Finnish age- and sex-specific, height-related cut-off limit that was settled at the level of -2 standard deviations (SD) (Z-score -1.96) in Finnish non-selected adults (Viljanen et al. 1982) Since Finnish references are old and newer updated national references were not available, we also defined the irreversible airway obstruction by using the recently published, multi-ethnic, age-, sex- and height-adjusted Global Lung Function Initiative 2012 (GLI 2012) limits for abnormal FEV1/FVC –ratio (Quanjer et al. 2012). On the basis of this criterion, irreversible obstruction was considered to be present if post-BD FEV1/FVC-ratio was below 5^{th} percentile (lower limit of normality), corresponding z-score -1.64 (FEV1/FVC<5^{th} percentile).

4.4.8 Skin prick testing and the definitions of atopy

SPTs were performed on the forearms of 206 study subjects. ALK Soluprick® extracts were used (ALK, Copenhagen, Denmark), including the following allergens: birch, common alder, timothy grass, mugwort, dog, cat, horse, cow, dust mites (*D. pteronyssinus*, *D. farinae*, and *Acarus siro*), and one mold (*C. herbarum*). A weal with a diameter of at least 3 mm and half of the width of the positive control (histamine dihydrochloride) was considered as positive (The European Academy of Allergology and Clinical Immunology 1993, Bousquet et al. 2012).

Atopy was defined as the presence of at least one positive reaction for tested allergens. Allergic rhinitis and conjunctivitis were defined if there were seasonal symptoms or symptoms triggered by animal contacts during the preceding 12 months. Atopic eczema was defined as itchy eczema at typical locations requiring treatment during the preceding 12 months. Clinical atopy was defined by the presence of allergic rhinitis, allergic conjunctivitis, or atopic eczema combined with atopic sensitization (one or more positive SPT results).

4.4.9 Home Peak Expiratory Flow Monitoring

PEF was measured using a Mini Wright PEF meter (Clement-Clarke International LTD, Harlow, Essex UK) three times every morning and every evening for two weeks. The best of the 3 values was included in the analyses if the difference between the two best values was less than 40L/min (Miller et al. 2005). Daily diurnal variability over 20% between the PEF morning and evening values was considered abnormal (Asthma: Current Care Guidelines 2012, Quanjer et al. 1997) if present at least twice during the follow-up. Daily diurnal PEF variability was calculated from twice daily PEF as [(day´s highest – day´s lowest) / mean of day´s highest and day´s lowest] x 100 (Global Initiative for Asthma 2014). During the second week, PEF was measured before and 15 min after the administration of inhaled bronchodilator in the morning (Salbutamol 0,4mg, Buventol easyhaler 0.1mg/dos, Orion Pharma, Finland) (Miller et al. 2005). PEF improvement of 15% or more (Asthma: Current Care Guidelines 2012), at least twice after the bronchodilator inhalation, was considered significant. PEF monitoring was considered appropriately completed if at least 7 acceptable morning and evening measurements and 3 days with acceptable pre- and post-treatment measurements were available. Of the 208 study subjects, 180 (87%) returned the PEF monitoring results, and 175 (84%) were considered as appropriately completed.

4.4.10 Definition on Asthma

Bronchial asthma was defined by two different ways to reflect the certainty of the diagnosis: doctor-diagnosed asthma and self-reported asthma.

For doctor-diagnosed asthma, an on-going regular maintenance medication with ICSs and a previously settled asthma diagnosis were required. In addition, study subjects who reported asthma-presumptive symptoms and/or repeated use of on-demand bronchodilators during the preceding 12 months and in addition had a pathological result in the home PEF monitoring were regarded to have doctor-diagnosed asthma. Repeated wheezing episodes, chronic night cough, and prolonged cough for more than 4 weeks apart from infection were regarded as asthma-presumptive symptoms.

For self-reported asthma, previously diagnosed asthma combined with asthma-presumptive symptoms or with repeated use of on-demand bronchodilators during the preceding 12 months was required. Cases with doctor-diagnosed asthma were included.

4.5 STATISTICAL ANALYSES

The data was analyzed using SPSS 19.0 - 21.0 software (SPSS Inc., Chicago, IL, USA). Chi-square and Fisher's exact tests were used in the analyses of the categorized data. The Mann-Whitney U-test was used in the analysis of the continuous SGRQ scores, pack-years data and blood eosinophil counts. These results are presented with medians, 25-75 interquartile ranges (IQR), and ranges. Logistic regression was used in the multivariate analyses of categorized data, and the results are presented as adjusted p-values or adjusted odds ratios (OR) and their 95% confidence intervals (95%CI). Analysis of variance (ANOVA) adjusted for asthma and current daily smoking was used in the analysis of continuous lung function testing data.

4.6 ETHICS

Consent for the original study plan was obtained from The Ethics Committee of Kuopio University Hospital on 26th May 1981. Parents were informed of the study and the voluntary nature of participation, but written consent for the participation of the child was not obtained. At the time of the study, blood tests and radiography were routine examinations in suspected cases of severe bronchiolitis or pneumonia. However, these examinations may have been omitted for some patients if they had not been participating in the study. Therefore, some of the patients in the study were exposed to blood tests and radiography as a result of their participation in the study, and all patients were exposed to increased follow-up visits. However, this was considered to be outweighed by the special attention paid to the diagnostics and follow-up of patients with hospitalized LRTI.

The Ethics Committee of Pohjois-Savo Health-Care District approved the 30-year follow-up study (Permission number 76/2009, dated 20th January 2010). Informed written consent was obtained from all individual participants included in the follow-up study. Participation was voluntary and study subjects were able to discontinue the study at any phase. Clinical evaluation included interviews with the doctor, physical examination, FeNO measurement, lung function test with bronchodilatation, SPTs and two-week PEF monitoring. All study subjects were questioned about previous adverse reactions to STPs and bronchodilatation tests. If any reactions were suspected, the examinations were not performed. All measurements were considered fairly harmless to adult study subjects when compared to the valuable information gained about the long-term effects of early childhood LRTIs. We provided all participants with individual results and gave personal medical advice and directed participants to contact their own doctors for further advice in cases that resulted in new asthma diagnosis or imbalanced asthma.

5 Results

5.1 ASTHMA IN ADULTHOOD AFTER EARLY CHILDHOOD BRONCHIOLITIS OR PNEUMONIA

5.1.1 Characteristics of study groups

There were 12 former bronchiolitis patients, 2 pneumonia patients and 28 control patients who returned the written questionnaires but did not attend the clinical study. There were no significant differences between those who did or did not attend the clinical study in presumptive asthma symptoms during the 12 month period, or prevalence of previously diagnosed (based on questionnaire only). In addition, there was no significant difference in the usage of continuous ICSs or on-demand bronchodilating drugs between those who did or did not attend the clinical study (data not shown). Those who did not attend the clinical study were excluded from the further analysis.

There were no significant differences in sex distribution between the three study groups (Table 4). Fourteen (29%) former bronchiolitis patients, 10 (46%) former pneumonia patients, and 17 (12%) control subjects were current daily smokers. The amount of smoked pack-years was also significantly higher in the bronchiolitis group compared to controls. There were no significant differences between study groups in prevalence of asthma presumptive symptoms, such as chronic night cough, prolonged cough, or repeated wheezing. However, the use of on-demand bronchodilators and regular ICSs were more common in former bronchiolitis patients than in controls (Table 4).

5.1.2 Asthma and Atopy

Allergic symptoms and atopic sensitization were common in all study groups. Atopic sensitization was found in 30 (64%) study subjects in the bronchiolitis group (p = 0.558 *vs.* controls), 12 (55%) in the pneumonia group (p = 0.690 *vs.* controls), and 79/136 (58%) in controls. In addition, 23 (48%) former bronchiolitis patients (p = 0.724 *vs.* controls), 10 (46%) former pneumonia patients (p = 0.674 *vs.* controls), and 66/136 (49%) controls were diagnosed to have clinical atopy, *e.g.*, positive reaction in SPT´s combined with allergic symptoms.

Doctor-diagnosed asthma was present altogether in 32/208 study subjects. Of these subjects 27 (84%) had previously diagnosed asthma at some time of life, and 22 had previously diagnosed asthma in addition to having used continuous ICSs during the previous 12 months. Ten study subjects were diagnosed to have doctor-diagnosed asthma due to asthma-presumptive symptoms and/or repeated use of inhaled bronchodilating drugs and pathology in PEF follow-up. Five of these had previously diagnosed asthma, so only 5 completely new asthma diagnoses were made in the whole study population, 1 in pneumonia group and 4 in control group. All former bronchiolitis patients who had doctor-diagnosed asthma also had previously diagnosed asthma at some time of life. Self-reported asthma was present in an additional 10 cases. Both doctor-diagnosed asthma and self-reported asthma were significantly more common in former bronchiolitis patients compared to controls (Figure 2). Asthma figures by both definitions were similar in the former pneumonia patients and in controls (Figure 2).

Doctor-diagnosed asthma was present in 10/43 (23%) former RSV LRTI patients and 11/86 (13%) controls (p=0.188; adjusted for age, sex, clinical atopy, and current daily smoking). In addition, self-reported astma was present in 28% of the former RSV LRTI patients compared to 17% in control group (adjusted p-value= 0.248). In line with these results, the FE_{NO} values were almost equal in both groups; the mean (95%CI) was 20 (13-27) in the RSV LRTI group and 20 (17-23) in controls (p=0.948). However, in subgroup analyses 9/27 (33%) former wheezing

RSV bronchiolitis patients had doctor-diagnosed asthma, which was significantly more compared to controls (p=0.038 *vs.* controls). There was no significant difference between RSV pneumonia patients (6%) and controls in the prevalence of asthma (p=0.160 *vs*. controls).

Table 4. Basic characteristics and the prevalence of asthma presumptive symptoms in the three study groups.

	Bronchiolitis N=48	**p-value[1]**	**Pneumonia N=22**	**p-value[1]**	**Control N=138**
Sex (male)	30 (63%)	0.326	8 (36%)	0.117	75 (54%)
Age	29.5 (0.72)	0.420	29.4 (0.58)	0.163	29.6 (0.75)
Current daily smoking	14 (29%)	0.007	10 (46%)	<0.001	17 (12%)
Smoked pack-years, median (range)[2]	0.1 (0.0-25.0)	0.036	0.5 (0.0-22.5)	0.064	0.0 (0.0-25.0)
Asthma symptoms					
Chronic night cough[3]	5 (10%)	0.311	5 (23%)	0.191	6 (4%)
Prolonged cough[3]	5 (10%)	0.861	5 (23%)	0.152	12 (9%)
Repeated wheezing[3]	16 (33%)	0.487	7 (32%)	0.898	37 (27%)
Use of asthma medication					
Bronchodilating drugs[3]	17 (35%)	0.002	2 (9%)	0.546	20 (15%)
Inhaled cortcosteroids[3]	10 (21 %)	0.023	1 (5%)	0.539	12 (9%)

[1] Paired comparisons vs. population controls

[2] Pneumonia group N=20, Control group N=135

[3] P-values are presented adjusted for age, sex, clinical atopy and current daily smoking

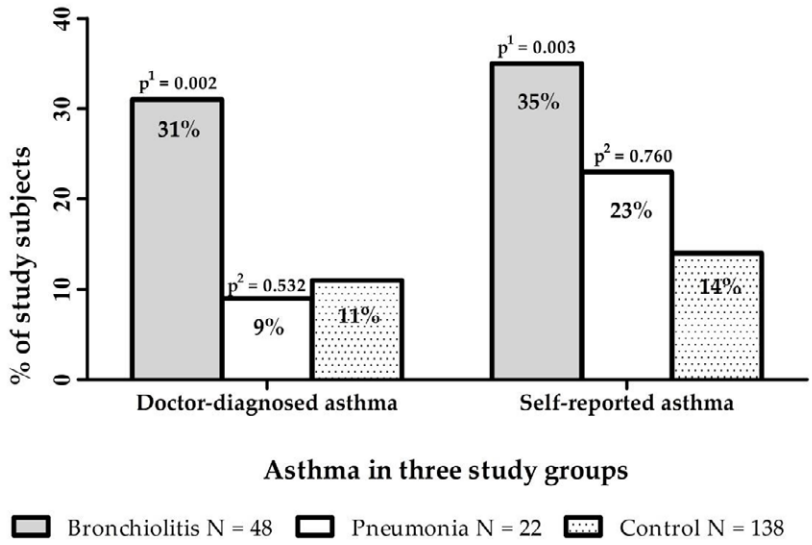


Figure 2. Asthma by two definitions at the age period of 28-31 years in the study subjects hospitalized for bronchiolitis or pneumonia at less than 24 months of age compared with population controls. [1]paired comparison between bronchiolitis and control group and [2]paired comparison between pneumonia and control group as adjusted for age, sex, clinical atopy, and current daily smoking.

5.2 LUNG FUNCTION IN ADULTHOOD AFTER EARLY CHILDHOOD LRTI

Pre-BD and post-BD FVC%, FEV1%, and FEV1/FVC% were lower in former bronchiolitis patients than in controls (Figure 3). Instead, the former pneumonia patients had lower pre-BD and post-BD FEV1% compared to controls (Figure 3). There were no significant differences between the bronchiolitis and pneumonia groups (Figure 3). Mean FEV1% response to bronchodilator was 4.3% (95%CI 3.5-5.2%) in bronchiolitis group, 4.3% (2.2-6.3%) in pneumonia group and 4.3% (3.5 – 5.2%) in control group with no significant differences between groups.

Post-BD FEV1/FVC% was below 88% of predicted in 10 (21%) former bronchiolitis patients, 2 (9%) former pneumonia patients, and 5 (4%) controls. The respective figures for FEV1/FVC<5th percentile, according to the GLI 2012 references, were 7(15%), 1(5%), and 2(1%). The study groups (bronchiolitis, pneumonia, control), asthma and current smoking were included as covariates in the logistic regression. Belonging to the bronchiolitis group was an independently significant risk factor for irreversible airway obstruction by the Finnish references and belonging to the bronchiolitis group and the presence of current asthma by the GLI 2012 references (Table 5).

There were no significant differences in pre-BD or post-BD FVC% values between the RSV LRTI and control group (Figure 4). However, both pre-BD and post-BD FEV1% and FEV1/FVC% were significantly lower in the former RSV LRTI patients compared to controls (Figure 4). The lung function disorders were of the obstructive type, *i.e.*, not responding to bronchodilators, which confirms the presence irreversible airway obstruction after early childhood RSV LRTI.

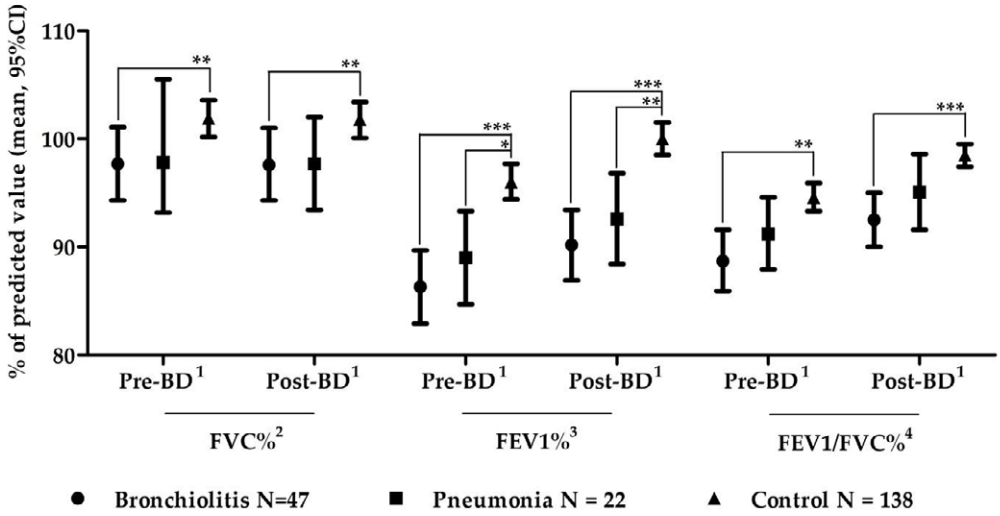


Figure 3. Pre- and post-bronchodilator lung function at the age period of 28-31 years after bronchiolitis or pneumonia in infancy compared to controls presented as means and 95% confidence intervals (95%CI). Analysis of variance and statistically significant differences between study groups are presented in the figure. P-values are adjusted with asthma and current daily smoking, * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$. [1]Pre-BD, pre-bronchodilator; post-BD, post-bronchodilator, [2]FVC%, forced vital capacity (% of predicted value, [3]FEV1%, forced expiratory volume in one second (% of predicted value, [4]FEV1/FVC%, FEV1/FVC ratio presented as % of predicted value

Table 5. Hospitalization for bronchiolitis or pneumonia in infancy, current asthma, and current daily smoking at 28-31 years of age as risk factors for irreversible airway obstruction.

Risk factors for irreversible airway obstruction	**FEV1/FVC% < 88%[1] N = 17**	**Adjusted OR[2] (95%CI)**	**FEV1/FVC<5th percentile[3] N = 10**	**Adjusted OR[2] (95%CI)**
Bronchiolitis group	10/47 (21%)	5.6 (1.7 – 18.2)	7/47 (15%)	7.1 (1.3 – 37.2)
Pneumonia group	2/22 (9%)	2.2 (0.3 – 13.6)	1/22 (5%)	1.7 (0.1 – 24.8)
Current daily smoking	15/41 (12%)	1.2 (0.4 – 4.0)	4/41 (10%)	2.2 (0.5 – 10.1)
Asthma	8/42 (19%)	2.8 (1.0 – 8.3)	7/42 (17%)	7.6 (1.8 – 32.6)

[1]Post-bronchodilator FEV1/FVC-ratio below 88% of predicted value

[2]All variables (group, current daily smoking and asthma) are included in the same logistic regression model

[3]FEV1/FVC-ratio below 5th percentile lower limit of normality (GLI 2013 references)

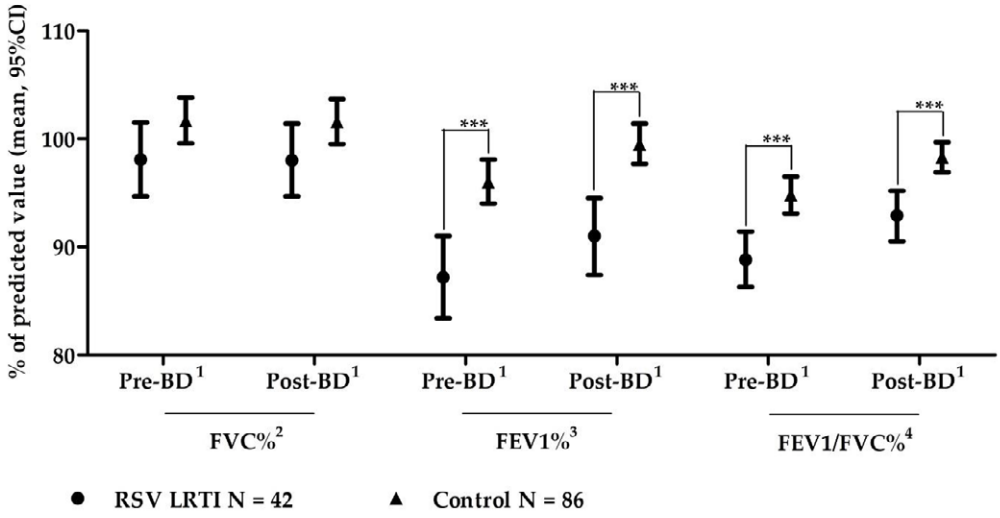


Figure 4. Pre- and post-bronchodilator lung function in adulthood after RSV lower respiratory tract infection (RSV LRTI) in infancy compared to controls presented as means and 95% confidence intervals (95%CI). Analysis of variance and statistically significant differences between study groups are presented in the figure. P-values are adjusted with age, sex, current daily smoking, and atopy, *** $p < 0.001$. [1]Pre-BD, pre-bronchodilator; post-BD, post-bronchodilator, [2]FVC%, forced vital capacity (% of predicted value, [3]FEV1%, forced expiratory volume in one second (% of predicted value, [4]FEV1/FVC%, FEV1/FVC ratio presented as % of predicted value.

5.3 THE SIGNIFICANCE OF EARLY RISK AND PROTECTIVE FACTORS FOR ASTHMA AND LUNG FUNCTION IMPAIRMENT IN ADULTHOOD

Previously described early risk factors for later asthma (*e.g.*, parental asthma, parental atopy, atopy at the age of less than 2 years, and non-RSV ethiology of bronchiolitis) had lost their significance at the age period of 28-31 years (Table 6). Repeated wheezing at the age of less than 2 years was a significant factor for asthma in adulthood (Table 6). However, this association was not independent of parental asthma, since all former bronchiolitis patients who had history of parental asthma experienced repeated wheezing by the age of 2 years. So, repeated wheezing under 2-years of age lost its significance as an independent asthma risk factor in multivariate analysis, including parental asthma, current smoking, early childhood atopy, and gender (OR, 95%CI 5.5, 0.8-37.1). None of these assumed risk factors had an association with FVC%, FEV1%, or FEV1/FVC% in adulthood when lung function was analysed as continuous variables. Results for FEV1/FVC% are presented in Figure 5. When lung function was analysed as categorized variables, those with the history of parental asthma had Post-BD FEV1/FVC<5th percentile significantly more often compared to those with no such history (OR, 95%CI 16.52, 1.09-249.88 in multivariate analysis with gender, current smoking, atopy, and repeated wheezing at under 2-years-of-age included).

Table 6. Prevalence of early life factors in 47 former bronchiolitis patients, with and without asthma, at the age period of 28-31 years.

	Self-reported asthma[1] N (%)	**No asthma N (%)**	**OR (95%CI)[2]**
Early childhood factor			
Parental asthma[3] N=7/44	3/14 (21%)	4/30 (13%)	1.8 (0.3 – 9.4)
Parental atopy[4] N=14/44	3/14 (21%)	11/30 (34%)	0.5 (0.1 – 2.1)
Repeated wheezing[5] N=31/45	15/17 (88%)	16/28 (57%)	6.2 (1.2 – 33.1)
Atopy[6] N=24/45	10/17 (59%)	14/28 (50%)	1.3 (0.4 – 4.7)
Non-RSV bronchiolitis N=33/47	11/17 (65%)	22/30 (73%)	0.7 (0.2 – 2.6)

[1]For definition of asthma, see the text
[2]Odd´s ratio and 95% confidence interval, adjusted for current daily smoking
[3]Doctor-diagnosed parental asthma present
[4]Doctor-diagnosed parental atopic dermatitis and/or hay fever present
[5]More than 2 doctor-diagnosed wheezing episodes before the age of 2 years
[6]Doctor-diagnosed atopic eczema and/or high serum IgE >60 IU//L at the age of less than 2 years

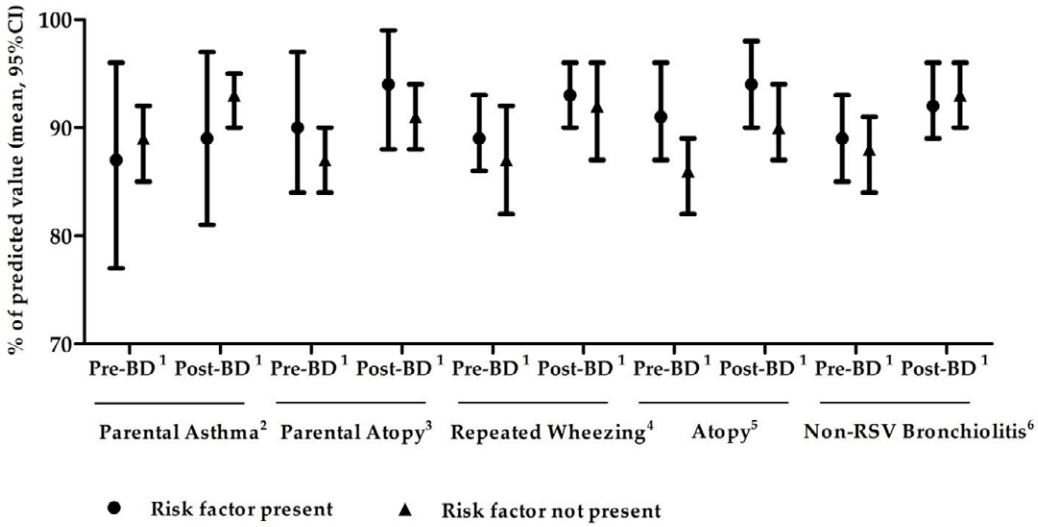


Figure 5. Pre- and post-bronchodilator FEV1/FVC% in adulthood in relation to early childhood risk factors presented as means and 95% confidence intervals (95%CI). Analysis of variance showed that no statistically significant differences were found, and p-values are not presented in the figure. P-values are adjusted with age, sex, current daily smoking. [1]Pre-BD, pre-bronchodilator; post-BD, post-bronchodilator, [2]Doctor-diagnosed parental asthma present, [3]Doctor-diagnosed parental atopic dermatitis and/or hay fever present, [4]More than 2 doctor-diagnosed wheezing episodes before the age of 2 years, [5]Doctor-diagnosed atopic eczema and/or high serum IgE >60 IU//L at the age of less than 2 years, [6]Bronchiolitis cause by other viruses than RSV

The median of eosinophils on admission among 47 study subjects included in the analysis was 0.11 x10E9/l (IQR 0.03 – 0.41); on convalescence the respective value was 0.24 x10E9/l (0.12 – 0.38). Study subjests with self-reported asthma in adulthood had significantly higher eosinophil counts on admission to hospital compared to those who did not have adulthood asthma (Figure 6). There were no significant differences between eosinophil counts on convalescence in early childhood between the study subjects with or without asthma in adulthood (Figure 6). We continued the analysis with categorizing eosinophil counts into high (>0.45x10E9/l) or low (<0.25x10E9/l) on admission or on convalescence. Study subjects with high eosinophil count on convalescence outside the infection had increased risk for asthma compared to those with normal or low eosinophil count on convalescence (Table 7), whereas low eosinophil count during bronchiolitis decreased the risk of asthma in adulthood (Table 7).

There were no significant differences between eosinophils on admission or eosinophils on convalescence and FEV1/FVC-ratio below 5th percentile in adulthood. However, high eosinophil count outside the infection was a significant risk factor for irreversible airway obstruction (FEV1/FVC-ratio below 5th percentile) in adulthood (OR 8.35, 95%CI 1.15 – 60.64). Analyses were adjusted with gender, current smoking and atopy in infancy, and all these associations were independent from atopic status in infancy.

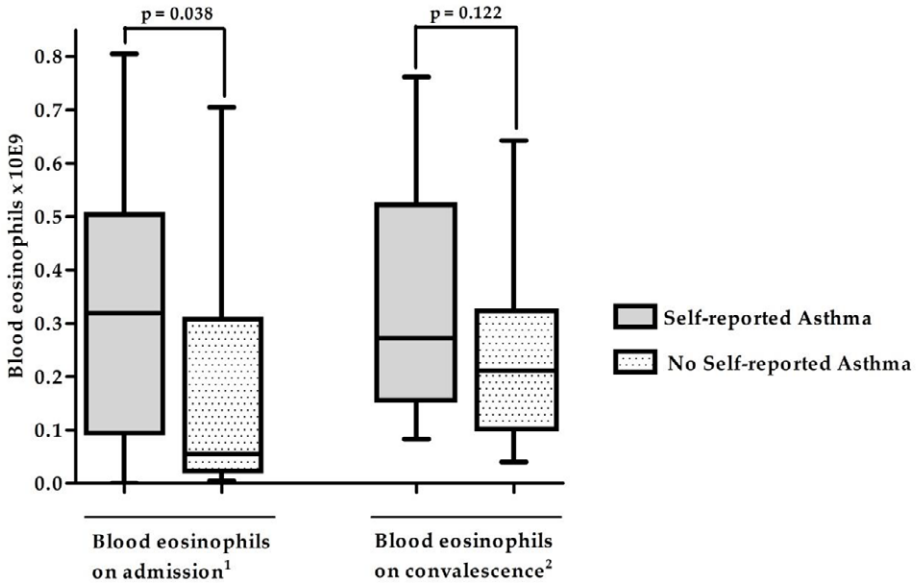


Figure 6. Blood eosinophils (median, interquartile range, range) on admission to hospital for bronchiolitis before the age of 2 years and on convalescence 4-6 weeks later in relation to self-reported asthma in adulthood. [1]Blood eosinophils on admission to hospital for bronchiolitis, [2]Blood eosinophils on convalescence 4-6 weeks after bronchiolitis.

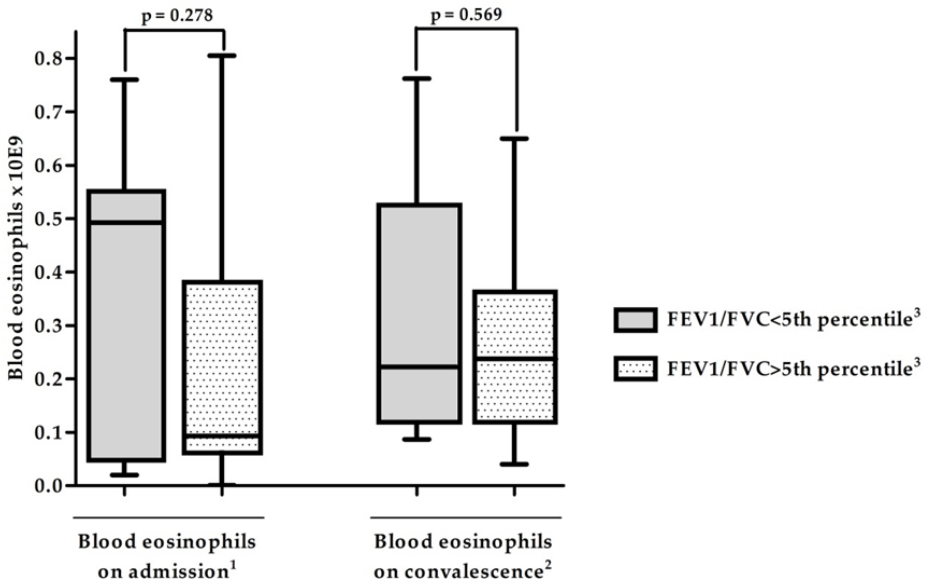


Figure 7. Blood eosinophils (median, interquartile range, range) on admission to hospital for bronchiolitis before the age of 2 years and on convalescence 4-6 weeks later in relation to FEV1/FVC-ratio below 5th percentile in adulthood. [1]Blood eosinophils on admission to hospital for bronchiolitis, [2]Blood eosinophils on convalescence 4-6 weeks after bronchiolitis, [3]FEV1/FVC below or above the 5th percentile of lower limit of normality.

Table 7. Blood eosinophils on admission to hospital for bronchiolitis and on convalescence in relation to self-reported asthma in adulthood in 47 former bronchiolitis patients.

	Self-reported asthma[1] N = 17	**No asthma N = 30**	**OR (95%CI)[2]**
Blood eosinophils <0.25x10/E9/l on admission[3] (N=28)	6 (35%)	22 (73%)	0.17 (0.04 – 0.68)
Blood eosinophils >0.45x10^9/l on admission[3] (N=11)	5 (29%)	6 (20%)	2.00 (0.44 – 9.14)
Blood eosinophils <0.25x10^9/l on convalescence[4] (N=25)	7 (41%)	18 (60%)	0.40 (0.11 – 1.47)
Blood eosinophils >0.45x10/E9/l on convalescence[4] (N=9)	7 (41%)	3 (10%)	6.30 (1.13 – 35.30)

[1]For definition of asthma, see the text, [2]Odds ratio, logistic regression: adjusted with gender, current smoking and atopy in infancy and 95% confidence interval, [3]On admission to hospital for bronchiolitis, [4]On convalescence, 4-6 weeks after bronchiolitis

5.4 HEALTH-RELATED QUALITY OF LIFE AFTER EARLY CHILDHOOD LRTI

Both former bronchiolitis patients and former pneumonia patients had significantly higher total scores in the SGRQ than controls (Table 8). The former bronchiolitis group differed from the control group in all parts of the questionnaire, whereas the former pneumonia group differed in terms of symptom scores (Table 8). The study subjects were divided into two groups on the basis of SGRQ scores (lower *vs.* higher than the median of the controls). In the bronchiolitis group, 73% of study subjects (OR, 95%CI 2.6, 1.5 – 5.6 *vs.* controls) had SGRQ total scores above the median of the controls, as adjusted with age, sex, current smoking and clinical atopy; in the pneumonia group, this value was 77% of study subjects (3.7, 1.2 – 11.2 *vs.* controls**),** indicating that these differences were independent from smoking.

After RSV LRTI in early childhood, the median total scores in SGRQ were 3.4 (IQ 25-75 1.1 – 15.2) in RSV LRTI and 1.5 (0.0 – 5.4) in control group (p=0.007), reflecting the lower respiratory health-related quality of life in adulthood after RSV LRTI in infancy.

Table 8. The scores calculated from the St. George's Respiratory Questionnaire in the three study groups

	Bronchiolitis N=48		**Pneumonia N=22**		**Control N=138**
SGRQ components	**Median** IQR[1] 25 - 75	**p – value[2]**	**Median** IQR[1] 25 - 75	**p – value[2]**	**Median** IQR[1] 25 - 75
Symptom score	**9.1** 0.0 – 26.3	**0.044**	**18.4** 5.1 – 29.9	**0.005**	**5.0** 0.0 – 16.3
Activity Score	**5.7** 0.0 – 12.1	**0.002**	**0.0** 0.0 – 13.4	**0.146**	**0.0** 0.0 – 6.0
Impact Score	**2.4** 0.0 – 9.5	**< 0.001**	**0.0** 0.0 – 8.4	**0.475**	**0.0** 0.0 – 2.4
Total Score	**5.4** 0.0 – 14.7	**< 0.001**	**4.9** 1.3 – 14.8	**0.012**	**1.5** 0.0 – 6.0

[1] Interquartile range

[2] Paired comparisons vs. controls; non-adjusted p-values

6 Discussion

6.1 STUDY DESIGN AND SUBJECTS

6.1.1 Study design

This study is a prospective follow-up of a cohort of children who were recruited in 1981-82 at the hospitalization for bronchiolitis or pneumonia under 24 months of age. This cohort has been followed-up for almost 30 years, and at the time of the present follow-up, the study subjects were adults between 28-31 years old. After the collection of early childhood data before the age of 3 years, 3 clinical follow-up studies have been carried out at the age periods of 4.5-6 years (Kuikka et al. 1994), 8.5-10 years (Korppi et al. 1994), and 18-20 years (Piippo-Savolainen et al. 2004). In addition, 2 postal questionnaire studies were carried out at the age periods of 13.5-16 years (Hyvarinen et al. 2005) and 26-29 years (Ruotsalainen et al. 2010a).

Previously, this cohort has provided information about the viral etiology and long-term outcome of of early childhood LRTIs (Piippo-Savolainen et al. 2004, Kuikka et al. 1994, Korppi et al. 1994, Hyvarinen et al. 2005, Korppi et al. 1986, Ruotsalainen et al. 2010a). The long-term outcome has been studied in relation to asthma, atopy, and lung function (Piippo-Savolainen et al. 2004, Kuikka et al. 1994, Korppi et al. 1994, Hyvarinen et al. 2005, Korppi et al. 1986, Ruotsalainen et al. 2010a). It has also provided information about the long-term outcome of LRTIs in relation to etiology of initial LRTI (Korppi et al. 2004, Piippo-Savolainen et al. 2007, Ruotsalainen et al. 2010b).

The present 30-year follow-up was perfomed to answer questions regarding the adulthood outcome of children who presented LRTI in early childhood (in terms of asthma prevalence, lung function, and HRQoL) as well as to determine the effect of RSV etiology of LRTI on these outcomes. This is the longest active post-LRTI cohort in the world, and it is uniquely positioned to answer the questions about the adulthood outcome of early childhood LRTIs in a prospective setting.

In practice, the present follow-up was performed as a moving clinic, and the study subjects were examined in their present home cities. All the equipment for study examinations were the same for all study subjects, and spirometry and FeNO were calibrated and performed as recommended by the international guidelines. All examinations were performed by two research doctors and one respiratory nurse, which reduces the variability of the findings.

6.1.2 Study subjects

Originally, 83 bronchiolitis and 44 pneumonia patients were recruited in the study. The study subjects represent a selected population of hospitalized LRTI patients, as it is known that about 30-40% of children develop bronchiolitis before the 2 years of age (Zorc & Hall 2010, Ralston et al. 2014), but only 1-3% are hospitalized for it (Nagakumar & Doull 2012, Smyth & Openshaw 2006, Henderson et al. 2005). The original bronchiolitis cohort represented 1-1.5% of the population under two years of age in the area and is therefore a representative and non-selected sample of hospitalized LRTI patients (Piippo-Savolainen 2006). Since non-wheezing pneumonia patients were also included in the study, the comparison between non-wheezing and wheezing LRTI patients was possible, adding to the uniqueness of this study.

The study design did not include controls from the beginning of the study. However, pneumonia patients were used as non-wheezing controls throughout childhood. Selected controls from a prospective atopy prevention study were used at the 8-10, 18-20 and 26-29 year follow-ups (Piippo-Savolainen et al. 2004, Korppi et al. 1994, Ruotsalainen et al. 2010a), and population based controls were used at the 26-29 year follow-up (Ruotsalainen et al.

2010a) and at the present 30-year follow-up. In 2010, at the age period of 28-31 years, 48(58%) bronchiolitis patients, 22(50%) pneumonia patients, and 166(34%) controls attended the clinical study. The attendance rate of the original study group was rather low, which is understandable, since the cohort has been followed-up for almost 30 years. There were no differences in gender or age distribution between the study groups.

6.2 ASTHMA AFTER EARLY CHILDHOOD BRONCHIOLITIS OR PNEUMONIA

6.2.1 Definitions of bronchiolitis and pneumonia

During the recruitment of study subjects less than 24 months of age in 1981-82, the definition of bronchiolitis included a prolonged expiratory phase and expiratory wheezing. Pneumonia patients were diagnosed based on symptoms of viral LRTI without wheezing but an interstitial infiltration on chest radiograph was required (Korppi et al. 1986). The definition of bronchiolitis age limit and symptoms varies in different countries. In the enrollment of patients, the age limit of 24 months was used for bronchiolitis as in other studies in the eighties (Wennergren et al. 1992). This age limit is still in use in several current guidelines (Ralston et al. 2014, Scottish Intercollegiate Guideline Network 2012). Wheezing in children under three years of age can be classified as two different clinical conditions, wheezing bronchitis and bronchiolitis (Tapiainen et al. 2015). To reduce the heterogeneity of clinical definitions, several studies and guidelines recently suggested an age limit of 12 months for bronchiolitis (Zorc & Hall 2010, Tapiainen et al. 2015, Mecklin et al. 2014, Smyth & Openshaw 2006, Henderson et al. 2005); wheezing from 12 months onward is called wheezing bronchitis (Tapiainen et al. 2015). However, bronchiolitis and wheezing bronchitis still have a significant overlap, and it has been suggested that the term bronchiolitis for the initial wheezing episode is irrelevant due to inaccurate, symptom-based classification (Brand et al. 2008). As has been done in previous study follow-ups, using the term "bronchiolitis" in these wheezing children is accurate enough and adheres to currently used guidelines supporting this definition (Ralston et al. 2014, Scottish Intercollegiate Guideline Network 2012).

There is also significant heterogenity in the definition of acute bronchiolitis symptoms. Some definitions emphaze audible wheezing, while in other definitions, wheezing is not required for the diagnosis (Elphick et al. 2007, Everard 2006). It can be argued whether or not our definition of pneumonia, especially in case of RSV pneumonia, is part of the same entity as bronchiolitis. However, it has been demonstrated that wheezing during LRTI may be a significant symptom when evaluating the later outcome of LRTI (Elphick et al. 2007). Our classification, also used in previous follow-ups of the cohort, has enabled us to differentiate the outcome of LRTI in terms of wheezing and non-wheezing LRTI.

6.2.2 Definition of asthma

The definition of asthma was based on the previous follow-ups of the cohort with only minor modifications (Piippo-Savolainen et al. 2004, Ruotsalainen et al. 2010a). Doctor-diagnosed asthma was based on regular use of ICSs and a previously settled asthma diagnosis or a pathological result in the home PEF monitoring combined with symptoms; so, the definition was rather strict.

It has been suggested that asthma may be a continuum and that choosing a cut-off point for a dichotomous asthma definition may unnecessarily reduce power of the study (Pekkanen et al. 2005). To avoid underdiagnosis of asthma, another definition based on less strict self-reported asthma was used as in previous follow-ups of the cohort (Piippo-Savolainen et al. 2004, Ruotsalainen et al. 2010a). Previous doctor-diagnosed asthma combined with asthma-presumptive symptoms or with repeated use of on-demand bronchodilators during the

preceding 12 months was required for the diagnosis of self-reported asthma. So this definition was very close to the definition of doctor-diagnosed asthma and was considered reliable to describe asthma prevalence in our study population. To avoid type 2 error in statistical analysis this definition was used in the analysis of early childhood risk factors. Only 5 new cases of doctor-diagnosed asthma were made in whole study population; they form 16% of all asthma cases. All others had previously diagnosed asthma at some time of their lives. This means that the definitions of asthma fits with real asthma morbidity in our study population rather well.

6.2.3 Prevalence of asthma

Asthma prevalence at the age period of 28-31 years was 31-35% in the bronchiolitis group, 9-23% in the pneumonia group, and 11-15% in the control group, depending on definiton. Bronchiolitis patients had asthma significantly more often compared to controls, but other differences were not significant. However there were no significant differences between the three study groups in asthma presumptive symtoms. This may reflect the proportion of treated asthma among former bronhiolitis patients, since inhaled conticosteroids were significantly more often used in the bronchiolitis group compared to controls.

In previous studies, the prevalence of asthma has been 5-9% in the Finnish adult population (Huurre et al. 2004, Pallasaho et al. 2011, Laatikainen et al. 2011). Compared to these figures, a 31-35% prevalence of asthma after bronchiolitis in early childhood seems high. Moreover, the asthma prevalence in the controls was 10-15%, which is slightly higher than the 5-9% asthma prevalence in the Finnish adult population in general. This probably demonstrates that symptomatic controls are more likely to attend studies than non-symptomatic ones. There is only one comparable prospective post-bronchiolitis study from Sweden that has continued to adulthood (Goksor et al. 2015). In line with our results, the 37% asthma prevalence after hospitalization for bronchiolitis was found in the latest follow-up of this cohort at the age period of 25-28 years (Goksor et al. 2015). In addition, at the age period of 17-35 years, the 38% asthma prevalence was established in hospitalized patients in a retrospective post-bronchiolitis study (Larouch et al. 2000).

Although the prognosis of early childhood wheezing is favorable in the majority of children, it has been established that wheezing illness in childhood is associated with an increased risk for persistent asthma or relapse in early adulthood (Stern et al. 2008, Sears et al. 2003). In the case of asthma remission, symptoms usually disappear during puberty and reappear in early adulthood (Stern et al. 2008, Sears et al. 2003, Butland & Strachan 2007). It has been demonstrated asthma relapse at the age of 22-26 years can be predicted by bronchial hyperreactivity (Stern et al. 2008, Rasmussen et al. 2002) and low airway function (Stern et al. 2008) at the age of 6 years, as well as late-onset or persistent wheezing (Stern et al. 2008), childhood atopy (Sears et al. 2003) and a younger age at onset of wheezing (Sears et al. 2003). This phenomenon of asthma remission and relapse after early childhood wheezing has also been described in the present cohort (Piippo-Savolainen & Korppi 2008). In the present cohort, 25% of children reported asthma at ages 4–6 years after bronchiolitis, as compared with only 14-15% at ages 8–15 (Korppi et al. 1993, Kuikka et al. 1994, Korppi et al. 1994, Hyvarinen et al. 2005). However, the prevalence of doctor-diagnosed asthma rose to 30-41% in early adulthood (ages 18–20 years) (Piippo-Savolainen et al. 2004). After the increase in asthma prevalence in early adulthood no further increase in asthma prevalence had happened at the age of 28-31 years. In the previous follow-up, between 26-29 years of age, asthma prevalence after bronchiolitis was 20-41%, but the diagnosis of doctor-diagnosed asthma was based on posted questionnaire only; therefore, the figures may not be totally comparable between these follow-ups (Ruotsalainen et al. 2010a).

In the present study, asthma risk after pneumonia in early childhood was not increased compared to controls, which is in line with the previous follow-up of the cohort (Piippo-Savolainen et al. 2004). The 20-year clinical follow-up of this cohort demonstrated 15-

21% asthma prevalence in former pneumonia patients (Piippo-Savolainen et al. 2004) and the asthma prevalence of 9-23% in the present follow-up was comparable to these figures. However, in the recent follow-up of the Tucson birth cohort increased asthma risk was demonstrated after early childhood pneumonia at the age of 26 years (Chan et al. 2015). It may be that in case of asthma prevalence after pneumonia in early childhood our study results should be interpreted with a caution because of small number of study subjects in the pneumonia group.

As a conclusion, asthma risk is increased at the age of 28-31 years after hospitalization for the early childhood bronchiolitis group compared to controls with no history of early childhood LRTI hospitalization. Asthma prevalence of 31-35% in adulthood after bronchiolitis is in line with previous study results and asthma prevalence remains quite stable between the ages of 20-30 years. Asthma risk after early childhood pneumonia was not increased compared to controls in the present follow-up, and these results are contradictory to those found in the recent 26-year follow-up of the Tucson cohort (Chan et al. 2015). Overall, studies about the asthma prevalence after early childhood pneumonia are scarce.

6.3 LUNG FUNCTION IN ADULTHOOD AFTER EARLY CHILDHOOD LRTI

6.3.1 Lung function impairment in adulthood after early childhood LRTI

Previous studies that collected childhood data retrospectively demonstrated that lung function abnormalities and the prevalence of COPD are increased in adulthood after LRTIs in infancy (Lamprecht et al. 2011, Barker et al. 1991, Svanes et al. 2010). In line with this, lung function impairment after early LRTI in childhood has been demonstrated in several prospectively followed-up cohorts in childhood (Sigurs et al. 2005, Kotaniemi-Syrjanen et al. 2008, Hyvarinen et al. 2007, Wennergren et al. 1997, Stein et al. 1999) and in adolescence or early adulthood (Piippo-Savolainen et al. 2004, Sigurs et al. 2010, Goksor et al. 2008, Korppi et al. 2004). Due to these previous findings, we hypothesized that signs of irreversible obstruction might be seen at the age of 30 years in our prospectively followed-up cohort. Irreversible obstruction is the typical lung function abnormality in COPD, and if found in adults with history of early childhood LRTI, it might suggest that early childhood LRTI patients are at inceased risk for COPD in later adulthood.

In the present 30-year follow-up, the FVC%, FEV1%, and FEV1/FVC-ratio% were decreased in adulthood before and after bronchodilatation in former bronchiolitis patients, and FEV1% was reduced before and after bronchodilatation in pneumonia patients. However, there were no significant differences between the three study groups in response to bronchodilating drugs. These findings alone suggest irreversible type of bronchial obstruction after bronchiolitis. In pneumonia patients, these findings were not so obvious but of similar type.

In categorized analysis, irreversible obstruction, defined as FEV1/FVC% <88% according to the Finnish reference values (Viljanen et al. 1982), was present in 21% of former bronchiolitis patients, in 9% of former pneumonia patients, and in 4% of controls. The respective figures for the FEV1/FVC<5th percentile, according to the GLI 2012 reference values (Quanjer et al. 2012), were 15%, 5%, and 1%, with significant differences between the bronchiolitis and control groups by both definitions.

Our results are in line with the results of two Swedish post-bronchiolitis cohorts. Reduced FEV1/FVC-ratio before and after bronchodiatation was demonstrated in adults 17-20 years old, indicating at least partial irreversibility of bronchial obstruction after early childhood bronchiolitis (Sigurs et al. 2010, Goksor et al. 2008). In the previous follow-up of our cohort, at the age of 18-20 years, the FEV1/FVC-ratio was also reduced, which is consistent with present results, but the bronchodilatation test was not performed during the follow-up (Piippo-Savolainen et al. 2004). An obstructive type of lung function reduction has been recently

described to be present after early childhood pneumonia, which is in line with our findings (Chan et al. 2015). The obstructive type of lung function reduction after both bronchiolitis and pneumonia in early childhood may also suggest that these diseases share the same predisposition and may also share a similar type of outcome in adulthood with regards lung function.

It has been proposed that FEV1/FVC<5th percentile should be used as a cut-off limit for COPD, because the GOLD cut-off criterion FEV1/FVC<0.7 underestimates the prevalence of COPD in young adults (Quanjer et al. 2012, Culver 2015). However, regardless of criterion used, the lung function data should always be assessed together with symptoms and prior probability of the COPD to diagnose the disease (Culver 2015). It was not our aim to assess the prevalence of COPD in our study population, and the diagnosis of COPD was not made. However, it is clear that signs of irreversible obstruction that is characteristic of COPD was found in our study subjects, since 15% of former bronchiolitis patients and 5% of pneumonia patients presented FEV1/FVC<5th percentile. The meaning of these findings in our study population remains unclear. However, in another study, modified FEV1/FVC<5th percentile was associated with an increased risk of death and prevalence of respiratory symptoms (Vaz Fragoso et al. 2010).

As maximal lung function is reached in early adulthood, subjects who start their adult life with a lower FEV1/FVC-ratio may attain the threshold of COPD earlier, during normal lung ageing, than those starting with a higher FEV1/FVC-ratio (Martinez 2009). The results of the 18-20 year follow-up and the present follow-up of our cohort demonstrate that subjects with the history of severe bronchiolitis in early childhood more often have obstructive airways in adolescence and adulthood compared to controls with no such history. At the present follow-up, when the cohort was studied at the age of 30 years, it became evident that these former LRTI patients never reach the full lung function capacity in early adulthood, and it is possible that these alterations progress to COPD during normal lung ageing in the future.

6.4 PREDICTIVE FACTORS FOR ASTHMA AND LUNG FUNCTION IN ADULTHOOD

6.4.1 Asthma and lung function in relation to viral etiology of LRTI

It has been shown that RSV bronchiolitis is strongly associated with wheezing and asthma in childhood, but this relationship decreases with increasing age (Regnier & Huels 2013) and turns insignificant at school age (Stein et al. 1999). However, in a Swedish post-bronchiolitis study, increased risk for asthma was still seen at the age period of 15-18 years (Sigurs et al. 2010). Definitions of bronchiolitis and viral-induced wheezing are based on symptoms and have a significant overlap (Brand et al. 2008). Most likely, it does not matter if this LRTI is called bronchiolitis, wheezing bronchitis or viral-induced wheezing. Thus, differences in the definition of bronchiolitis between studies may explain part of the differences in the subsequent asthma risk.

Non-RSV etiology, especially rhinovirus etiology of bronchiolitis, has been associated with increased asthma risk even more distinctly compared to RSV etiology (Kotaniemi-Syrjanen et al. 2003, Reijonen et al. 2000, Piippo-Savolainen et al. 2007, Mikalsen et al. 2012, Beigelman & Bacharier 2013, Koponen et al. 2012). In the 18-20 year follow-up of the present cohort, 41-50% of former non-RSV bronchiolitis patients and 18-27% of RSV patients had asthma, and thus, non-RSV was a strong predictor for asthma in adulthood (Piippo-Savolainen et al. 2007). However at the age period of 26-29 years, this difference could not be demonstrated (Ruotsalainen et al. 2010a).

In the present follow-up 43% of former RSV bronchiolitis patients and 33% of non-RSV patients had self-reported asthma. Viral etiology of bronchiolitis had lost its significance since no significant difference was found between RSV or non-RSV bronchiolitis patients in

relation to asthma or lung function in adulthood. It may be that, like in case of RSV infection, the importance of non-RSV etiology of viral wheezing as a future asthma risk factor decreases with increasing age, probably due to several other environmental factors that are faced by the host in later life. However, there are no other studies to support this hypothesis.

In the present follow-up, former RSV LRTI patients were also compared with population controls, and there was no significant difference in asthma prevalence in adulthood. This finding is in line with the previous follow-up of this cohort, since at the age period of 18-20 years, no significant associations were found between RSV LRTI and asthma (Korppi et al. 2004). In addition, it was recently presented that non-hospitalized RSV LRTI plays no role as a risk factor for asthma at the age period of 26-29 years of age (Voraphani et al. 2014).

However, when only bronchiolitis patients who had wheezing during LRTI in infancy were included in the subgroup analysis and compared with controls, it turned out that 33% of former RSV bronchiolitis patients had doctor-diagnosed asthma, which was significantly more often compared to controls (17%). Significant differences were not found between the RSV pneumonia group and controls. In line with our results, an increased risk for respiratory symptoms and atopy has been found in children who presented RSV LRTI with wheezing in early childhood but not in those who presented crepitations in auscultation during infection (Elphick et al. 2007). Our classification was a little different, but altogether it seems that wheezing provoked by RSV is an important indicator for further asthma risk. Thus, underlying host factors are likely to determine, at least partly, which children are about to wheeze during viral infection (Elphick et al. 2007, Bonnelykke et al. 2015). It has been suggested that these host affect the future asthma risk more than the virus itself (Elphick et al. 2007, Bonnelykke et al. 2015, Thomsen et al. 2009, Kuehni et al. 2009, Beigelman & Bacharier 2013), and our results give undirect suppot to this hypothesis.

Different kinds of lung function abnormalities in later life have been found depending on the viral etiology of bronchiolitis. Rhinovirus bronchiolitis has been associated with bronchial hyperreactivity (Kotaniemi-Syrjanen et al. 2008), whereas irreversible obstruction (Sigurs et al. 2010, Sigurs et al. 2005) or more restrictive pattern (Hyvarinen et al. 2007) has been demonstrated after RSV bronchiolitis. In the present study, FEV1% and FEV1/FVC% were reduced before and after RSV LRTI compared to controls without differences in bronchial reversibility after bronchodilatation. Whether these differences, or lung function impairment overall, are caused by viruses remains an unanswered question. A comparable lung function impairment has been described to be present before and after bronchiolitis at very early ages suggesting that bronchiolitis itself is not a determinant of future lung function (Turner et al. 2002). On the other hand, there is clear evidence that RSV itself is capable of causing damage to airways that leads to bronchial hyperreactivity, peribronchial and perivascular inflammation, and subepithelial fibrosis several months after the initial infection in mice (Jafri et al. 2004, You et al. 2006). Severe forms of RSV LRTI are characterized with severe small airway inflammation containing mixtures of inflammatory cells, fibrin, edema and mucus (Bem et al. 2011, Johnson et al. 2007). Allergic sensitization combined with viral infection or very early primary viral infection can lead to TH2-biased immune responses in the lungs. This is characterized by increased type-2 cytokine production, airway eosinophilia and remodelling (You et al. 2006, Becnel et al. 2005, Schneider et al. 2012, Hong et al. 2014, Siegle et al. 2010, Culley et al. 2002, Dakhama et al. 2005).

Taken together, the findings of the numerous birth cohorts and post-bronchiolitis cohorts have established that lung function impairment is present after early childhood LRTI. In the present study, irreversible obstruction was found in study subjects with a history of RSV LRTI. Animal models have demonstrated that viruses such as RSV and HRV are capable of altering pulmonary function and exacerbating pulmonary immunopathology, especially in the presence of other contributing factors like allergic sensitization or a very young age at the time

of the primary infection. However, at least part of the lung function deficits, which are also seen in post-bronchiolitis studies, seem to reflect premorbid changes in the airways,.

6.4.2 Risk factors for asthma and lung function impairment

Overall, many assumed early childhood risk factors for development of subsequent asthma had lost their significance in adulthood in the present study. This finding is in line with the recent follow-up of the Swedish post-bronchiolitis cohort that identified only parental asthma and female gender as risk factors for adulthood asthma, while other assumed risk factors had lost their significance (Goksor et al. 2015). This may be explained by the fact that patients with infant bronchiolitis have faced numerous disease modifying factors during the subsequent 30-year follow-up.

As asthma risk factors were evaluated in the present study in relation to subsequent asthma in adulthood, early or current clinical atopy did not play a role as risk factors. Clinical atopy, defined as combined positive SPT and allergic symptoms, was common and found in 46-49% of study subjects, with no differences between groups.

Atopy is one of the most important risk factors for persistence of wheezing and development of asthma in childhood (Martinez et al. 1995, Kusel et al. 2007, Kusel et al. 2012, Jackson et al. 2012). Early atopic dermatitis or other kind of manifestation of atopic diseases have been included in every asthma predictive algorithms, as presented previously in this thesis (Piippo-Savolainen & Korppi 2008, Castro-Rodriguez et al. 2000, Kurukulaaratchy et al. 2003, Hafkamp-de Groen et al. 2013). Sensitization for *Alternaria alternata* at the age of 6 years (Stern et al. 2008) and atopy before the age of 2 years (Piippo-Savolainen et al. 2006) have been associated with increased asthma risk up to the the age period of 18-22 years. However, our results are in line with the studies that suggest that this association turns insignificant in early adulthood by the age period of 25-29 years (Goksor et al. 2015, Ruotsalainen et al. 2010a). This may be the result of several other confounding and disease modifying factors as well as the rise in respiratory atopic diseases during later childhood and early adulthood, which affect the subsequent asthma risk after early wheezing.

Allergy and atopy in wheezing children are strongly associated with persistent wheezing symtoms in adulthood as well as an increased likelihood of asthma relapse in young to middle adulthood (Guerra et al. 2004). Allergic asthma, which usually commences in childhood, has been recognized as a distinct asthma phenotype (Global Initiative for Asthma 2014, Mathur & Viswanathan 2014). Current clinical atopy, however, was not a risk factor for asthma in the present follow-up or in the 25-28 year follow-up of the Swedish post-bronchiolitis cohort (Goksor et al. 2015). The lack of asthma phenotyping and a high prevalence of atopy among controls may explain these results. In the present cohort, the majority of former bronchiolitis and pneumonia patients presented atopic sensitization. In addition, 59% of former bronchiolitis patients who had asthma in adulthood presented atopy in very early childhood. In the bronchiolitis and pneumonia groups, all bronchiolitis patients had doctor-diagnosed asthma and all exept one pneumonia patient had previously diagnosed asthma. It is probable that the majority of asthmatic patients in our cohort represent an early-onset allergic asthma phenotype.

Family history of asthma has been associated with increased risk for asthma after early wheezing in childhood (Martinez et al. 1995, Sigurs et al. 2000) and in adulthood (Stern et al. 2008, Goksor et al. 2006, Sigurs et al. 2010, Piippo-Savolainen et al. 2006, Goksor et al. 2015). However, in the present follow-up, this association could not be demonstrated. Instead, repeated wheezing at the age period of 1-2 years and under 2 years of age were significant risk factors for asthma at the age period of 28-31 years in univariate analysis. However, all children who had history of parental asthma had repeated wheezing under 2 years of age, and due to this strong interaction, repeated wheezing in early childhood was not any more a significant risk factor in the multivariate analyses. Even though family history of asthma was not a significant risk factor for asthma, it was a significant predictor for irreversible obstruction in

lung function tests in adulthood, which agrees with previous studies (Piippo-Savolainen et al. 2006, Kotaniemi-Syrjanen et al. 2008). This finding suggests a significant role for heredity in lung function.

In addition to parental asthma, prenatal smoke-exposure (Piippo-Savolainen et al. 2006, Goksor et al. 2007, Hyvarinen et al. 2007) and early atopy (Hyvarinen et al. 2007) have also been previously associated with lung function impairment after early childhood LRTI. However, both parental asthma and prenatal smoke-exposure have also been identified as risk factors for lung function impairment in the neonatal period (Martinez et al. 1988, Tager et al. 1993, Dezateux et al. 1999, Murray et al. 2002, Young et al. 1991, Lodrup Carlsen et al. 1997, Bisgaard et al. 2009). It is probable that these risk factors found in post bronchiolitis studies reflect the underlying changes in the airways that have been present even before the initial LRTI.

6.4.3. Blood eosinophils in relation to adulthood outcome

We demonstrated that study subjects with asthma in adulthood had higher eosinophil count at hospital admission compared to those without asthma. Low eosinophil count (<0.25 x10E9/l) during bronchiolitis was a significant protective factor for adulthood asthma. In addition high eosinophil count (>0.45 x 10E9/l) on convalescence presented as a significant risk factor for asthma in adulthood. These findings are consistent with previous studies regarding the relationship of blood eosinophils at early age and subsequent asthma. Blood eosinophilia during (Kotaniemi-Syrjanen et al. 2002, Midulla et al. 2014, Ehlenfield et al. 2000) or outside (Castro-Rodriguez et al. 2000, Piippo-Savolainen et al. 2007a) the viral infection has been previously recognized as a risk factor for the development of asthma. However, a decrease in blood eosinophils seems to be the normal response to viral infection (Ehlenfield et al. 2000, Rosenberg et al. 2009), and a lack of this response predicted asthma even up to the age period of 28-31 years in the present cohort. In line with our results, low eosinophils during infection (Martinez et al. 1988) or persistenty (Just et al. 2008) have been protective from persistent wheezing. In the present study, the associations between eosinophil levels in infancy and asthma or lung function deficiency in adulthood were independent from early atopic status, which is in line with previous findings in the Tucson birth cohort (Karakoc et al. 2002).

It has previously been demonstrated that eosinophilic inflammation of the lungs is a crucial factor in the development of asthma (Rosenberg et al. 2013, Zagai et al. 2004). However, lung eosinophilia is not present in all asthma phenotypes (Wenzel 2012). Persistent eosinophilic inflammation in the lungs can lead to airway remodeling, characterized by increased reticular basement membrane thickness and smooth muscle hypertrophy (Woolnough & Wardlaw 2015). These changes eventually lead to persistent airflow limitation in adults with asthma (ten Brinke 2008, Guerra et al. 2008). In the present study, we demonstrated that blood eosinophilia during bronchiolitis is associated with irreversible airway obstruction in adulthood. This association could reflect eosinophil derived remodelling in the lungs of our study subjects. However, the peripheral blood eosinophil count is a balance between eosinophil production and the rate of entry of eosinophils into the lungs, so the association between blood and lung eosinophilia is not straightforward (Woolnough & Wardlaw 2015).

It has also been demonstrated that eosinophilic inflammation of the lungs is not present at an early age in children with wheezing in infancy (Malmstrom et al. 2013). More specifically, in a Finnish study, eosinophilic inflammation was not found in the bronchial biopsies or bronchoalveolar lavage (BAL) samples of infants with wheezing before the age of 2 years (Saglani et al. 2005). However, in a recent study, a positive association between the amount of CD8+ lymphocytes and neutrophils in BAL samples and the thickness of reticular basement membrane in the endobronchial biopsy was found. This suggests that cells other than eosinophils may induce conditions required for airway remodeling in young children (Malmstrom et al. 2014).

It can be concluded that the association between early age blood eosinophilia and subsequent asthma is well established, and eosinopenic reaction during viral wheezing illness seems to protect against asthma development. In addition, blood eosinophilia during wheezing in childhood seems to be a risk factor for irreversible airway obstruction in adulthood. However, the pathologic processes that determine the development of lung function and the inception of asthma after early childhood wheezing are largely unknown.

6.4.4 Early lung function, LRTIs and later respiratory morbidity

It has been proposed that the development of COPD is not only due to accelerated age-related decline, but also due to a failure to achieve the expected peak lung function during early adulthood because of previous adverse exposures to childhood respiratory infections (Stocks et al. 2013). This proposition can be extended further and concluded that the development of lung function and later respiratory morbidity is a complex process in which prenatal factors (*e.g.*, low birth weight (Canoy et al. 2007, Kotecha et al. 2013), familial asthma (Martinez et al. 1988, Young et al. 1991), or maternal smoking during pregnancy (Martinez et al. 1988, Tager et al. 1993, Landau 2008, Lodrup Carlsen et al. 1997, Bisgaard et al. 2009, Murray et al. 1992)) predispose patients to low lung function in neonatal period. Early lung function impairment alone, or probably together with aberrant immune responses, further predisposes patients to respiratory infections in early childhood. These alone, together or in interaction with passive or active smoking or atopic heredity, may cause further damage and remodeling of the lungs which may lead to impaired lung function and respiratory morbidity in later life (Figure 8).

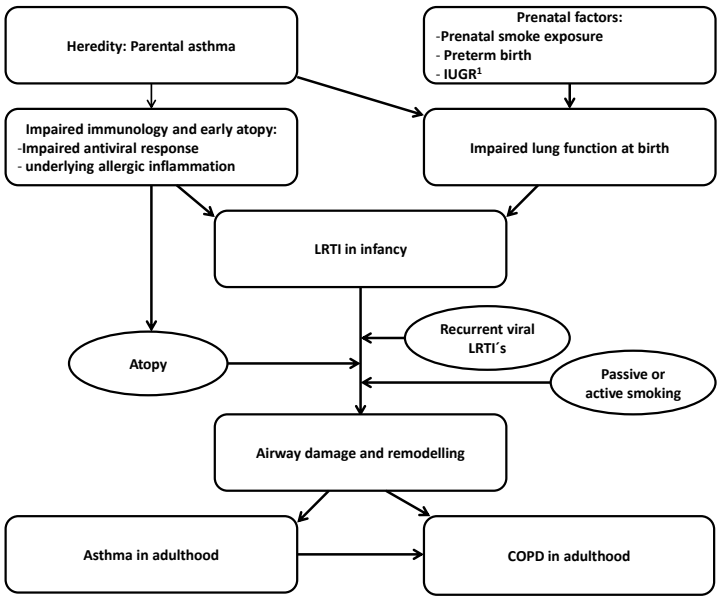


Figure 8. Risk factors affecting the adverse adulthood outcome of early childhood respiratory infections. In the favorable situation, a "healthy", not predisposed child gets a viral LRTI in early childhood, and the symptoms resolve after the acute phase. However, in other circumstances, low infantile lung function and impaired immunology predispose the subject to LRTIs in infancy. During the rapid lung development at early age LRTIs alone, together or in interaction with factors like passive and/or active smoking or atopic inflammation, cause airway remodeling and predispose to lung function impairment and to the development of asthma and/or COPD in adulthood.[1]IUGR, Intrauterine growth retardation

6.5 HEALTH-RELATED QUALITY OF LIFE AFTER LRTI IN EARLY CHILDHOOD

6.5.1 Impaired HRQoL after early childhood LRTI

Studies about HRQoL after early bronchiolitis or pneumonia are scarce. The longest follow-up so far has been 3 years with RSV bronchiolitis patients (Bont et al. 2004). These children presented impaired quality of life after RSV bronchiolitis (Bont et al. 2004). In addition, pneumonia has been described to affect HRQoL in the short term in children (Shoham et al. 2005).

Our own questionnaire was not sensitive enough to find differences in respiratory symptoms between the groups, such as repeated wheezing, chronic night cough, or prolonged cough. However, symptom scores in the SGRQ were significantly higher in former bronchiolitis and pneumonia patients compared to controls; this suggests an increased prevalence of respiratory symptoms after early childhood LRTI. Also, in the bronchiolitis group, the activity scores, which describe activities limited by respiratory symptoms and impact scores that describe social and psychological burden of respiratory symptoms, were increased compared to controls. Both bronchiolitis and pneumonia patients had higher total scores in SGRQ, reflecting impaired HRQoL in adulthood after early childhood LRTI.

SGRQ scores have been demonstrated to correlate with lung function and have been validated in several studies (Jones et al. 1991, Jones et al. 1992, Bae et al. 2011). In previous trials, the difference of 4 or more points in the SGRQ total score has been considered clinically significant (Jones et al. 1991, Jones 2005). The scores of the former bronchiolitis patients were 3.9 points higher compared to controls. Pneumonia patients had 3.4 points higher total scores compared to controls. This means that the SGRQ findings of the present study at 28-31 years of age after bronchiolitis or pneumonia in infancy are probably clinically significant, especially in term of bronchiolitis patients. This finding is strengthened by the fact that decreased HRQoL found after early childhood bronchiolitis or pneumonia in the present study is in line with the previously described findings of impaired airway function in this thesis.

In previous studies, SGRQ scores have been higher in smokers than in non-smokers (Ferrer et al. 2002, Spencer et al. 2001). However, when the results of the SGRQ data were categorized and adjusted with smoking, our results did not change. These analyses suggest an independently significant role of early childhood LRTI on HRQoL in adulthood. In addition, the further analysis that included only study subjects with RSV LRTI in early childhood revealed that RSV LRTI is also an independent risk factor for impaired HRQoL in adulthood.

6.6 MAIN STRENGTHS AND SHORTCOMINGS OF THE STUDY

6.6.1 Strengths of the study

The main strength of the present study is the long follow-up time from early childhood until adulthood. In fact, this 30-year follow-up is thus far the longest ongoing prospective post-bronchiolitis study. Kuopio University Hospital serves as the only hospital offering inpatient care for children in the area. So, even though the cohort was higly selected, including only hospitalized bronchiolitis and pneumonia patients, it is a representative sample of severe forms of LRTI.

Early childhood data was collected carefully and prospectively during repeated early childhood visits. At the time of the hospitalization, viral and bacterial samples were included in the study protocol, and methods were advanced at the beginning of the follow-up thirty years ago, including viral antigen assays from NPA´s and antibody assays from paired serum samples (Korppi et al. 1986, Korppi et al. 1991). Blood eosinophils were measured twice: at the time of the hospitalization and outside the infection. This enabled the analysis on the relationship between blood eosinophils and later asthma or lung function.

Later childhood and early adulthood data has been collected in well-conducted questionnaire studies and clinical follow-up visits (Piippo-Savolainen et al. 2004, Korppi et al. 1993, Kuikka et al. 1994, Korppi et al. 1994, Hyvarinen et al. 2005, Ruotsalainen et al. 2010a). The clinical follow-ups have included spirometry and prick tests from the 10-year follow-up onwards (Piippo-Savolainen et al. 2004, Korppi et al. 1994).

The clinical study at the age period of 28-31 years included a structured questionnaire, the widely used and validated SGRQ, home PEF monitoring, prick tests, F_{ENO} measurement, and spirometry. Spirometry was performed according to the international standards (Miller et al. 2005) before and after bronchodilatation by a trained respiratory nurse of the research group. The same spirometer was used in all measurements, making the evaluation of lung function parameters reliable. The 30-year follow-up was appropriately controlled, since age- and sex-matched population controls who were born in the same area were examined by an identical way as cases.

6.6.2 Shortcomings of the study

The main shortcoming of the study was undoubtedly the small number of subjects, especially in the groups of former bronchiolitis and pneumonia patients. We were able to contact 48/83 (58%) of the former bronchiolitis patients and 22/44 (50%) of the former pneumonia patients. The attendance rate was acceptable for a thirty-year follow-up, but the numbers are small, since the original study groups were also rather small. There is a risk for type 2 error, especially in subgroup analyses, which were therefore made with caution.

The number of clinically examined controls was sufficient; however, the 28% participation rate in the control group was rather low. This can be seen as a selection of controls, since the asthma prevalence in the controls was 10-15%, which is higher than the asthma prevalence in non-selected Finnish young adults (Huurre et al. 2004)). Thus, the results may be biased to the direction of under-estimation, rather than over-estimation, of the differences between the bronchiolitis or pneumonia cases and the controls. Because the population-based controls were not recruited at the beginning of the study, it was not possible to compare early risk factors between bronchiolitis or pneumonia groups and controls or present longitudinal analysis of lung function parameters between the study groups.

Finnish reference values for lung function (Viljanen et al. 1982), which were used in the previous adulthood follow-up of the study (Piippo-Savolainen et al. 2004) are old, but new reference values for the Finnish population were not available at the time of the study. As irreversible obstruction was used as a categorized variable, we decided to also use recently published, multi-ethnic, age-, sex- and height-adjusted GLI 2012 limits for the abnormal FEV1/FVC –ratio (Quanjer et al. 2012). The use of two reference values may cause some confusion when evaluating the results. However, despite the reference values used, the results in regard the prevalence of irrebersible airway obstruction remained unchanged.

The definition of the RSV LRTI group was based on positive RSV antigen or antibody testing (Korppi et al. 1986). In addition, we included those children who were hospitalized during RSV epidemics for bronchiolitis or pneumonia, but had negative viral testing. We assumed that most of these children were RSV positive because the methods for viral testing were not as sensitive as the polymerase chain reaction test currently available (Popow-Kraupp & Aberle 2011). However, this definition of the RSV group is more inaccurate than if it was based solely on viral testing.

A surprising finding was that both former bronchiolitis and pneumonia patients smoked regularly more often than controls. Former bronchiolitis patients had also smoked significantly more pack-years compared to controls, which means heavier and more long-lasting smoking. In year 2010, the daily smoking rate in the Finnish population-based survey was 19% among young adults (Helakorpi et al. 2011), so the 12% smoking rate in population controls was slightly less. Smoking is the most important risk factor for the development of

chronic airway obstruction, characteristic for COPD, and the harmful effects of smoking on respiratory symptoms and lung function abnormalities have been widely documented (Global Initiative for Asthma 2014, Landau 2008, Mullane et al. 2013). A harmful interaction between the RSV LRTI in childhood and smoking in later life relation to adulthood asthma has also been demonstrated (Voraphani et al. 2014). There were some concerns that differences found between groups in smoking rates might affect our results, as it regards asthma prevalence and lung function. However, it has been documented that in smokers a greater than age-related decline in lung function will occur from the fourth decade of life onwards (Landau 2008). All our main outcomes were adjusted with current daily smoking and smoked pack years. These adjustments did not change our main results, and as the statistics were carefully performed, one can say that the differences found between study groups are independent of smoking.

6.6.3 Summary

In conclusion, carefully and prospectively collected data of the present study from early childhood up to adulthood provides unique information about the long-term outcome of hospitalized early childhood bronchiolitis and pneumonia in a clinical setting. Especially negative results have to be interpreted with caution due to the small number of study subjects.

7 Conclusions

In the present study we evaluated the adulthood respiratory outcome in terms of asthma prevalence, lung function, and HRQoL in study subjects who had been hospitalized for bronchiolitis or pneumonia at less than 2 years of age. We investigated the effect of RSV etiology of initial LRTI on these outcomes. In addition, we indentified potential risk or protective factors affecting these outcomes in adulthood.

Asthma prevalence of 31-35% after bronchiolititis in early childhood was significantly increased compared to 11-15% asthma prevalence in the control group. Asthma prevalence was not increased after pneumonia in early childhood compared to controls. Asthma prevalence remained stable between the 20- and 30-year follow-ups of the present cohort.

Lung function was impaired after early childhood bronchiolitis and pneumonia compared to population controls with no history of early childhood LRTI. FVC%, FEV1%, and FEV1/FVC-ratio% were all reduced in former bronchiolitis patients, and FEV1% was reduced in pneumonia patients before and after bronchodilatation. These findings demonstrate irreversible airway obstruction in adulthood after early childhood bronchiolitis. In pneumonia patients, these findings were not so obvious, but they were of similar type.

HRQoL as measured by SGRQ is impaired in adulthood after early childhood bronchiolitis and pneumonia. Pneumonia patients had higher symptom scores compared to controls, whereas bronchiolitis patients had higher symptom activity and impact scores compared to controls.

Asthma prevalence after RSV LRTI was increased only if wheezing was present during the initial LRTI in early childhood. It seems that wheezing provoked by RSV is an important indicator for further asthma risk rather than RSV infection itself. Irreversible airway obstruction and impaired HRQoL are present in adulthood after early childhood RSV LRTI.

Most assumed early life asthma risk factors were non-significant at the age period of 28-31 years, so these risk factors seem to lose their importance with increasing age. Even though family history of asthma was not a significant risk factor for asthma, it was a significant predictor for lung function impairment in adulthood.

Study subjects with asthma in adulthood had a higher blood eosinophil count in admission to hospital for bronchiolitis compared to those who did not develop asthma. In addition, low blood eosinophil count during bronchiolitis protected from adulthood asthma and high blood eosinophil count during bronchiolitis was associated with irreversible airway obstruction. These findings highlight the importance of eosinophil-mediated inflammation in the development of asthma and lung function impairment in children with the history of early childhood bronchiolitis.

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Katri backman

Long-term Outcome of Early Childhood Lower Respiratory Tract Infections

Bronchiolitis and pneumonia in early childhood have been associated with respiratory morbidity in adulthood, but the prospective research evidence in this area is limited. This longitudinal 30-year follow-up study investigated the adulthood outcome of bronchiolitis and pneumonia patients who were hospitalized at less than 2 years of age. The increased asthma risk was present at the age of 28-31 years after early childhood bronchiolitis, and lung function impairment and decreased quality of life after bronchiolitis and pneumonia.

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