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Marja Ruotsalainen

Do Wheezing Infants Grow Up to be Asthmatic Adults?

Asthma Prevalence in Relation to Early-Life and Current Risk Factors

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ABSTRACT

Wheezing associated with respiratory infection is common in infancy and early childhood. Viral bronchiolitis, especially if requiring hospitalization, is a major risk factor for subsequent wheezing and asthma. The link from bronchiolitis and subsequent asthma is dependent on host factors and virus-specific effects.

In 1981-1982, 130 infants aged 1-23 months were hospitalized for bronchiolitis or pneumonia. Clinical and laboratory data were collected on admission and during convalescence and at the follow-up visits until 20-35 months of age. The allergy and asthma status of the children was evaluated at 4.5-6 years, 8.5-10 years and 18-20 years of age. A selected control group with a family history of atopy was followed from birth. In 1992-1993, 100 infants aged 1-23 months were hospitalized for wheezing associated with respiratory infection. Clinical and laboratory data, including RSV and rhinovirus aetiology, were collected on entry. The asthma and allergy of the children were evaluated at the median ages of 4.0, 7.2 and 12.3 years.

In 2008, a postal questionnaire was sent to two cohorts (median ages 27.3 and 16.5 years), to a selected control group and to non-selected population based controls (Population Register Centre, Finland). The questions focused on asthma, allergy, smoking and weight status. Asthma was classified to doctor-diagnosed asthma and self-reported asthma.

In adulthood (cohort 1981-1982), doctor-diagnosed asthma was present in 20% of the former bronchiolitis patients, compared with 5% in two control groups. The respective figures for self-reported asthma were 41% and 7-10%. Current allergic rhinitis and smoking were associated with asthma, but overweight was not. Early-life wheezing was an independent risk factor of asthma, as was RSV hospitalization. In adolescence (1992-1993 cohort), doctor-diagnosed asthma was present in 30% of the former bronchiolitis patients but only in 5% of controls. The respective figures for self-reported asthma were 64% and 11%. Self-reported asthma was more common in the former rhinovirus (83%) than in the former RSV patients (48%). Overweight had no significant association with doctor-diagnosed or self-reported asthma, allergy or the use of inhaled corticosteroids. Atopic dermatitis in infancy was the only independently significant early life predictor of doctor-diagnosed asthma.

In conclusion, the increased asthma risk in children with early-life wheezing symptoms continues until at least 27 years of age. Hospitalization due to RSV in infancy is a risk factor for asthma in adolescence and adulthood, and in adolescence rhinovirus bronchiolitis had a greater impact on the risk of self-reported asthma. Weigh status had no significant association with asthma or allergy in adolescence and in adulthood after hospitalization for bronchiolitis in infancy.

National Library of Medicine Classification: WC 207, WF 102, WF 150, WF 553, WS 280
Medical Subject Headings: Asthma/epidemiology; Asthma/diagnosis; Bronchiolitis; Child, Hospitalized; Follow-Up Studies; Hypersensitivity, Immediate; Pneumonia; Questionnaires; Respiratory Sounds; Respiratory Syncytial Virus Infections; Risk Factors

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TIIVISTELMÄ

Imeväisiässä ja varhaislapsuudessa vinkuna on yleistä hengitystieinfektion yhteydessä. Viruksen aiheuttama ilmatiehyttulehdus eli bronkioliitti, erityisesti johtaessaan sairaalahoitoon, lisää riskiä myöhempään vinkuna oireeseen ja astmaan. Bronkioliitin ja astman yhteys on riippuvainen potilaan taustoista ja virus spesifisistä tekijöistä.

Vuosina 1981–1982 kutsuttiin tutkimukseen 130 alle 2-vuotiasta lasta, joita hoidettiin sairaalassa bronkioliitin tai keuhkokuumeen vuoksi Sairaalahoitojakson aikana ja 4-6 viikkoa myöhemmin kerättiin lapsista tarkat taustatiedot ja otettiin laboratorionäytteitä. Tiedot hengitystieoireilusta kerättiin 20–35 kuukauden ikään asti ja kliiniset seuranta käynnit järjestettiin 4.5-6, 8.5–10 ja 18–20 vuoden ikäisinä, jolloin kartoitettiin tiedot allergioista ja astmasta. Kontrolliryhmänä toimivat terveet, atopia perhetaustan omaavat lapset. Vuosina 1992–1993 tutkimukseen kutsuttiin 100 samanikäistä lasta, joita hoidettiin sairaalassa alahengitystieinfektion aiheuttaman uloshengitysvaikeuden vuoksi. Heiltä kerättiin myös taustatiedot ja otettiin laboratorionäytteitä, mm. respiratory syncytial virus (RSV) ja rhinovirus näytteet, ja kliiniset kontrollikäynnit olivat 4.0, 7.2 ja 12.3 vuoden ikäisinä, jolloin kartoitettiin tiedot allergioista ja astmasta.

Vuonna 2008 tutkimukseen kerättiin kontrolliryhmä väestörekisterikeskuksesta vastaavan ikäisistä ihmisistä, joilla ei ollut taustalla sairaalahoitoista uloshengitysvaikeutta varhaislapsuudessa. Tutkittaville ja kahdelle kontrolliryhmälle lähettiin kirjekysely, jossa kartoitettiin heidän astma, allergia ja hengitystieoireilua sekä tupakointia ja painotiedot. Vastauksien perusteella astma määriteltiin kahdella tavalla: lääkärin toteama astma ja kliininen astma.

Aikuisuudessa (kohortti 1981–1982) 20 % sairasti lääkärin toteamaa astmaa tai 41 % kliinistä astmaa. Vastaavat luvut kontrolliryhmissä olivat 5 % ja 10 %. Allerginen nuha ja tupakointi olivat yhteydessä astmaan, johon ylipaino ei näyttänyt vaikuttavan. Varhaislapsuuden uloshengitysvaikeus ja sairaalahoitoa vaatinut RSV infektio olivat itsenäisiä astman riskitekijöitä. Nuoruusiässä (kohortti 1992–1993) 30–64% tutkittavista oli astma tai kliininen astma. Vastaavat luvut kontrolliryhmässä olivat 5-11 %. Rhinoviruksen aiheuttaman alahengitysinfektion sairastaneilla oli enemmän kliinistä astmaa (83 %) kuin RSV infektion sairastaneilla (48 %). Ylipaino ei ollut yhteydessä astmaan, allergioihin eikä hengitettävien kortikosteroidi lääkkeiden käyttöön. Atooppinen ihottuma varhaislapsuudessa ennusti astmaa nuoruusiässä.

Yhteenvetona voidaan todeta, että varhaislapsuudessa sairastettu uloshengitysvaikeus, mikä johtaa sairaalahoitoon lisää astmariskiä aikuisuudessa ainakin 27-vuoden ikään asti. Sairaalahoitoinen RSV infektio lisää astmariskiä nuoruus ja aikuisiässä ja rhinoviruksen aiheuttama alahengitystieinfektio lisää ainakin kliinisen astman riskiä nuoruusiässä. Ylipainolla ei ollut vaikutusta astmaan eikä allergioihin näillä tutkittavilla.

Yleinen Suomalainen asiasanasto: astma – riskitekijät; bronkioliitti; hengitys – äänet; keuhkokuume; kyselytutkimus; lapset; sairaalahoito; seurantatutkimus; virustaudit

To Timo, Topi, Matias ja Lauri

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Marja Ruotsalainen

List of the original publications

This dissertation is based on the following original publications:

I Ruotsalainen M, Piippo-Savolainen E, Hyvärinen MK, Korppi M. Adulthood asthma after wheezing in infancy: A questionnaire study at 27 years of age. *Allergy 65:503-509, 2010*.

II Ruotsalainen M, Piippo-Savolainen E, Hyvärinen MK, Korppi M. Respiratory morbidity in adulthood after RSV hospitalization in infancy. *Pediatr Infect Dis J 29:872-874, 2010.*

III Ruotsalainen M, Sidoroff V, Piippo-Savolainen E, Hyvärinen MK, Korppi M. Association between overweight and asthma or allergy: Results from a prospective 27-year post-bronchiolitis follow-up. *Curr Pediatr Res 16:95-100, 2012.*

IV Ruotsalainen M, Hyvärinen MK, Piippo-Savolainen E, Korppi M. Adolescent asthma after rhinovirus and respiratory syncytial virus bronchiolitis. *Pediatr Pulmonol 48:633-639, 2013.*

V Ruotsalainen M, Hyvärinen MK, Saari A, Piippo-Savolainen E, Korppi M. No association between overweight and asthma or allergy in adolescence after wheezing in infancy. *Acta Paediatr 102:167-171, 2013.*

Contents

Abbreviations

AOR	Adjusted odds ratio
AD	Atopic dermatitis
B-Eos	Blood eosinophils
BMI	Body mass index
BMI-SDS	BMI-standard deviation score
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
ECP	Eosinophil cation protein
ECT	Exercise challenge test
FVC	Forced vital capacity
FEV1	Forced expiratory volume in one second
FVS	Flow volume spirometry
HRV	Human rhinovirus
HMPV	Human metapneumovirus
IFN-γ	Interferon-γ
IgE	Immunoglobulin E
LRI	Low respiratory infection
NPA	Nasopharyngeal aspirate
OR	Odds ratio
PCR	Polymerase chain reaction
PEF	Peak expiratory flow
RSV	Respiratory syncytial virus
SPT	Skin prick test
Th-cell	T-helper cell

1 Introduction

Wheezing in early childhood is a heterogeneous condition; it is rather common in infants and young children with respiratory infection. More than one in every three children will suffer from wheezing by the age of three years (Martinez et al. 1995, Taussig et al. 2003, Illi et al. 2004) and 2% percent of all infants suffer from wheezing severe enough to require hospitalization (Korppi et al. 1986, Boyce et al. 2000, Koehoorn et al. 2008). Bronchiolitis is usually defined as the first wheezing episode in infancy, but there is no global consensus about other criteria such as clinical features, viral findings, or exact age limits. The long-term prognosis varies: some children may become completely symptom-free other develop chronic asthma and suffer reduced lung function continuing until adulthood as documented in two prospective birth cohort studies (Larouche et al. 2000, Stern et al. 2007, Stern et al. 2008), and in two prospective post-bronchiolitis follow-up studies (Piippo-Savolainen et al. 2004, Korppi et al. 2004, Goksör et al. 2006, Goksör et al. 2007, Goksör et al. 2008), and in one respiratory syncytial virus (RSV) bronchiolitis follow-up study (Sigurs et al. 2010).

Nearly all children have experienced at least one RSV infection by the age of two years, and 0.5 – 2.0 % of them require hospitalization due to this infection. Severe RSV infection is a leading cause of hospitalization in infants in both the industrialized and the developing nations (Kneyber et al. 2000). There are also other viruses, e.g. rhinovirus, human metapneumovirus, and human bocavirus, which can trigger bronchiolitis needing hospitalization. In particular rhinovirus has been associated with wheezing episodes in infancy (Jartti et al. 2004a, Kotaniemi-Syrjänen et al. 2003, Jackson et al. 2008, Busse et al. 2010, Jartti and Korppi 2011), with subsequent wheezing and asthma at preschool age (Jackson et al. 2008), and even with asthma and bronchial hyper-responsiveness at school age (Kotaniemi-Syrjänen et al. 2003, Hyvärinen et al. 2005b).

A number of studies have evaluated genetic and early life factors which can influence the risk of asthma and allergy. A family history of asthma has been associated with recurrent wheezing and persistence of asthma into childhood (Martinez et al. 1995, Carroll et al. 2007, Lim et al. 2009, Jartti et al. 2009a, Carroll et al. 2012) and also in adulthood (Piippo-Savolainen et al. 2006). Blood eosinophilia has been found in association with RSV and rhinovirus bronchiolitis in several studies (Wennergren et al. 1997, Ehlenfield et al. 2000, Kim et al. 2003, Jartti et al. 2006, Piippo-Savolainen et al. 2007a, Hyvärinen et al. 2010). The presence of atopic dermatitis (AD) and atopic sensitization in infants are factors predicting childhood asthma until school age (Castro-Rodrieguez et al. 2000, Taussig et al. 2003, Morgan et al. 2005, Hyvärinen et al. 2005b), particularly if the child has suffered from wheezing already in early life. Eosinophilic inflammation is a typical finding in asthma, thus, it has been a subject of interest to determine whether eosinophilia during bronchiolitis would be a risk factor for later asthma. The results of the studies have been conflicting. Similarly, the influence of early exposure to inhalant allergens to the risk of later asthma is also unresolved. In Multicentre Allergy Study (MAS) from Germany, an exposure to indoor allergens in early life was associated with wheezing symptoms in their teenage years (Matricardi et al. 2008). In Finnish bronchiolitis studies, an exposure to indoor allergens in early life increased the risk for asthma until the teenage years, but no longer in adulthood (Hyvärinen et al. 2005a, Hyvärinen et al. 2005b, Piippo-Savolainen et al. 2006). Exposure to tobacco smoke both during pregnancy, in infancy and in childhood has increased the risk of wheezing and asthma in several studies (Stein et al. 1999, Taussig et al. 2003, Lannerö et al. 2006, Goksör et al. 2007). Furthermore active smoking in adolescence and adulthood also increases the risk of current asthma (Strachan et al. 1996, Sears et al. 2003).

Asthma and obesity have been linked together. The prevalence of overweight and obesity among children and young adults has increased in epidemic proportions in western countries concomitantly with the asthma and allergy epidemics (Ford 2005, Flaherman and Rutherford 2006). Epidemiological studies have shown a modest association between overweight or obesity and the prevalence of asthma in adults (Ford 2005, Hancox et al. 2005, Jartti et al. 2009) but investigations in children have given conflicting results (To et al. 2004, Guerra et al. 2004, Vignolo et al. 2005, Flaherman and Rutherford 2006, Mannino et al. 2006, Mamun et al. 2007, Del Rio-Navarro et al. 2013). At least in adults, obesity-related asthma seems to be a disfined asthma phenotype not showing any association with eosinophilic inflammation in the airways (Lugugo et al. 2010). The association between weight status and allergy in less studied. Many authors have not shown the association between overweight and allergic diseases or atopic sensitization (Jarvis et al. 2002, Ma et al. 2010) or opposite to the expectations, underweight has been associated with atopic sensitization (Van Glysel et al. 2009) and allergic rhinitis (Silverberg et al. 2011) at school age. However, overweight has been associated with atopic dermatitis (Silverberg et al. 2011, Kusunoki et al. 2008) and food allergies in teenager (Visness et al. 2009).

The main aim of this thesis was to examine, if early-life risk factors exert any influence on the risk of later allergy or asthma after hospitalization for wheezing in infancy, if former bronchiolitis patients carry a higher asthma risk in adolescence and adulthood compared with population controls and if overweight or obesity has an association with asthma or allergy in later life after wheezing in infancy.

2 Review of the Literature

2.1 WHEEZING DISORDERS AND PHENOTYPES IN CHILDHOOD

Wheezing children form a heterogeneous group with different genotypes and phenotypes leading to different outcomes. One out of every three children has at least one episode of wheezing prior to their third birthday, and the cumulative prevalence of wheeze is almost 50% at the age of six years (Martinez et al. 1995, Bisgaard et al. 2007). Some of the children become symptom free, while others develop allergies and asthma as they grow up (Wennergren et al. 1997, Taussig et al. 2003, Piippo-Savolainen et al 2004).

Bronchiolitis is one of the most common viral infectious respiratory conditions of early childhood and the leading cause of hospitalization of infants (Boyce et al. 2000, Carroll et al. 2008). It is characterized by acute inflammation, edema and necrosis of epithelial cells lining small airways, increased mucus production and bronchospasm. Cellular debris, inflammatory cells and fibrin cause airway obstruction. Mucus plugs can partly or totally occlude the bronchioli, causing diffuse air trapping or atelectasis. It is usually defined as the first wheezing episode in infancy, but there is no global consensus on the other criteria such as clinical features, viral findings or age limits. The American Academy of Pediatrics (AAP) has proposed an upper age limit of 24 months (American Academy of Pediatrics 2006), but both 24 months (Piippo-Savolainen et al. 2004, Goksör E at al. 2006, Piippo-Savolainen and Korppi 2009) and 12 months (Piippo-Savolainen and Korppi 2009, Sigurs et al. 2010) have been used in different studies. About 2 % of all infants suffer from bronchiolitis severe enough to warrant hospitalization (Boyce el al. 2000, Kneyber et al 2000, Koehoorn et al. 2007).

There are two main classifications of the phenotypes of early childhood wheezing that have been used to evaluate and predict asthma and allergy symptoms in school age and later in adulthood.The first was based on onset and duration of wheezing. For example, this was applied in the Tucson birth cohort study, the wheezing children could be classified into three main phenotypes: transient early wheezers (wheezing before the age of three years but not at six years of age), persistent wheezers (wheezing both before the age of three years and at six years of age) and late-onset wheezers (no wheezing before three years of age, but wheezing at six years of age) (Taussig et al. 2003, Morgan et al. 2005). Early transient wheezers form the majority, 60%, of all early-childhood wheezers, and display wheezing symptoms only during respiratory infections (Taussig et al. 2003). About half of the rest of the wheezers become sensitized to inhalant allergens before school age, and in terms of sensitization, they are classified into atopic and non-atopic wheezers (Sherrill et al. 1999, Taussig et al. 2003).

In the report of Task Force of the European Respiratory Society (ERS) it was recommended that the definition of the phenotypes of early childhood wheezing should be based on the temporal pattern of wheezing symptoms (Brand et al. 2008). Children with intermittent wheezing associated with clinical evidence of the viral respiratory tract infection, with no wheezing symptoms in between, were classified as having episodic viral wheeze. Children with wheezing symptoms that exhibit discrete exacerbations, but also experience symptoms between episodes, were classified as having multiple-trigger wheeze (Brand et al. 2008). Episodic viral wheeze was proposed to be the type with less risk of developing subsequent asthma (Brand et al. 2008), while multiple-trigger wheezers are believed to reflect chronic airway inflammation with an increased risk of developing allergic asthma (Brand et al. 2008, Sonnappa et al. 2010). Some researchers have criticized this classification claiming that it is more a marker of severity rather than a definition of wheezing phenotype (Garcia-Marcos and Martinez 2010).

Subsequetly, obesity-related asthma has been suggested as its own asthma phenotype for both adults (Lessard et al. 2008, Lang et al. 2011, Wenzel 2013) and children (Jensen et al. 2011). In children, the lung function disorders seems to start at 6-11 years of age with symptoms appearing at 12-17 years of age (Lang et al. 2011), but not being associated with atopy (von Mutius et al. 2001).

In addition to the phenotypes of wheezing and asthma, some investigators have proposed that there are also asthma endotypes, such as allergic asthma, preschool wheezers with positive asthma-predictive indices, late-onset hypereosinophilic asthma, noneosinophilic asthma, elite-athlete asthma, infection-induced asthma and airflow obstruction caused by obesity. These are thus different forms of classification from phenotypes which describe distinct disease entities with defining etiologies and characteristic pathophysiological mechanisms (Lötvall et al. 2011)

2.2 RESPIRATORY VIRUSES

Respiratory syncytial virus is the predominant wheezing-associated virus in < 12 months old infants whereas rhinovirus prevalence increases with age (Rakes et al. 1999, Jartti et al. 2009, Sigurs et al. 2010, Jartti and Korppi 2011, Mansbach et al. 2012). Metapneumovirus seems to be the third in the order in < 12 months (Wolf et al. 2006) and bocavirus in 13-24 months old children (Allander et al. 2007). In addition, influenza A and B viruses, parainfluenza viruses (types 1-4), adenovirus, coronavirus and enterovirus are significant pathogens causing respiratory tract infections (Mahony 2008, Brand et al. 2012).

2.2.1 Respiratory syncytial virus

The primary RSV infection occurs at six weeks to two years of age, and is usually symptomatic involving the lower respiratory tract and presenting with wheezing, atelectasis and pneumonia. Subsequent infections, usually limited to the upper airways, are common (Ogra 2004). By two years of age, 80% to 90% of all children have experienced at least one RSV infection and 0.5% to 2.0% have needed to be treated in hospital (Kneyber et al. 2000).

Most RSV infections occur between late fall and early spring with a peak prevalence in winter (Hall et al. 2001, Smyth 2007). In Finland, RSV epidemics have occurred in two-year cycles, with a minor epidemic in the spring preceding the major epidemic in the autumn (Jartti et al. 2004b).

2.2.2 Rhinovirus

There are more than 100 serotypes and more than 150 genotypes of human rhinoviruses (HRV) (Heymann et al. 2005, Lee et al. 2007, Mahony 2008, Lee et al. 2012). The species can be classified as HRV-A, HRV-B or HRV-C viruses based upon genetic homology (Peltola et al. 2008, Jartti et al. 2008, Lee et al. 2012). In a recent study, patients with asthma exacerbations more often had HRV-C, and HRV-C infection was associated with more severe disease (Bizzintino et al. 2011).

Rhinovirus infections occur all year round, with peaks in late spring and early fall and are responsible for two-thirds of cases of the common cold outside RSV seasons, and these are associated with wheezing and asthma exacerbations from the age of 12 months onward (Lemanske 2002, Lemanske et al. 2005, Kusel et al. 2007, Jackson et al. 2008, Midulla et al. 2012).

HRV-induced wheezing episodes in infancy have been identified as an important predictor of recurrent wheezing and childhood asthma in several studies (Kotaniemi-Syrjänen et al. 2003, Lemanske et al. 2005, Lehtinen et al. 2007, Kusel et al. 2007).

2.3 LONG-TERM OUTCOME STUDIES AFTER HOSPITALIZATION FOR BRONCHIOLITIS

There are numerous retrospective and prospective cohort studies investigating the outcome of childhood wheezing and on the development and prevalence of asthma and allergy in childhood. Whether the association between bronchiolitis and subsequent asthma is due to causality or a reflection of predisposition may be dependent on host factors and virus-specific effects. This review only includes studies on bronchiolitis severe enough to require hospital care with a follow-up of the patients until adulthood.

2.3.1 Prospective birth cohort studies

The Tucson Children´s Respiratory Study is thus far the only prospective birth cohort study (Taussig et al. 1989). That study began in 1980, and in all, 1246 subjects have been followed from birth to adulthood. The basic information has been collected by questionnaires and lung function measurements, skin prick tests (SPT) and also laboratory determinations have been concluded at the follow-up visits. Data was also collected during lower respiratory infection (LRI) in the first three years of life. The study has facilitated the assessment of the natural history and outcome of acute LRI in young children, and the development and risk factors of chronic lung disorders, especially asthma, and atopy later in life (Taussig et al. 2003).

In the Tucson cohort, the prevalences of wheezing associated with respiratory infection were 32.0%, 17.3% and 12.0% during the first, second, and third years of life, respectively (Taussig et al. 2003). RSV infection in early childhood seemed to be an independent risk factor for subsequent wheezing and the development of asthma up to age 11 years but not at age 13 (Stein et al. 1999). If the lung function measured in infancy was in the lowest quartile, the values for forced expiratory volume in one second (FEV_1) / forced vital capacity (FVC) ratio, and FEV_1, remained reduced up to age 22 years (Stern et al. 2007).

More than 80% of children who wheezed during the first year of life were transient wheezers (Taussig et al. 2003). One important finding emerging from the Tucson Children's Respiratory Study was that these children had lower lung function at birth which improved with time but did not "catch up" with those of children who never wheezed during their growing years (Taussig et al. 2003). Most children who will go on to develop atopic asthma in later life experience their first wheezing symptoms during the first six years of life (Taussig et al. 2003). Sensitization against *Alternaria alternata* showed the strongest association with this form of wheezing (Halonen et al. 1999) and was associated with later physician-diagnosed asthma (Taussig et al. 2003).

The Tucson Children's Respiratory Study identified the phenotypes of early childhood wheezing and their different outcomes, and the prevalence of active asthma diagnosed by a physician increased at each survey until age 16 years (Taussig et al. 2003, Morgan et al. 2005). From 16 to 22 years of age, the incidence of asthma was 12.6 per thousand person-years, 27% asthma cases were new and 73% were chronic or relapsed asthma cases (Stern et al. 2008). Bronchial hyper-responsiveness, low lung function at six years, and late-onset and persisting wheezing predicted newly diagnosed asthma at age 22 years (Stern et al. 2008).

2.3.2 Prospective post-brochiolitis studies

Children with wheezing severe enough to need hospital treatment at less than 24 months of age represent a group at particular risk for developing asthma and other respiratory disorders in later life (Piippo-Savolainen and Korppi 2008). There are only three prospective follow-up studies after hospitalization for bronchiolitis (Table 1), one from Finland and two from Sweden, which have continued up to adolescence even to adulthood (Korppi et al. 1986, Wennergren et al. 1992, Sigurs et al. 1995, Wennergren et al. 1997, Sigurs

et al. 2000, Piippo-Savolainen et al. 2004, Hyvärinen et al. 2005a, Sigurs et al. 2005, Goksör et al. 2006, Sigurs et al. 2010).

Sigurs et al. examined RSV bronchiolitis patients, and age- and gender-matched controls, on admission and at later control visits (Sigurs et al. 1995, Sigurs et al. 2000, Sigurs et al. 2005, Sigurs et al. 2010). At the early adulthood control visit, the research protocol included a questionnaire, clinical examination, SPT, lung function measurements, analyses for serum IgE antibodies to inhaled allergens and blood eosinophil count. The prevalence of asthma and/or recurrent wheezing (39% vs. 9%), and that of atopic sensitization (30% vs. 1%), were still present at the median age of 18 years (Sigurs et al. 2010). In the former RSV group, lung functions were reduced in comparison with controls irrespective of the presence of asthma (Sigurs et al. 2010). Thus, hospitalization for early-life RSV bronchiolitis was associated with an increased prevalence of allergic asthma into early adulthood (Sigurs et al. 2010).

The other Swedish prospective post-bronchiolitis study included children hospitalized for wheezing before two years of age and age-matched controls with later follow-up visits (Wennergren et al. 1992, Wennergren et al. 1997, Goksör et al. 2006). The research protocol included a questionnaire, clinical examinations, SPT, lung function measurements, and determination of serum IgE antibodies to inhaled allergen and of blood eosinophils at 17 - 20 years of age (Goksör et al. 2006). In the former bronchiolitis group, the prevalence of asthma was 43 % vs. 15 % in the age-matched control group, and a family history of atopy, tobacco smoke exposure in infancy, and female gender were the significant early-life risk factors of asthma in early aduldhood (Goksör et al. 2006). Lung functions were reduced in the early life children with acute wheezing, especially in females with current asthma, compared with age-matched controls (Goksör et al. 2008). Current allergy was strongly associated with current asthma in the bronchiolitis cohort (Goksör et al. 2006).

In the present Finnish post-bronchiolitis cohort, the children were also under two years of age on admission for bronchiolitis (Korppi 1986). The control group consisted of infants without a family history of atopy, and with no history of wheezing symptoms in infancy (Pöysä et al. 1988), and both groups were followed-up (Korppi et al. 1993, Kuikka et al. 1994, Korppi et al. 1994, Hyvärinen et al. 2005a, Piippo-Savolainen et. al 2004). Asthmatic and atopic symptoms were screened by a written questionnaire at the median age of 14.9 years and current asthma was present in 14% in the bronchiolitis group (Hyvärinen et al. 2005a). There were three early asthma-predictive factors which could be identified in infancy wheezing, atopic dermatitis and elevated blood eosinophil numbers (Hyvärinen et al. 2005). The research protocol included a questionnaire, clinical examinations, SPT, and lung function measurements in the early adulthood control visit (Piippo-Savolainen et al. 2004). At the median age 19 years, asthma was present in 30% of the former bronchiolitis group vs. 11 % in the control group (Piippo-Savolainen et al. 2004a). Atopy was seen to be an independent risk factor for asthma. Lung functions were normal both in the former bronchiolitis group and in the control group, however, abnormal values in flow volume spirometry (FVS) were more common in the bronchiolitis group (Piippo-Savolainen et al 2004). In early adulthood, the early asthma-predictive factors were parental asthma and repeated wheezing (Piippo-Savolainen et al. 2006), but eosinophilia did not predict wheezing or asthma in adulthood (Piippo-Savolainen et al. 2007a).

Table 1. Overview of prospective post-brochiolitis studies

	Starting time	Bronchiolitis patients (N)	Control group (N)	Age at inclusion	Control visits	Viruses studied (RSV %)
Sigurs	1989-90	47	93 Age and gender matched, no early RSV	< 12 months (mean 116 days)	1y, 3y, 7.5y, 13.4y, 18y (mean)	RSV only (100%)
Wennergren, Goksör	1984-85	101	294 Age matched	< 24 months (median 10 months)	3-4.5y, 10y, 17-20y	6 (50%)
Korppi, Piippo-Savolainen	1981-82	83	72 No atopic heredity, no wheeze < 2y	< 24 months (median 10 months)	2-3y, 4.4-6y, 8-10y, 14.9y, 18-21y	7 (40%)

y = year

2.3.3 Other long-term follow-up studies

In Canada, 42 subjects aged 17-35 years with a past history of hospitalization for bronchiolitis in the first 18 months of life and 42 controls, were evaluated (Larouche et al. 2000). The study included SPTs, flow-volume spirometry, metacholine challenge test, blood samples and a detailed questionnaire. In the group with past bronchiolitis, there was an elevated risk for asthma, airway hyperresponsiveness was increased, and the ventilation fuctions (FEV_1, FEV_1 / FVC) were lower. There were no significant differences between the groups in terms of atopy, blood eosinophil count or IgE level (Larouche et al. 2000).

In Spain, 71 subjects aged 19 - 24 years with a history of viral bronchiolitis in infancy and 32 controls, were evaluated (Gómez et al. 2004). The study included SPTs, FVS, and metacholine challenge test. The bronchiolitis group had a higher prevalence of respiratory symptoms and bronchial hyperresponsiveness than controls. FVS, expect peak expiratory flow (PEF), and SPT responses did not differ between the groups (Gómez et al. 2004).

2.4 EARLY-LIFE PREDICTIVE FACTORS FOR LONG-TERM OUTCOME AFTER WHEEZING IN INFANCY

There are numerous reports describing the risk factors for subsequent wheezing and later asthma in children with bronchiolitis in infancy. In this review, only the most commonly reported in long-term studies until adolescence or adulthood have been included.

2.4.1 Age

The immune system in infancy is different than the immune system in later childhood and in adulthood. Though innate immunity is working adequately, the lack of prior exposure to pathogens means that there is a deficient immune memory. This has a critical impact on susceptibility to respiratory viral infection (Adkins et al. 2004). Age under six months predicts the need for hospital care and severe bronchiolitis which is, at least partly, attributable to immature immunity (Voets et al. 2006, Mansbach et al. 2012). Severe RSV infection in infancy is a risk factor for both recurrent wheezing and asthma until school age, showing a decreasing impact with age (Régnier and Huels 2013), and the risk may continue into the teenage years (Sigurs et al. 2005). On the other hand, the risk of post-bronchiolitis asthma seems to be higher, if wheezing starts after 12 months of age, and especially, if there is repeated wheezing in the period 1 – 3 years of age (Taussig et al. 2003, Jackson et al. 2008, Piippo-Savolainen and Korppi 2008). Age and number of previous wheezing episodes are linked to inflammatory and virologic risk factors of asthma (Jartti et al. 2009).

2.4.2 Viruses

Respiratory viral infection works together with allergy to produce inflammatory changes and even damage to the immune system in the airways necessary for triggering asthma (Busse et al. 2010, Callaway and Kim 2011). The timing of the birth in relation to the winter virus peak, especially RSV peaks, may impact on asthma development. An increased risk was found among children aged four months during the winter virus peak (Wu et al. 2008). The rural question as to whether this is primarily a viral or a host-response effect has not been resolved (Jackson et al. 2010, Zhang et al. 2009).

In infants, RSV bronchiolitis displays many similarities with acute asthma: small airway inflammation, rapid breathing to compensate for the hypoxemia, often wheezing, and sometimes airway complications (Hall et al. 2009). The risk of developing chronic respiratory conditions, including asthma, is elevated among those hospitalized for RSV infection in infancy (Sigurs et al. 2005, Korppi et al. 2004, Henderson et al. 2005, Sigurs et al. 2010) and that increased risk may persist into adulthood (Sigurs et al. 2010). In a Danish twin registry study, however, it was claimed that severe RSV infection in infancy did not cause asthma, but asthma was merely due to a genetic predisposition forwards asthma (Thomsen et al. 2009).

HRV has been recognized as an important risk factor for asthma among young wheezing children (Kotaniemi-Syrjänen et al. 2003, Lemanske et al. 2005, Lehtinen et al. 2007, Kusel et al. 2007, Jackson et al. 2008, Carroll et al. 2008, Jartti and Korppi 2011, Lukkarinen et al. 2013). Recent studies have identified that lower respiratory HRV infection could lead to airway damage and remodeling and later on the development of asthma (Jackson 2010). It has been appeared that the age at which HRV illnesses occurred had significant prognostic value with regarded to the subsequent risk of asthma. Wheezing with HRV infection during the first three years of life was associated with a dramatic increase in the risk of asthma at school age (Jackson 2010). Wheezing associated with HRV, even cases representing the first wheezing episode, may be the first sign of childhood asthma (Kotaniemi-Syrjänen et al. 2003). HRV bronchiolitis has been linked also to atopy-related factors (Rakes et al. 1999, Korppi et al. 2004, Jartti et al. 2006, Kusel et al. 2007). Thus, the final roles of the host and viral factors are thus far unresolved.

2.4.3 Parental asthma and allergy

A family history of asthma has been associated with the severity or incidence of bronchiolitis during infancy and with the risk of asthma in childhood (Martinez et al. 1995, Carroll et al. 2007, Lim et al. 2009, Carroll et al. 2012, Bacharier et al. 2012). Delayed immune maturation at birth, as indicated by blood cytokine levels or responses to stimulation in vitro, has been detected in infants born to parents with allergy or asthma (Sly and Holt 2011). In the Swedish follow-up after RSV bronchiolitis in infancy, parental asthma was a risk factor for current asthma and recurrent wheezing symptoms over 18 years after hospitalization (Sigurs et al. 2010). In a Finnish follow-up study parental asthma predicted adulthood asthma after wheezing in infancy (Piippo-Savolainen et al. 2006). Recurrent wheezers tended to have more often parents with asthma than first-time wheezers (Jartti et al. 2009). In some studies, maternal asthma has had a greater impact for the asthma risk of their children than whose fathers are asthmatics (Lim et al. 2010, Bacharier et al. 2012).

A family history of allergy, if the parents are not asthmatic, has not been associated with the severity of bronchiolitis (Just et al. 2010, Semple et al. 2011). However, in a Norwegian study, parental atopy predicted asthma at 11 years of age if the child had experienced recurrent wheezing in infancy (Mikalsen et al. 2013). The German Multicentre Allergy Study is a birth cohort follow-up which has evaluated the relationship of early atopic sensitization and a family history of atopy with subsequent wheezing symptoms (Matricardi et al. 2008). In that study, family history of atopy was a strong risk factor for persisting wheezing at 11-13 years of age. The Swedish study identified chain of links starting from atopy in family members to the development of atopy and further to the development of adulthood asthma after early childhood wheezing (Goksör et al. 2006).

2.4.4 Eosinophilic inflammation

A number of studies have demonstrated eosinophilia during or after RSV and/or HRV bronchiolitis (Wennergren et al. 1997, Ehlenfield et al. 2000, Kim et al. 2003, Piippo-Savolainen et al. 2007a, Hyvärinen et al. 2010). Eosinophilia has been higher during HRV than RSV infections. The results of different studies, however, have been conflicting. In a Swedish study, no association was found between eosinophilia during bronchiolitis and and persistent asthma at 10 years of age (Wennergren et al. 1997). In another study, blood eosinophilia at the time of bronchiolitis predicted the development of persisting wheezing at seven years of age (Ehlenfield et al. 2000). In Finnish studies, eosinophilia during bronchiolitis was not associated with wheezing symptoms or asthma in later life (Piippo-Savolainen et al. 2007a, Hyvärinen et al. 2010), but elevated levels of eosinophils during convalescence predicted an increased asthma risk until preschool and early school years although no longer thereafter (Piippo-Savolainen et al. 2007a). Even more than viral effects, eosinophilia in early infancy may reflect the Th2-oriented imbalance and allergic sensitization occurring during pregnancy or during infancy (Frischer et al. 2000).

A French cohort study reported that eosinophilia was an important biological variable associated with the persistence of asthma and the lack of eosinophilia predicted the future remission of wheezing symptoms at the age of six years after experiencing wheezing in infancy (Just et al. 2008, Just et al. 2010). Similarly, eosinophilia greater than 4 % under the age of three years was a significant predictor of persistent wheezing in the Tucson birth cohort, and even more clearly, repeatedly measured low eosinophilia counts less than 2 % predicted the absence of asthma and wheezing at school age (Karakoc et al. 2002).

Eosinophil cationic protein (ECP) is a mediator, which activated eosinophil release from their granules. Elevated levels of nasopharyngeal aspirate (NPA) ECP have predicted subsequent wheezing (Reijonen et al. 1997) and were considered to be a risk factor for persistent childhood asthma (Hyvärinen et al. 2010). However elevated blood ECP concentration during bronchiolitis exerted no influence on the future risk of wheezing symptoms or asthma (Wennergren et al 1997, Rakes et al. 1999, Hyvärinen et al. 2010).

2.4.5 Early exposure to inhalant allergens

Over twenty years ago David Strachan first postulated the so-called hygiene hypothesis where infections in early childhood might prevent the development of allergic diseases later in life (Strachan 1989). Subsequently, a lifestyle with early exposure to allergens, such as living in a farm, has appeared to prevent later asthma and allergy (Braun-Fahrlander et al. 2002, Ege et al. 2011, Michel et al. 2013, MacNeill et al. 2013). Later, epidemiological studies have demonstrated that IgE-mediated sensitization to inhalant allergens is an important risk factor for asthma, particularly in childhood living in the developed countries (Custovic et al. 2010). The severity of asthma increases among atopic patients exposed to high levels of sensitizing allergen and the synergism between high allergen exposure and respiratory virus infection increases the risk of asthma exacerbation (Custovic and Simpson 2012).

Aeroallergen sensitization develops slowly and it does not offer much help in the early identification of high risk children. In infants aged < 12 months one cannot determine any aeroallergen sensitization in children with recurrent wheezing episodes. In children aged < 24 months and < 36 months, the figures were 13% and 16%, respectively (Jartti et al. 2009a). Nonetheless if there is sensitization to perennial allergens during the first three years of life, there is an association with a loss of lung function at school age (Illi et al. 2006). In the Prevention and Incidence of Asthma and Mite Allegy study, early house dust mite and cat allergen exposure often led to sensitization, and cat allergen sensitization further led to persistent wheeze at four years of age (Brussee et el. 2005). In the German birth cohort Multicentre Allergy Study, wheezing at the age of 13 years was associated with exposure to high levels of indoor allergens during early life and IgE sensitization to common allergens (Matricardi et al. 2008). In Finnish bronchiolitis cohorts, early allergy, especially sensitization to inhaled allergens, was a significant risk factor for asthma until teenage, but no longer in adulthood (Hyvärinen et al. 2005a, Hyvärinen et al. 2005b, Piippo-Savolainen et al. 2007c).

Some studies have reported that high exposure to cat allergen can protect against cat sensitization (Platts-Mills et al. 2001, Simpson et al. 2003). In line with hygienic hypothesis the GABRIEL project in Poland and Alpine regions of Germany, Austria and Switzerland showed that children living on a farm were at significantly reduced risk of suffering asthma, hay fever, atopic dermatitis and atopic sensitization compared with nonfarm children (Illi et al. 2012). Consequently no evidence-based recommendations on allergen avoidance as a means of preventing allergic disease can be provided (Custovic and Simpson 2012).

2.4.6 Tobacco smoke exposure

Tobacco smoke is the most common and important indoor environmental pollutant to which infants and young children are exposed. Several epidemiological studies have recognized an association between parental smoking and acute lower respiratory infections in children. Maternal smoking during pregnancy and other types of environmental tobacco smoke exposure have been associated with bronchiolitis severity and later asthma (Stein et al. 1999, Lannerö et al. 2006, Semple et al. 2011, Singh et al. 2011). After hospitalization due to early wheezing, pre- and post-natal smoke exposure was reported to increase the risk of asthma in early adulthood (Goksör et al. 2007). The Australian birth cohort study noted an association with wheezing symptoms and active smoking among those with reduced lung function in infancy (Mullane et al. 2013). In Finnish bronchiolitis follow-up studies, however, the association between tobacco smoke exposure and asthma has not been found, but maternal smoking at 0-2 years of age of the children was a significant risk factor for lung function abnormalities in adulthood (Piippo-Savolainen et al. 2006). A recent review article stated that exposure to prenatal and passive smoking increased the incidence of wheezing and asthma in children and young people by at least 20% with the most intense

effect from prenatal maternal smoking on asthma being detected in children aged less than two years (Burke et al. 2012).

Exposure to environmental tobacco smoke in early infancy has been reported to increase the risk of IgE sensitization to indoor inhalant and food allergens (Lannerö et al. 2008), and this may be the link between passive smoking, allergy and asthma.

2.5 ASTHMA IN ADOLESCENTS AND YOUNG ADULTS

Asthma is an inflammatory disease of the lower airways. Typical symptoms of asthma are cough, wheezing and shortness of breath. Asthma is diagnosed based on measurements of pulmonary function revealing variable or reversible airways obstruction.

2.5.1 Prevalence

Asthma is a serious public health problem throughout the world, affecting people of all ages (Global Initiative for Asthma, 2012). In last decades, the prevalence of asthma has increased significantly in most western countries, with a similar trend also apparent in low and middle incomes countries (Eder et al. 2006). The World Health Survey evaluated the global prevalence of asthma in adults in 70 countries using a questionnaire related to asthma diagnosis and respiratory symptoms (To et al. 2012). The prevalence of doctor-diagnosed asthma varied extensively between the participating countries, ranging from 0.2 % in China to 21.0 % in Australia, with the global prevalence of doctor-diagnosed asthma estimated at 4.3 %. The global prevalence of self-reported asthma including wheezing symptoms was 8.3 % (To et al. 2012). In a recent Swedish study the prevalence of doctor diagnosed asthma was 9.5 % in the adolescent age group of 16 to 20 years of age (Wennergren et al. 2010). In a recent epidemiological, population-based study in Finland the prevalence of asthma in the Finnish 16-year old population was 3 % (Huurre et al. 2004), with a reported prevalence of 4 % in adulthood (Pallasaho et al. 2011).

2.5.2 Diagnostics

Asthma is a chronic inflammatory disorder of the airways. This airway inflammation may be associated with variable changes in airway hyperresponsiveness, airflow limitation, respiratory symptoms and disease chronicity. The development of airflow limitation is the result of bronchoconstriction, airway edema and mucus secretion. It is recognized that airway remodeling, characterized by thickening of the wall, can exert profound consequences on the mechanics of airway narrowing and contribute to the chronic progression of the disease. Asthma is classically recognized as the typical Th 2 disease, with increased IgE levels and eosinophilic inflammation in the airway, but much work still needs to be done before it will be possible to understand in detail the different phenotypes of asthma (Lemaske et al. 2003, Kudo et al. 2013, Martinez and Vercelli 2013).

It is necessary to carry out measurements of pulmonary function to come to a diagnosis of asthma and these parameters are also useful for monitoring the course of asthma and the patient's response to therapy. Abnormalities in pulmonary function provide measures of the degree of airflow obstruction, and reflect the consequence of asthma on airway mechanics. In asthma, these pulmonary function abnormalities are reversible.

Measurement of peak expiratory flow (PEF) at home by using the peak flow meter can be an important aid in both diagnosis and monitoring of asthma (Quanjer et al. 1997). The methods for evaluating PEF variability are to compare the difference between the maximum and minimum value during the day (more than 20 % and 60 L/min) (Quanjer et al. 1997, Global Initiative for Asthma, 2012), or to compare the difference of PEF value before and after bronchodilator inhalation (at least 15 % and 60L/min) Quanjer et al. 1997, Global Initiative for Asthma, 2012). It is recommented that the measurements shoud be

done over a period of two weeks (Reddel et al. 1995, Quanjer et al. 1997, Global Initiative for Asthma, 2012).

FVS is the preferred method for measuring airflow limitation and reversibility to establish an asthma diagnosis. Measurements of forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), and FEV1/FVC ratio are the most important in asthma diagnosis. An increase in FEV1 or FVC of at least 12 % and 200 ml from the pre-bronchodilator value is indicative of the presence of asthma (Bright and Burge 1996, Pellegrino et al. 2005, Global Initiative for Asthma, 2012).

Physical activity is an important cause of asthma symptoms in most asthma patients. A six- to eight-minute running protocol is easily performed in clinical practice and can establish a firm asthma diagnosis (Anderson et al. 2002). Pulmonary function measurements via the FEV1 are determined before and after exercise. The decrease of value FEV1 of at least 15 % after exercise is a characteristic of asthma (Anderson et al. 2002).

Airway hyperresponsiveness is a physiologic characteristic of asthma and its presence can be helpful in establishing the diagnosis of asthma. It can be identified and quantified by using bronchial challenge or provocation techniques, such as inhalation provocation with methacholine (Nieminen 1992) or with histamine (Sovijärvi et al. 1993).

In most epidemiological studies, the definitions of asthma include, in addition to doctor diagnosed asthma with objective criteria, also clinical or self-reported asthma which mostly includes asthma diagnosed by a doctor previously and asthmalike symptoms during the preceding 12 months.

2.5.3 Risk factors

A number of factors that influence an individual's risk of developing asthma have been identified. These can be divided into host factors and environmental factors. The most important host factors are genetic features, obesity and sex. The environmental factors include allergens, infections, tobacco smoke, air pollution, and dietary and occupational allergens and other irritants (Global Initiative for Asthma, 2012).

It is believed that multiple genes are involved in the pathogenesis of asthma. There are recent findings indicating that genetic factors of childhood-onset asthma differ from those of adult-onset asthma (Dijk et al. 2013). Variants at the 17q21 locus were associated with asthma in children who had had HRV wheezing illnesses and these were associated with expression of the two genes at this locus (Caliskan et al. 2013). While genes modulate many aspects of the natural history of asthma, such as susceptibility to atopy, altered lung development, and susceptibility to more severe disease, genetic markers have not improved the ability to predict the natural history of asthma independently (Holloway et al. 2010). Most probably, asthma is a combination of many multifactorial symptoms which are influenced by different genetic and environmental factors.

Male sex is a risk factor for asthma in childhood and adolescence. Doctor-diagnosed asthma is more common among boys until the of 16 years, but after that, the prevalence of asthma starts to increase among girls and at the age of 23 years of age the prevalence is higher in girls (Anderson et al 1992, Sears et al. 2003). The prevalence of asthma then remains higher in women during the remainder of the lifespan (Pallasaho et al. 2011).

The prevalence of sensitization to inhalation allergens continues to increase in adults; the risk factors for allergic sensitization are young age, a family history of allergy and living in an urban area (Warm et al. 2013). The prevalence of both allergic and non-allergic rhinitis doubles the risk of asthma (Shabaan et al. 2008, Pallasaho et al 2011).

The role of outdoor air pollution in causing asthma remains controversial (American Thoracic Society 2000), but outbreaks of asthma exacerbations have been shown to occur in parallel with increased levels of air pollution (To et al. 2013).

Occupational sensitizers are estimated to be responsible for about 1 in 10 cases of asthma among adults of working age (Nicholson et al. 2005). Over 300 substances have identified as being been associated with occupational asthma, which is defined as asthma caused by

exposure to an agent encountered in the work environment (Malo et al. 2004). Most occupational asthma is immunologically mediated and has a latency period of months to years after the onset of exposure (Sastre et al. 2003).

2.5.4 Tobacco smoking

As discussed earlier, early-life exposure to tobacco smoke has been associated with an increased risk of developing asthma, other respiratory symptoms and lung function disorders in later life (Rylander et al. 1993, Lodrup Carlsen et al 1997, Stein et al. 1999b, Taussig et al. 2003, Lannerö et al. 2006, Piippo-Savolainen et al. 2006, Goksör et al. 2007, Hedman et al. 2011, Burke et al. 2012, Rehan et al. 2012). Similarly, tobacco smoke is also harmful in adulthood, being the major environmental cause of lung function impairment in adults. Active smoking in adolescence and adulthood has been found to increase the risk of current asthma (Strachan et al. 1996, Sears et al. 2003), and it is associated with an accelerated decline of lung function in people with asthma (O'Byrne et al. 2009).

In an adulthood study, European Community Respiratory Health Survey identified that participants, who had been exposed to prenatal tobacco smoke and whose parents smoked in the participants' childhood, reported more wheezing symptoms and symptoms typical for asthma, even after accounting for their own smoking behavior, exposure to environmental tobacco smoke, and occupational exposures (Accordini et al. 2012). They also had lower lung function (Cerveri et al. 2012, Accordini et al. 2012). However, bronchial reactivity and current adult-onset asthma were not associated with parental smoking (Accordini et al. 2012).

In an epidemiological study on the Genetics and Environment of Asthma, the incidence of asthma in adulthood was higher among current smokers compared to never smokers and former smokers, i.e. values of 9.7 %, 5.8 % and 3.0 %, respectively (Vignoud et al. 2011). On the other hand, asthma and chronic obstructive pulmonary disease (COPD) are prevalent obstructive lung diseases, both of which are characterized by airflow limitations. Although both conditions represent distinct pathogenetic entities, there can be significant clinical and physiological overlap between these two disorders leading to potential management difficulties for the clinician (Carolan and Sutherland 2013).

2.5.5 Role of overweight or obesity

Epidemiological studies have shown that overweight and obesity have increased concomitantly with the increase of asthma and allergy, and there has been claimed to be an association between obesity and asthma in industrialized countries in both childhood and adulthood (Shaheen et al. 1999, Kim and Camargo 2003, Gilliland et al. 2003, Gold et al. 2003, Ford 2005, Flaherman and Rutherford 2006, Beuther and Sutherland 2007, Matricardi et al. 2007, Jartti et al. 2009b, Visness et al. 2010, Papoutsakis et al. 2013). A recent review of obesity co-morbidities revealed that obesity preceded and was associated with the persistence and intensity of the symptoms of asthma in adolescence (Noal et al. 2011a). Excessive weight gain has been associated with respiratory symptoms, asthma diagnoses and decreased lung function but not necessarily with bronchial hyper-reactivity (Flaherman and Rutherford 2006, Noal et al. 2011b).

In a recent meta-analysis reviewing adult studies, being overweight (body mass index, BMI >25 kg/m^2) carried a mean 1.5-fold risk and obesity (BMI >30 kg/m^2) a 1.9-fold risk for the incidence of asthma within one year (Beuther and Sutherland 2007). The same effect was seen in young adults in a Finnish study (Kilpeläinen et al 2006). Obese asthma has been suggested as representing a distinct phenotype of adulthood asthma (Lugugo et al. 2010).

Obesity is generally found to be more consistenly associated with asthma in women than men (Camargo et al. 1999, Shaheen et al. 1999, Beckett et al. 2001, Huovinen et al. 2003, Kim and Camargo 2003). However, there are also studies where gender had no influence on the

relationship between asthma and obesity (Shaheen et al. 1999, Luder et al. 2004, Ford et al. 2004).

When obese asthmatics were compared to non-obese subjects they were noted to report more frequent daytime and night-time symptoms and limitations of social activities or exercise tolerance due to their asthma (Lavoie et al. 2006, Lessard et al. 2008). It has been suggested that obesity increases the severity of asthma (Akerman et al. 2004, Mosen et al. 2008) although its influence seems mainly to make asthma more difficult to control (Lavoie et al. 2006, Saint-Pierre et al. 2006, Cazzoletti et al. 2007, Lessard et al. 2008). Potential factors which are involved in poorer control of the asthma in obese individuals are changes in lung mechanical properties, resistance to controller therapy, psychological factors, contribution of increased comorbidities and de-conditioning lifestyle (Boulet 2013). Obesity significantly affects symptoms, medication use, and quality of life, and in addition, obese individuals with asthma have a 4.6-fold increased risk of hospitalization for asthma compared with their non-obese asthmatic counterparts (Mosen et al. 2008).

Obesity seems to be a predisposing factor for the development of asthma, but the underlying mechanisms of its influence are still unclear. Various hypotheses have been generated to explain the link between obesity and asthma such as a common genetic predisposition, developmental changes, altered lung mechanics, the presence of a systemic inflammatory process, and an increased prevalence of associated comorbid conditions (Weiss and Shore 2004, Schaub and von Mutius 2005, Beuther et al. 2006, Shore 2008, Boulet 2013).

3 Aims of the Study

The aims of the study were to evaluate the adolescence and adulthood outcome in subjects who had been hospitalized for bronchiolitis in early childhood, to find the possible early-life risk factors for adulthood asthma and to assess the role of overweight and obesity to asthma prevalence.

The specific aims of the study were:

1. To describe the prevalence of asthma, allergy and respiratory symptoms among adolescents and adults who had required hospitalization for bronchiolitis in their early life compared with controls without a history of wheezing problems at that time.

2. To evaluate the risk of asthma in adolescence after hospitalization for RSV and rhinovirus bronchiolitis during infancy, using the within-study comparisons and comparisons with population controls.

3. To evaluate the association between weight status and asthma and allergy after early life wheezing compared with population controls in adolescence and adulthood.

4. To define the influence of early-life risk factors, like sensitization to inhaled allergens, eosinophilia and repeated wheezing episodes in early childhood, for later asthma.

4 Subjects and Methods

This thesis data comprises of two separately collected groups of study patients who had been hospitalized for bronchiolitis or pneumonia during infancy and of their selected and non-selected population controls.

4.1 BASELINE DATA OF STUDY GROUP 1981-1982

4.1.1 Study subjects

Between September 1st 1981 and August 31st 1982, 130 children with low respiratory infection (LRI), including 83 children who were hospitalized for bronchiolitis (Group 1981-1982) and 47 children who were hospitalized for pneumonia at the age of 1-23 months (median age 10 months) in the Department of Pediatrics at Kuopio University Hospital, Finland, were recruited into the study (Figure 1) (Korppi et al. 1986). Bronchiolitis was diagnosed by the presence of tachypnoea, expiratory wheezing or prolonged expirium during lower respiratory infection. A chest radiograph was taken from all children and pneumonia was diagnosed if an infiltration was detected radiologically. Three children from the pneumonia group were not included in the analyses after 3 years of age due to inappropriate follow-up data.

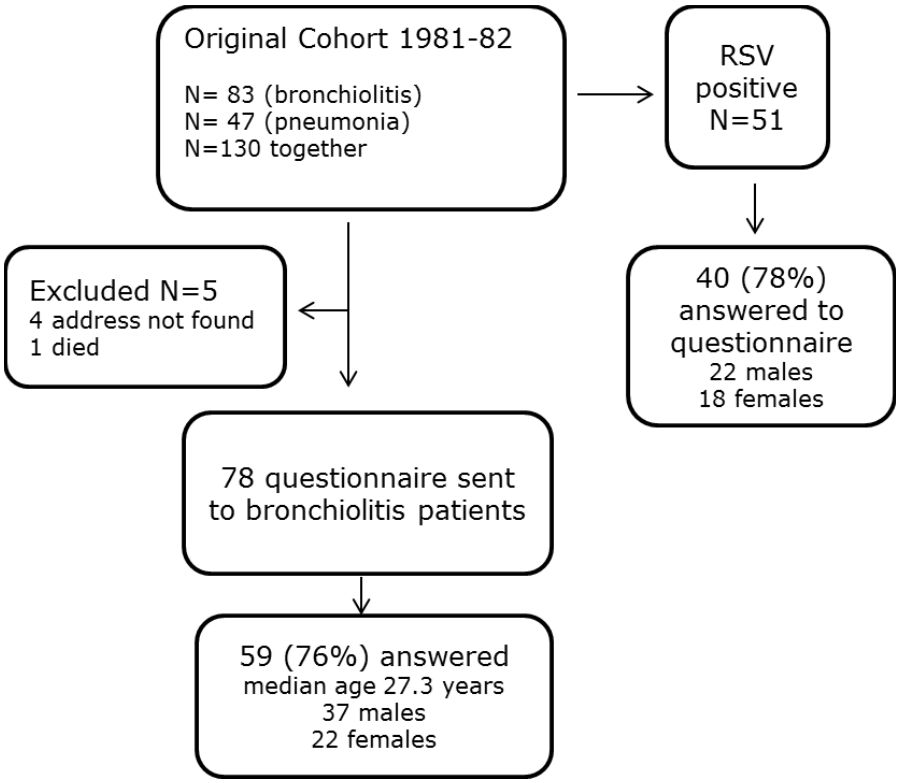

Figure 1. The flow chart of the study on cohort 1981-1982.

4.1.2 Collection of baseline data

The family history and case history of each child were obtained by interviewing the parents on admission and during the follow-up visits until the age of 20-35 months (Korppi et al., 1993), about asthma and allergy with only doctor-diagnosed disease being utilized (Kuikka et al. 1994). Wheezing episodes of the children were separately recorded for the age periods of 0-12 months and 12-24 months, and if wheezing was present at least 3 times before 24 months of age (including the index episode), it was classified as repeated (Korppi et al., 1993). The diagnosis of atopic and non-atopic dermatitis was confirmed by a dermatologist in all cases in whom there was dermatitis in the child reported by a parent (Korppi et al. 1994)

4.1.3 Laboratory tests and early-life data on allergy

Virus etiology for seven common respiratory viruses (RSV, parainfluenza viruses types 1, 2 and 3, adenovirus and influenza A and B viruses) was determined from antigen and antibody assays from nasopharyngeal aspirates (NPA) and paired serum samples which were obtained from 33 patients with bronchiolitis and from 19 subjects with pneumonia.

Total serum levels of immunoglobulin E (IgE) (ALK, Allergologiska Laboratorium, Copenhagen, Denmark) was determined and was considered as elevated if the concentration was more than +2SD above the mean for non-atopic Finnish children (≥ 60 kU/l) (Saarinen et al., 1982) at either of the two measurements at 6-11 and/or 18-23 months of age (Kuikka et al., 1994). Sensitization was studied by assaying for allergen-specific IgE (ALK, Allergologiska Labratorium, Copenhagen, Denmark) to 8 common inhalant allergens (birch, timothy grass and mugwort pollens, spores of *Cladosporium herbarum*, cat and dog epithelial dander, and two house dust mites, *Dermatophagoides farinae* and *D. pteronyssimus*)

in serum at 18-23 months (N=67) or at 30-35 months of age (N=76). A concentration over the detection level (0.35 kU/l) on either occasion was regarded as evidence of sensitization to that allergen (Paganelli et al. 1998)

Blood eosinophils (B-Eos) counts were determined on admission during acute infection and 4-6 weeks later during convalescence using a counting chamber (Lewis et al., 1975). These determinations were done on both occasions in 79 (95%) children. The cell counts were expressed as continuous absolute values, and eosinophilia was defined by > 0.45 x 10^9 /l (Eisen 1980).

4.1.4 Previous follow-up of the cohort

Since the index episode of wheezing in the children with bronchiolitis and pneumonia, they were prospectively followed up during clinical visits at 4.5-6 years (pneumonia cases not included) (Kuikka et al. 1994), at 8.5-10 years of age (Korppi et al. 1994) and at the age of 18-21 years (Piippo-Savolainen et al. 2004). A postal questionnaire on asthma symptoms and medication was sent to study subjects at the age of 13.5-16 years (Hyvärinen et al. 2005a). In every clinical study phase, asthma and allergy status was carefully examined and screened also via a questionnaire. Asthma was defined as ≥ 3 wheezing episodes ever in life at the age of 8.5-10 years (Korppi et al. 1994) and physician diagnosed or treated asthma or wheezing symptoms within the preceding 12 months at the age of 13.5-16 (Hyvärinen et al. 2005a) and 18-21 years (Piippo-Savolainen et al. 2004).

4.2 BASELINE DATA ON STUDY GROUP 1992-1993

4.2.1 Study subjects

Between January 1st 1992 and November 2nd 1993, 100 children aged 1-23 months (median age 10 months) were recruited into the prospective follow-up study in the Department of Pediatrics at Kuopio University Hospital, Finland (Figure 2) (Reijonen et al. 1995). The inclusion criteria were the presence of wheezing and respiratory distress during acute respiratory infection. Patients were excluded if they had a history of chronic cardiorespiratory disease, including asthma, if they had been received bronchodilators within six hours, or if the acute respiratory failure was threatening.

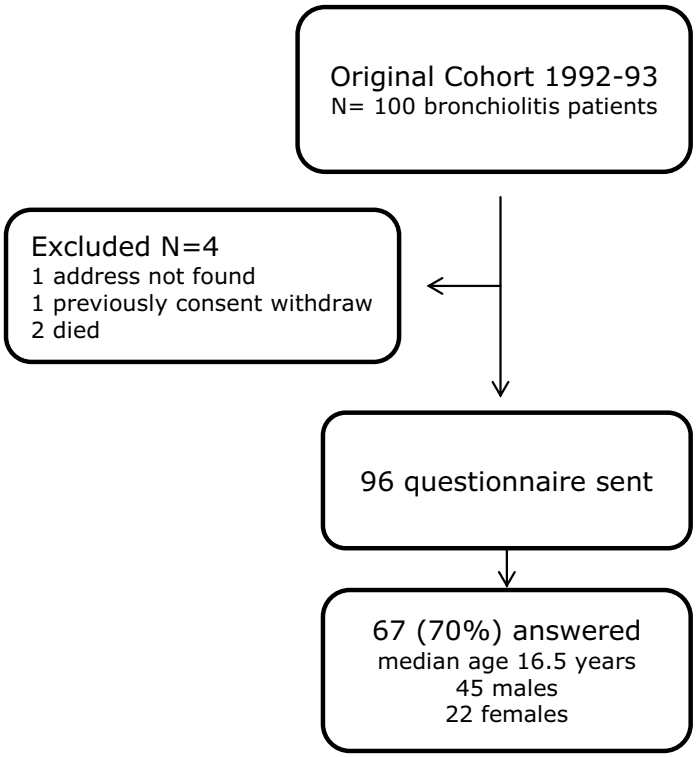

*Figure 2.*The flow chart of the study on cohort 1992-1993.

4.2.2 Collection of baseline data

The family history of asthma, allergy and atopic dermatitis and baseline data in the child were obtained by interviewing the parents on admission of the children by using a structured questionnaire. The diagnoses made by physician were utilized in these analyses. The wheezing history, as well as those of maternal smoking during pregnancy and passive smoking during infancy were also recorded (Reijonen et al. 1995).

4.2.3 Laboratory tests

A venous blood sample was drawn from each patient during the index episode of wheezing and at the control visits 6 and 16 weeks later (Reijonen et al. 1997). Serum levels eosinophil cation protein (S-ECP), B-Eos and total IgE were determined. S-ECP was determined according to the instructions of the manufacturer (Pharmacia ECP RIA, Pharmacia, Uppsala, Sweden) and B-Eos were counted in an automated cell counter (Coulter Counter STKS, Coulter Electronics, Hialeah, FL). The cut-off limits for the elevated values were > 16 μg/l for S-ECP (Peterson et al. 1991), > 0.45 x 10^9/l for B-Eos (Eisen 1980) and ≥ 60 kU/l for total IgE (Saarinen et al. 1982). All the primary results have been described earlier in detail (Reijonen et al. 1997a).

In 2000, allergen specific IgE (sIgE) antibodies (Phadiatop Combi®) were determined from frozen serum samples, which had been obtained during the index episode of wheezing, by fluoroenzyme-immunometric assay, UniCAP™ (Pharmacia, Uppsala, Sweden). First, the presence of sIgE antibodies to mixtures of inhalant allergens (timothy grass, birch and mugwort pollens, cat, dog and horse epithelial danders, spores of *Cladosporium herbarum* and house dust mites, *Dermatophagoides pteronyssimus*) and food

allergens (egg white, cow´s milk, fish, wheat, peanut and soya bean) was screened by the detection limit ≥ 0.35 kU/l (Paganelli et al. 1998) and if it was positive, serum sIgE antibodies were measured with same limit.

On admission, NPAs were taken by suctioning a mucus specimen from the nostrils with a disposable extractor. Direct detection of viral antigens by time-resolved fluoroimmunoassay (TR-FIA) was available for RSV, parainfluenza virus types 1, 2 and 3, influenza A and B viruses, and adenovirus (Reijonen et al. 1997). Serology by complement fixation (CF) was examined for the same respiratory viruses in paired sera taken 6 weeks apart: four-fold or greater increases in titers were defined as a positive result (Reijonen et al., 1997a).

In 2000, 81 frozen good-quality NPA samples were evaluated by reverse transcription-polymerase chain reaction (RT-PCR) assay for detection of rhinoviruses, enteroviruses and coronaviruses (strains 229E and OC-43) (Kotaniemi-Syrjänen et al. 2003b). In 2002, the RSV genome was detected by RT-PCR from NPA samples in 61 cases (Kotaniemi-Syrjänen et al. 2005).

The ECP concentration was determined from the frozen NPA samples according to the instructions of the manufacturer (Pharmacia ECP RIA, Pharmacia, Uppsala, Sweden). The ECP concentration was expressed as nanograms (ng)/g of NPA (NPA ECP) after correction for dilution 0.9% NaCl (Reijonen et al. 1997b). The receiver operating characteristic (ROC) curve analysis was applied to determine the cut-off concentration for NPA ECP which would maximize true positive cases and minimize false positive cases; the best cut-off limit for NPA ECP was 815.0 ng/g with relation to both teenage asthma and its relationship to persistent childhood asthma (Hyvärinen et al. 2010).

4.2.4 Previous follow-up of the cohort

After the index episode of wheezing, the study subjects visited the outpatient clinic at 6 and 16 weeks, 8 and 12 months and 3 years later (Reijonen et al. 2000) to monitor the respiratory status and to check for allergic manifestations in the children. At the 3-year follow-up visit, the children were between 3.2-5.1 years of age. Children having at least 3 episodes of physician-diagnosed bronchial obstruction (the index episode included) were considered as asthmatic. The clinical follow-up visits were arranged also at 5.8-8.8 years (Kotaniemi-Syrjänen et al. 2002) and 10.9-13.7 years of age (Hyvärinen et al. 2005). Symptoms suggestive of asthma and allergies were recorded and the baseline pulmonary function was examined by flow volume spirometry (FVS) (Medikro, Kuopio, Finland). The FVS was followed by the exercise challenge test (ECT), which consisted of 8-minute free running outdoors at the heart rate of ≥ 80% of maximum (Kotaniemi-Syrjänen et al., 2002, Hyvärinen et al., 2007). Asthma was considered to be present if 1) the child was on continuous maintenance or intermittent anti-inflammatory medication for asthma or if 2) she/he had suffered from repeated (≥ 2) episodes of wheezing or prolonged (≥ 4 weeks) cough not related to infections during the preceding 12 months as reported by parents, and ECT was regarded as positive (Kotaniemi-Syrjänen et al., 2002, Hyvärinen et al., 2007).

4.3 CONTROL SUBJECTS

This study had two various control groups. In 1979-1980 72 newborns without a family history of atopy were recruited as controls with no intervention in a birth cohort study on atopy prevention (Pöysä et al. 1988) and there after they have been prospectively followed up (Pöysä et al. 1991, Piippo-Savolainen et al. 2004). None of these controls have required hospitalization for bronchiolitis or other lower respiratory infections before the age of two years. This group was used as a control group for the group 1981-1982 in earlier phases of the study (Piippo-Savolainen et al. 2004) and now in the first study of the present thesis.

For this study a separate control group was recruited from the Population Register Centre, Finland. These subjects in the control group were nonselected population-based controls who were born in the primary area of Kuopio University Hospital similarly to the bronchiolitis patients and they were also matched for gender and the birth month.

4.4 QUESTIONNAIRE FOLLOW-UP IN 2008

In the spring of 2008 a questionnaire was sent to the two study groups and to the controls. The questions in the questionnaire were focused on asthma, allergy, respiratory symptoms and family history of asthma and allergy.

4.4.1 Study subjects in Group 1981-1982

The questionnaire was sent to 78 study subjects and fifty-nine subjects (76%), 37 males and 22 females, from the Group 1981-1982 responded to the follow-up questionnaire in the spring 2008 at the median age of 27.3 years (range 26.3-28.6).

Fifty-one subjects with early RSV LRI hospitalization in years 1981-1982, and 40 (78%) of them, 22 males and 18 females, answered. Their median age was 27.0 years (range 26.4-28.5). The presentation of RSV LRI in infancy was classified by clinical and radiological criteria (obstruction and/or infiltration in lung). Twelve of them had infiltration in the lung but no obstruction, 14 subjects had obvious obstruction, but they did not have any infiltration evident in the thoracal x-ray and 14 of them had both obstruction and the infiltration in the lung.

Fifty-eight study subjects from the Group 1981-1982 reported their weight and height values in the questionnaire.

4.4.2 Study subjects in Group 1992-1993

The questionnaire was sent to a total of 96 Group 1992-1993 study subjects for whom a current address was available and 67 (70%), 45 males and 22 females, answered at a median age of 16.5 years (range 15.1-18.1). On average, the follow-up time from the hospitalization for wheezing in infancy was 15.6 years.

From 67 study subjects, the causative agent for bronchiolitis in infancy was RSV in 22 cases which in 16 cases RSV was the only virus, in one case there was a mixed infection with rhinovirus and in five cases there was a mixed infection with other viruses. In 19 cases the causative agent was rhinovirus. In 16 cases rhinovirus was the only virus which was found. In one case there was mixed infection with RSV and in two cases mixed infection with other viruses.

Sixty of the study subjects from the Group 1992-1993 reported their weight and height values in the questionnaire.

4.4.3 Control subjects

Thirty-nine subjects (54%) from control group in the atopy prevention study, 21 males and 18 females, responded to the questionnaire at median age of 28.5 years (range 28.2-28.7)

For the Group 1981-1982, it was possible to obtain a 4:1 ratio for the 82 cases (55 males and 27 females: one study subject had died) by accessing the nonselected population-based, gender and age matched controls from the Population Register Centre (Finland). The questionnaire was sent to 328 controls and 121 (37%) answered. From these 121 subjects, a control group of 105 subjects was constructed. This group included 60 females, two controls for each of the female cases selected according to the closest birth days (+/- 30 days) and all 61 males who answered to the questionnaire, on average 1.65 controls for each the male case.

For 51 subjects with RSV LRI hospitalization in 1981-1982, it was also possible to obtain population-based controls in a 4:1 ratio. The questionnaire was sent to 204 controls and 99 answered. From this group a control group of 80 subjects was selected, two controls for

each of the 40 cases who answered to the questionnaire. The controls chosen were matched for gender and birth month.

A population-based control group was also obtained for the Group 1992-1993. For the 99 cases (71 males and 28 females; one subject had earlier declined to partiapate in future follow-ups) the questionnaire was sent to 396 controls of whom 155 (39%) answered to and all of them, 104 males and 51 females, were included in the control group.

4.4.4 Posted questionnaire

The questionnaire comprised questions on the presence of wheezing symptoms, over four weeks of persistent cough not relation to an infection, repeated night cough and doctor-diagnosed asthma. In the case of doctor-diagnosed asthma, the time of the asthma diagnosis was recorded as follows: during the preceding 12 months, during the preceding 24 months or ever in life. The use of maintenance medication (inhaled corticosteroids or leukotriene antagonists) and that of on-demand bronchodilator medication for asthma were recorded but only for the preceding 12 months.

The presence of nasal or eye symptoms (runny or stuffy nose, itchy or bloodshot eyes not related to infection) was inquired as was the presence of skin symptoms which could be suggestive of atopic dermatitis.

Doctor-diagnosed asthma was recorded separately for the mother, father and siblings and the children of the subjects.

The participants were asked to estimate how many cigarettes they smoked daily. The daily consumption of one or more cigarettes during the preceding 12 months was defined as current smoking.

In addition, the weights and heights were inquired in orders to permit calculation of body mass index (BMI).

4.4.5 Definition of asthma

Bronchial asthma was defined by two different ways reflecting the degree of certainty of the diagnosis. (1) Current doctor-diagnosed asthma: either the asthma had been diagnosed by a doctor during the preceding 24 months, or the subject had been using maintenance medication for asthma during the preceding 12 months. (2) Current self-reported asthma: either the subject used weekly on-demand bronchodilating drugs or asthma had been diagnosed by a doctor previously and the subject had experienced the presence of wheezing symptoms, prolonged cough or repeated night cough during the preceding 12 months. Current doctor-diagnosed asthma was an inclusion criterion with both definitions.

4.4.6 Definition of allergy

The months when the subject had suffered symptoms like runny or stuffy nose, itching or bloodshot eyes were recorded for the preceding 12 months. The calendar year was divided into four periods (spring from March to May, summer from June to August, autumn from September to November and winter from December to February). Allergic rhinitis and allergic conjunctivitis were defined to be present if nasal and/or eye symptoms, respectively, occurred during the spring or summer time (hay fever).

There was evidence of atopic dermatitis if the study subject reported itchy eczema in typical areas.

4.4.7 Definition of overweight and obesity

Body mass index (BMI) was calculated by using the equation: weight (kg) / height $(m)^2$. Overweight was defined as BMI > 25 kg/m^2 and obesity as BMI > 30 kg/m^2. Age- and sex-specific BMI standard deviation score (BMI-SDS), also called the Z-score, was assessed for all less than 18 years of age study subjects and controls using the recently published population-based Finnish growth references (Saari et al. 2011). BMI-SDS > 1.16 in females

and 0.78 in males corresponds to BMI > 25 kg/m^2 in adolescents and refers to overweight and BMI-SDS > 2.10 in females and > 1.70 in males corresponds to BMI > 30 kg/m^2 in adolescents and represents obesity (Saari et al. 2011).

4.5 STATISTICAL ANALYSES

The data were analyzed using SPSS 14.0-19.0 software (SPSS Inc., Chicago, IL, USA). In the univariate analyses, Pearsons´s Chi square test and Fisher´s exact test were used for dichotomous data. Fisher´s exact test was used when the expected frequency for any cell was < 5. The result was considered as statistically significant if the p value was < 0.05. The risks are expressed as odds ratios (OR) and their 95% confidence intervals (95% CI).

The logistic regression was used in the multivariate analyses to calculate the adjusted ORs (aOR) and related 95% CIs.

4.6 ETHICS

The study was approved by the Research Ethics Committee of Kuopio University and Kuopio University Hospital. Informed written consent was obtained from the study subjects and if needed from at least one of the parents.

5 Results

5.1 OUTCOMES IN ADULTHOOD AFTER WHEEZING IN INFANCY (GROUP 1981-1982)

5.1.1 Prevalence of asthma and wheezing symptoms (I, II)

The family history of asthma in parents and in siblings is shown in Figure 3.

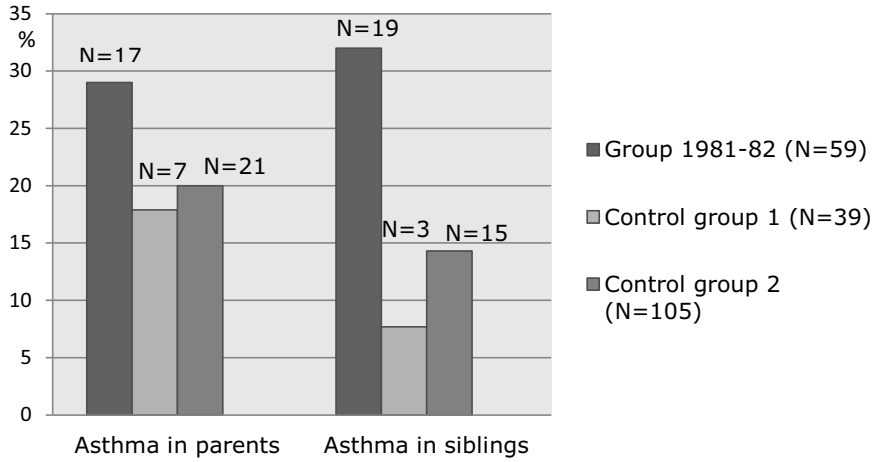

Figure 3. A family history of asthma (%) in Group 1981-1982, in selected control group (Control group 1) and in nonselected population based controls (Control group 2). There was a statistically significant difference between Group 1981-1982 and both control groups (controls from nonatopic families followed-up from birth, Control group 1; and nonselected population based controls, Control group 2) for asthma in siblings (OR 5.68, 95% CI 1.55-20.86, and aOR 2.84, 95% CI 1.30-6.18), but not for asthma in the parents.

Twenty-eight (48%) of the Group 1981-1982 members suffered from wheezing, prolonged cough or night cough, but compared with Control group 1 and Control group 2, the difference was statistically significant only for wheezing (Table 2). As many as 41% of subjects in Group 1981-1982 smoked, compared with 17% in Control group 2 (OR 3.3, 95% CI 1.5-6.0). There were no significant differences in the incidences of allergic rhinitis or atopic dermatitis between Group 1981-1982 and either of the two control groups.

Table 2. Questionnaire data in Group 1981-1982, in selected control group (Control group 1) and in nonselected population based controls (Control group 2)

Questionnaire data	Group 1981-1982 (N=59)	Control group 1 (N=39)	OR (95% CI)	Control group 2 (N=105)	OR (95% CI)*
Wheezing symptoms	25 (42%)	11 (28%)	1.87 (0.8-4.5)	22 (21%)	2.93 (1.4-6.0)
Prolonged cough (smokers/non-smokers)	5/1 (8.5/1.7%)	3/2 (7.7/5.1%)	0.77 (0.2-2.7)	3/3 (2.8/2.8%)	1.66 (0.5-5.6)
Night cough	5 (8.5%)	7 (18%)	0.42 (0.1-1.5)	6 (5.7%)	1.44 (0.4-5.0)

*adjusted for sex and age

Current doctor-diagnosed asthma was present in 20% of the Group 1981-1982 subjects, compared with 5% in the two control groups. The risk of doctor-diagnosed asthma in Group 1981-1982 was 2.8-fold when compared with Control group 1 and 5.0 fold when compared with Control group 2.

Self-reported asthma was present in 41% of the Group 1981-1982 subjects. The figures in control groups 1 and 2 were 10% and 7%, respectively. The risk of self-reported asthma in Group 1981-1982 was 13.5-fold (95% CI 2.90-63.0) *vs.* Control group 1, and 11.0 fold (95% CI 4.19-29.1) *vs.* Control group 2, respectively. The results were robust and remained significant even after to adjustments for age, gender, current smoking and allergic rhinitis.

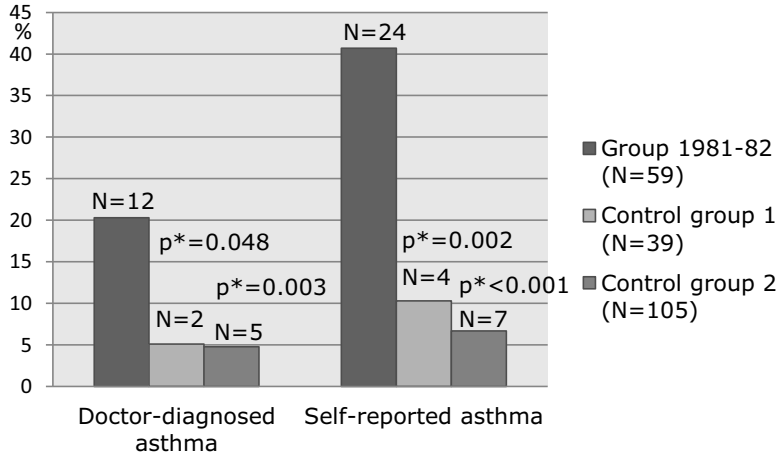

Figure 4. Asthma by two definitions in Group 1981-1982, in selected control group (Control group 1) and in nonselected population based controls (Control group 2). p* Group 1981-1982 vs Control group 1 / Control group 2

When a subgroup of 24 young adult with self-reported asthma (doctor-diagnosed asthma included) were compared with the two control groups, there were significant differences in the presence of current wheezing symptoms, current allergic rhinitis and previous asthma, as well as with the presence of asthma in siblings and in current smoking (Table 3). When an identical comparison was performed for the subgroup of 12 subjects with current doctor-diagnosed asthma, the differences were significant only for current wheezing symptoms, previous asthma and asthma in siblings (data not shown).

Table 3. Questionnaire data in 24 young adults with current self-reported asthma (doctor-diagnosed included) from Group 1981-1982, compared with Control group 1 and with Control group 2

Questionnaire data	**Current self-reported asthma (N=24)**	**OR (95% CI) vs. Control group 1**	**OR (95% CI)* vs. Control group 2**
Asthma in siblings	13 (54%)	13.79 (3.3-57)	7.47 (2.8-20)
Current smoking	11 (46%)	2.15 (0.7-6.2)	4.00 (1.5-11)
Wheezing symptoms	22 (92%)	28.00 (5.6-140)	42.20 (9.2-190)
Allergic rhinitis	16 (67%)	3.43 (1.2-10)	2.66 (1.0-6.8)

*adjusted for sex and age

In the LRI group, there were 22 (55%) men and 18 women who had RSV infection. This group (N=40) was compared with age and gender matched population-based controls (N=80), overweight (aOR 3.3; 95% CI 1.5-7.3), smoking (aOR 2.7; 95% CI 1.1-6.3), wheezing symptoms (aOR 2.8; 95% CI 1.15-6.75), and self-reported asthma (aOR 11.4; 95% CI 3.0-44) were more common in cases than in controls.

5.1.2 Early predictive factors for adulthood asthma (I)

Early-life risk factors, including parental asthma, and atopic dermatitis, non-RSV bronchiolitis, eosinophilia > 0.45 x 10^9/l, total IgE > 60 IU/l, presence of allergen-specific IgE, and repeated wheezing, assessed at < 24 months of age, were analyzed within Group 1981-1982. None of the early-life factors were significant as risk factors for doctor-diagnosed or self-reported asthma in adulthood.

5.1.3 Comparison between RSV and non-RSV bronchiolitis

There were 22 (55%) men and 18 women who had suffered a RSV infection including both bronchiolitis and pneumonia cases. When they were compared with age and gender matched population-based controls, overweight (aOR 3.3; 95% CI 1.5-7.3), smoking (aOR 2.7; 95% CI 1.1-6.3), wheezing symptoms (aOR 2.8; 95% CI 1.2-6.8), and self-reported asthma (aOR 11.4; 95% CI 3.0-44) were more common in the cases than in the controls. The analyses were adjusted for age and gender.

5.1.4 Overweight or obesity (III)

The mean BMI of the Group 1981-1982 was 25.95 kg/m^2 at median age of 27.3 years; 54.4% were overweight and 13.6% were obese. The corresponding figures had been 24.17 kg/m^2, 37.2% and 11.1% at median age of 19.0 years. There were no significant differences in BMIs between the Group 1981-1982 and Control group 2 at median age of 27.3 years, or between the measurements at median age of 27.3 and 19.0 years.

There were no significant differences between the overweight and normal weight subjects in Group 1981-1982 in the extent of respiratory symptoms or allergic manifestations at 26-29 years of age or at 18-20 years of age. The result remained negative at both ages also when obese subjects were compared with normal weight subjects (data not shown). Overweight displayed no significant association with doctor-diagnosed asthma, self-reported asthma or the use of inhaled corticosteroids at the median age of 27.3 years. As expected, asthma by all definitions was more common in Group 1981-1982 than in Control group 2. However, in overweight subjects, the difference between the cases and controls was significant only for self-reported asthma (Figure 5).

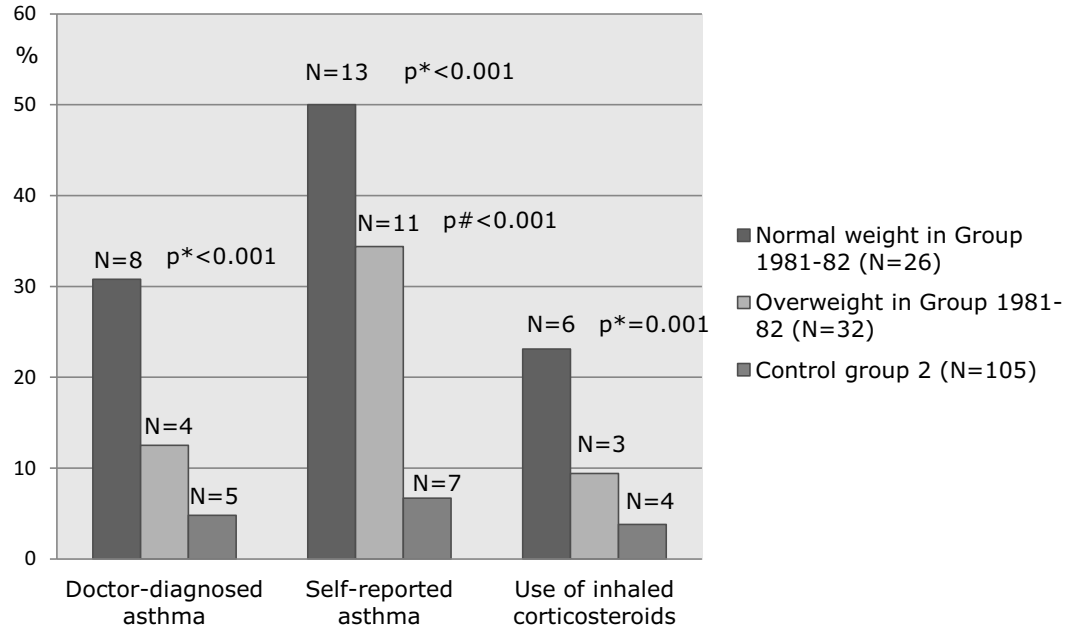

Figure 5. Outcome in Group 1981-1982 at 26-29 years of age in relation to weight status. p*= Normal weights in Group 1981-1982 vs Control group 2, p#= Overweights in Group 1981-1982 vs Control group 2

Overweight had no significant association with doctor-diagnosed asthma, self-reported asthma or use of inhaled corticosteroids at median age of 19.0 years (data not shown). Being overweight at 18-20 years of age did not predict asthma at 26-29 years of age.

5.2 OUTCOME IN ADOLESCENCE AFTER WHEEZING IN INFANCY (GROUP 1992-1993)

5.2.1 Prevalence of asthma and wheezing symptoms (IV)

There were more parents with asthma (aOR 2.6; 95% CI 1.3-5.0), siblings with asthma (aOR 2.1; 95% CI 1.0-4.3) and current wheezing symptoms (aOR 3.4; 95% CI 1.7-6.8) in Group 1992-1993 as compared with the population-based controls in an analysis adjusted for sex and age. There were no statistical differences in cough symptoms, allergic rhinitis or atopic dermatitis between Group 1992-1993 subjects and controls.

Thirty (30%) of Group 1992-1993 subjects had current doctor-diagnosed asthma and 64% had self-reported asthma. The respective figures in the control group were 5% and 11%, and these differences were statistically significant in multivariate analysis (Table 4). In the multivariate model adjusted for sex, age, smoking, allergic rhinitis asthma in parents and asthma in siblings, bronchiolitis in infancy remained as an independent risk factor for asthma at 15-18 years of age.

Table 4. Asthma as evidenced by two definitions in Group 1992-1993 and in population-based control group

Definition of asthma	**Group 1992–1993 (N=67)**	**Control group (N=155)**
Current doctor-diagnosed asthma	20 (30%)	8 (5.2%)
OR (95% CI)*	7.94 (3.3-19.3)	1.00
OR (95% CI)#	10.65 (3.8-29.7)	1.00
Current self-reported asthma	43 (64%)	17 (11%)
OR (95% CI)*	14.69 (7.2-30.0)	1.00
OR (95% CI)#	20.08 (8.9-45.4)	1.00

* adjusted for sex and age, # adjusted for sex, age, smoking, allergic rhinitis, asthma in parents, asthma in siblings.

Asthma in parents was associated with both current doctor-diagnosed asthma (aOR 3.8; 95% CI 1.4-10.2) and self-reported asthma (aOR 2.8; 95% CI 1.3-5.8) compared with control group in analysis adjusted for sex and age. Wheezing symptoms during the preceding 12 months were associated with current asthma by both definitions; doctor-diagnosed asthma (aOR 13.7; 95% CI 4.7-39.6) and self-reported asthma (aOR 5.9; 95% CI 2.8-12.8). Allergic rhinitis was associated only with doctor-diagnosed asthma (aOR 2.7; 95% CI 1.1-7.0).

5.2.2 Early predictive factors for adolescence asthma (IV)

The presence of atopic dermatitis in infancy (aOR 5.2; 95% CI 1.1-25.5) and elevated blood eosinophils > 0.45 x 10^9/l on admission (aOR 10.4; 95% CI 1.2-90.6) were significant predictors of self-reported asthma. The results were also similar and significant if only cases of doctor-diagnosed asthma were included. The presence of at least one allergen-specific IgE > 0.35 kU/l predicted doctor-diagnosed asthma (aOR 6.0; 95% CI 1.1-33.0) but not self-reported asthma. Maternal smoking during pregnancy, passive smoking during infancy,

pre-bronchiolitis wheezing, serum ECP > 16 μg/l, NPA ECP > 815 ng/g were not significant risk factors for the presence of doctor-diagnosed or self-reported asthma in adolescence.

When viral etiology of bronchiolitis in infancy (RSV, mixed included; RV, mixed included; non-RSV non-RV), asthma in parents, atopic dermatitis in infancy, eosinophilia in infancy, and positive allergen-specific IgE at < 24 months of age were included in the same logistic regression model, only atopic dermatitis remained as an independently statistically significant early life predictor of doctor-diagnosed asthma in adolescence in Group 1992-1993 (OR 4.4; 95% CI 1.1-18.4), and none of the factors was an independent predictor of self-reported asthma in adolescence (data not shown).

5.2.3 Comparison between RSV and non-RSV bronchiolitis (IV)

Current doctor-diagnosed asthma was presented in 23.8-25.0% of Group 1992-1993 subjects with RSV bronchiolitis and in 25.0-27.8% of Group 1992-1993 with HRV bronchiolitis, depending on whether mixed infection with other viruses was included or excluded. The respective values for self-reported asthma were 47.6-50.0% (RSV) and 81.3-83.3% (HRV) (Table 5). Current self-reported asthma was more common in non-RSV than in RSV patients and more common in HRV than RSV patients in Group 1992-1993 (83.3% vs 47.6%, p=0.023, mixed infections included; 81.3% vs 50.0%, p=0.067, mixed infections excluded).

RSV and HRV bronchiolitis in infancy increased the asthma risk at 15-18 years of age according to both univariate and multivariate analyses. In the multivariate analyses the statistical significance of the differences between the groups was assessed with logistic regression analysis, adjusted first for age and gender and further also for current smoking, allergic rhinitis, asthma in parents, and asthma in siblings.

Table 5. Viral etiology of hospital-treated bronchiolitis in infancy as a risk factor for asthma in adolescence

Viral etiology of bronchiolitis	**Current doctor-diagnosed asthma OR (95%CI)[#]**	**Current self-reported asthma OR (95% CI)[#]**
RSV, mixed infections included (N=21)	5 (24%)	10 (48%)
	5.7 (1.6-20.2)	7.2 (2.6-19.8)
RSV, mixed infections excluded (N=16)	4 (25%)	8 (50%)
	6.5 (1.6-26.2)	7.6 (2.5-23.1)
Non-RSV	15 (33%)	33 (73%)
(N=45)	9.1 (3.5-23.7)	23.5 (10.0-55.2)
HRV, mixed infection included (N=18)	5 (28%)	15 (83%)
	7.3 (2.1-26.0)	46.7 (11.6-188)
HRV, mixed infection excluded (N=16)	4 (25%)	13 (81%)
	6.3 (1.6-24.8)	41.1 (10.0-169)
Non-HRV	11 (32%)	21 (62%)
(N=34)	8.8 (3.2-24.4)	13.8 (5.7-33.0)

[#]logistic regression, adjusted for age and sex

5.2.4 Overweight or obesity (V)

Weight and height data were available from 60 participants in Group 1992-1993 subjects and from 152 population controls. Only three (5.0%) were obese in Group 1992-1993, and 11 (18.3%) were overweight. There were no significant differences between the groups in BMI-SDS or in the presence of overweight or obesity. There were only four subjects (two in both groups, all males) who were underweight.

In Group 1992-1993, only two (14.3%) of the overweight subjects reported current wheezing symptoms versus 20 (43.5%) of the normal weight subjects (p=0.047). There were no other significant differences in respiratory or allergic symptoms or manifestations between the overweight and normal weight in Group 1992-1993. One of the three obese subjects in Group 1992-1993 reported previous asthma, but no-one had current wheezing symptoms or allergic rhinitis or conjunctivitis.

Current doctor-diagnosed asthma, current self-reported asthma and use of inhaled corticosteroids were more common in normal weight subjects in Group 1992-1993 than in population controls (Figure 6). The values were rather similar in normal weight and in overweight subjects in Group 1992-1993 (Figure 6).

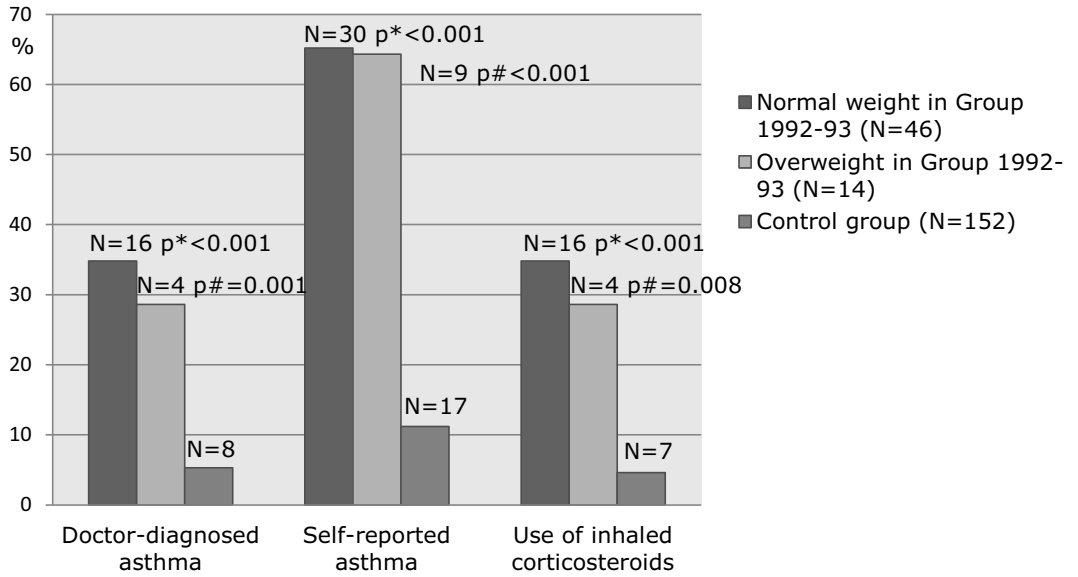

Figure 6. Outcome in Group 1992-1993 at 15-18 years of age in relation to weight status. p*= statistical significance between normal weight in Group 1992-1993 and control group, p#= statistical significance between overweight in Group 1992-1993 and control group.

In the Group 1992-1993 subjects, there were no significant associations between overweight or obesity and doctor-diagnosed asthma, self-reported asthma, use of asthma medication or the presence of allergic rhinitis or conjunctivitis in control group (data not shown).

Weight and height data were available from the control visit at 12-13 years of age for 54 of 60 subjects in the Group 1992-1993. Being overweight or obese at that age did not predict current asthma by either definition nor did it predict allergic rhinoconjunctivitis (data not shown).

6 Discussion

6.1 DESIGN OF THE STUDY

This postel questionnaire study was a prospective follow-up including two separately collected study groups of patients (Group 1981-1982 and Group 1992-1993) who had been hospitalized for either bronchiolitis or pneumonia in their infancy (Korppi 1986) and population based controls. The field phase of the study was carried out in 2008.

The bronchiolitis groups were primary constructed during two different decades - 1981-1982 and 1992-1993. The study subjects were hospitalized at the age of 0-23 months, and data on early-life risk factors were carefully collected by interviewing the parents when the child was being admitted to hospital by using a structured questionnaire (shown in the appendices)(Korppi et al. 1986, Korppi et al. 1993, Korppi et al. 1994, Kuikka et al. 1994, Reijonen et al. 1995, Reijonen et al. 1996), by identifying the causative viruses via antibody and antigen assays (Korppi et al. 1986, Reijonen et al. 1998), supplemented by PCR (Group 1992-1993) (Kotaniemi-Syrjänen et al. 2003b, Kotaniemi-Syrjänen et al. 2005), by determining blood eosinophil numbers (Kuikka et al. 1994, Reijonen et al. 1997) and markers of atopy (Kuikka et al. 1994, Reijonen et al. 1997a). Both bronchiolitis groups were followed-up during regular visits to the clinic (Kuikka et al. 1994, Korppi et al. 1994, Piippo-Savolainen et al. 2004, Reijonen et al. 2000, Kotaniemi-Syrjänen et al. 2002, Hyvärinen et al. 2005).

The original study designs did not include healthy control children, instead pneumonia patients formed a non-wheezing control group for Group 1981-1982 throughout childhood. In adulthood studies, the subjects from a prospective atopy prevention study, started at birth in 1979-1980, formed a suitable control group for Group 1981-1982 (Pöysä et al. 1988). For this present study, nonselected population-based controls were obtained from the Population Register Centre for Group 1981-1982 and Group 1992-1993. The cases and controls were of similar age and gender; they came from the same population and lived in the same geographical area. Thus, for Group 1981-1982 there were two different control groups. The questionnaire was sent to study subjects for whom a current address was available. Some of them have not provided permission for the authorities to give their addresses to outsiders and three study subjects had died. The questionnaire had minor modifications, and basically was the same as that used in previous phases of this post-bronchiolitis follow-up study, as also were the definitions of doctor-diagnosed and self-reported asthma (Kuikka et al. 1994, Hyvärinen et al. 2005a).

6.2 PREVALENCE OF ASTHMA AND WHEEZING SYMPTOMS

In this present study, bronchial asthma was defined in two different ways reflecting the degree of certainty of the diagnosis, i.e. current doctor-diagnosed asthma and current self-reported asthma. The definition of self-reported asthma was based, with minor modifications, on earlier follow-up studies and with asthma definition studies (Pekkanen et al. 2005, Vianna et al. 2007).

In Group 1981-1982, the increased risk for bronchial asthma after suffering bronchiolitis at an age less than 24 months of age continued until 27 years of age, when compared with either the selected controls from non-atopic families with no early-life wheezing followed from infancy, or with the non-selected population-based controls enrolled into the present study. Depending on the definition of asthma, the prevalence of asthma was 20 – 41 % in

Group 1981-1982. The respective figures were 5 - 10 % in selected controls not at risk of asthma and allergy, and 5 - 7 % in nonselected controls. According to population-based studies the prevalence of asthma in Finnish adults is between 4 to 5% (Huurre et al. 2004, Pallasaho et al. 2011). Thus, both the selected and non-selected controls of the present study reflected well the situation in the age-specific population. In the same experimental cohort, eight years earlier the prevalence of asthma had been 30 – 41 % (Piippo-Savolainen et al. 2004), and thus, the prevalence values have remained rather constant. Further, the results are rather similar to the findings of a Canadian study (Larouche et al. 2000), where asthma was diagnosed clinically at the age of 17 – 35 years, with information about early-life wheezing of the study subjects being collected retrospectively from the patient records of two hospitals. The prevalence of asthma was 38 % after prior hospitalization for bronchiolitis before the age of 18 months, and this was significantly higher than in controls with no such history. In contrast, wheezing in infancy was not associated with asthma in adulthood in a birth cohort study from the United Kingdom (Rhodes et al. 2001, Rhodes et al. 2002). In that cohort, data on wheezing had been gathered prospectively, but the number of infants with wheezing was too small to permit any proper risk estimation. In the Tucson birth cohort study, the prevalence of asthma was 30 % at 22 years of age (Stern et al. 2008), which is in accordance with the values in the present study. In Group 1981-1982, there were more smokers than in control groups. There were no differences between smoking habits of the parents, so we can-not explain this difference between these groups.

In Group 1992-1993, there were more wheezing symptoms than in population-based controls, at the median age of 16.5 years. Doctor-diagnosed asthma was present in 30 % and self-reported asthma in 64 % of the former bronchiolitis patients. Four years earlier the prevalence of doctor-diagnosed asthma was 40 % in the same cohort, when about 30 % reported asthma, in line with the present study, and in about a further 10 %, the diagnosis was determined at the study visit (Hyvärinen et al. 2005b). In the control group, the doctor-diagnosed prevalence of asthma was 5.2 %. Ten years ago, the prevalence of asthma was 3 % in the 16-year-old, non-selected Finnish population (Huurre et al. 2004) which is rather close to the asthma prevalence in the controls in the present study. Recently, the prevalence of doctor diagnosed asthma in the Swedish population was 9.5 % stayed to be about in the age group 16 to 20 years (Wennergren et al. 2010). In a post-bronchiolitis study from Gothenburg, Sweden, 30 % of the bronchiolitis patients were suffering from asthma at ten years of age (Wennergren et al. 1997) and more, 43 %, at 17 - 20 years of age (Goksör et al. 2006). Changes in the prevalence of asthma in four post-bronchiolitis follow-up studies continued until teenage or adulthood could be seen in Figure 7. In the Tucson birth cohort study the asthma values after parent-reported early childhood wheezing treated at home were, as expected, somewhat lower, 30 % at 13 years (Stein et al. 1999) and 20 % at 16 years of age (Morgan et al. 2005).

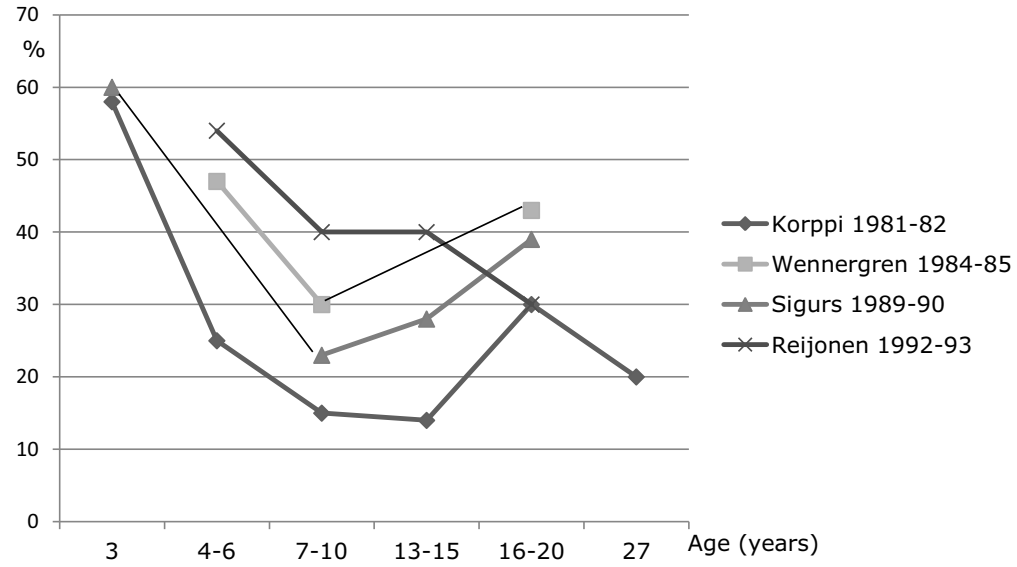

Figure 7. Prevalence of asthma after hospitalization for bronchiolitis in early life; results from four cohorts prospectively followed up until teenage or adulthood.

6.3 OUTCOME IN RELATION TO VIRAL ETIOLOGY OF BROCHIOLITIS AND EARLY-LIFE RISK FACTOR

The current knowledge about the long-term prognosis of an early RSV infection has emerged from bronchiolitis studies. In a systematic review, hospitalization for RSV bronchiolitis was associated with wheezing until the age of six years but not subsequently (Kneyber et al. 2000). In the most recent meta-analysis, 9 of the 15 included studies reported a significant increase in asthma prevalence after RSV hospitalization before the age of 3 years (Régnier and Huels 2013). The ages at follow-up have varied from one to 12 years, and the association weakened by age, consistently with the follow-up studies until early adolescence (Sigurs et al. 2005, Hyvärinen et al. 2005a). In young adults, the prevalence of asthma again increases (Piippo-Savolainen et al. 2004, Goksör et al. 2006, Sigurs et al. 2010). In the Swedish RSV bronchiolitis study, which included patients hospitalized at 0-11 months of age, 28 % had asthma at 13 years of age (Sigurs et al. 2005) and 33 - 39 %, depending on the definition of asthma, at 18 years of age (Sigurs et al. 2010). In Norway the prevalence of asthma was 34 % in former bronchiolitis patients at 10-16 years of age (Hovland et al. 2013). In a recent Finnish post-bronchiolitis follow-up study, the strongest independent risk factor for recurrent wheezing was rhinovirus detection followed by sensitization age less than one year and eczema in the age 7 years (Lukkarinen et al. 2013).

In the present 1981-1982 cohort, hospitalization for RSV LRI in infancy increased the risk of asthma by more than 10-fold, when compared with controls not at risk, at the median age of 27 years, independently from confounding factors such as allergy, smoking and being overweight. The risk of asthma was highest, 36 %, after pneumonia with wheezing and the risk of wheezing was highest, 50 %, after pneumonia without wheezing. The prevalence of doctor-diagnosed asthma was 13 %, and the prevalence of self-reported-asthma was 30 % in former RSV LRI patients, much higher than the values of 1.3 % and 3.8 % in the matched population-based controls. Self-reported asthma was assessed by nearly the same criteria at the median age of 9 years, and that time point, the prevalence was 22 % (Korppi et al. 2004). This slight increase observed in the prevalence of asthma in young

adulthood is in line with recent post-bronchiolitis follow-ups from the Scandinavian countries (Goksör et al. 2006, Piippo-Savolainen et al. 2004). Instead, it was not possible to confirm the link between non-RSV bronchiolitis in infancy and later asthma, though this has been observed in the earlier phases of this cohort (Piippo-Savolainen et al. 2004, Piippo-Savolainen et al. 2007b), as well as in the other bronchiolitis cohort earlier (Kotaniemi-Syrjänen et al. 2004, Hyvärinen et al. 2005b). During long-term follow-ups which start in infancy, the study subjects are faced with numerous later risk factors and disease modifying factors which weaken the effect of the early-life risk factors. Another explanation may be that ultimately only 12 – 14 subjects, depending the definition on asthma, suffered from adulthood asthma, and these numbers are too small to permit multivariate analyses which would separate the effects of early-life and later risk factors.

The risk of asthma was about 10-fold in the former rhinovirus versus former RSV bronchiolitis patients at the median age of 7.2 years in the 1992-1993 bronchiolitis cohort (Kotaniemi-Syrjänen et al. 2003). At the median age 12.3 years, the asthma risk in the former non-RSV versus former RSV bronchiolitis patients had declined to 2.5-fold and in the former rhinovirus versus non-rhinovirus bronchiolitis patients to 1.4-fold (Hyvärinen et al. 2005b). In the present 1992-1993 cohort, both RSV bronchiolitis and rhinovirus bronchiolitis in infancy were significant risk factors for both doctor-diagnosed asthma and self-reported asthma at 16.5 years of age compared with population-based controls. The lowest asthma risk, under 50 %, was found after RSV bronchiolitis and the highest, over 80 %, after rhinovirus bronchiolitis. In addition to viruses, these values emphasize the importance of the age of the subjects in bronchiolitis studies; RSV positives are usually under six months of age and rhinovirus positives over 9 months old with different outcomes (Kotaniemi-Syrjänen et al. 2003, Jartti and Korppi 2011, Koponen et al. 2012). Though RSV was the most commonly identified virus in the 0 – 23 months old infants with bronchiolitis, nearly half of the rhinovirus positive patients have been younger than six months in the most recent multicenter study from the United States (Mansbach et al. 2012).

Atopic dermatitis in infancy and positive allergen-specific IgE at less than 24 months of age are early-life features of atopy and were still predictive of asthma in adolescence in the 1992-1993 cohort. If one considers the eosinophilia markers, then it seemed that blood eosinophilia at admission did predict asthma in adolescence, but elevated serum and nasopharyngeal ECP had no predictive value for asthma. Atopy and eosinophilia often cluster in the same high-risk patients, and may even be associated with particular viruses like rhinoviruses (Jartti and Korppi 2011, Busse 2011). Atopic sensitization and viral infection may exert a synergistic effect mediated through certain receptors of innate immunity (Sly and Holt 2011). In a recent birth cohort of babies at risk for asthma and allergy, atopic sensitization preceded rhinovirus wheeze at preschool and early school-aged children, but the converse was not true, interpreted as evidence for a causal role of atopic sensitization in asthma development (Jackson et al. 2012). In the present 1992-1993 cohort, only atopic dermatitis remained as an independent predictor of current asthma in adolescence, when the factors significant in the univariate analyses were incorporated into the same multivariate model. In the present 1981-1982 cohort, none of the early-life factors were significant as predictor of asthma in adulthood.

6.4 OUTCOME IN RELATION TO OVERWEIGHT OR OBESITY

In the present study, the presence of doctor-diagnosed or self-reported asthma or the use of inhaled corticosteroids displayed no association with overweight or obesity in adolescence in Group 1992-1993 or in early adulthood in Group 1981-1982. There was also no significant association between overweight or obesity and atopic dermatitis, allergic rhinitis or allergic conjunctivitis. In the 1981-1982 bronchiolitis cohort, the results were similar at 18 – 20 years

of age. Against expectations, allergic rhinoconjunctivitis was even more common in the population-based controls.

Epidemiological studies have revealed an association between excessive weight gain and presenting or emerging asthma, at least when asthma has been assessed via the symptom history or drug consumption (Flasherman and Rutherford 2006, Beuther 2010, Noal et al. 2011). It has even been claimed that there might be a dose-response relationship between increasing asthma occurrence and increasing BMI in adults (Kilpeläinen et al. 2006, Coogan et al. 2009). In a meta-analysis, overweight (BMI > 25 kg/m^2) increased the mean risk of emerging asthma by 1.5-fold and obesity (BMI > 30 kg/m^2) by a mean of 1.9-fold in adults (Beuther and Sutherland 2007). In addition, asthma has improved after weight loss in adults, and this reversibility provides convincing evidence that overweight may be a significant risk factor for asthma (Eneli et al. 2008). The conflicting results obtained from epidemiological studies conducted in large population samples from those in clinical asthma studies, such as the present study, may be due to different statistical powers available for the analyses. The present results were negative also in the combined analyses of both cases and controls, which were done to check the consistency of the results after increasing the statistical power. In addition, asthma, as classified by all definitions, was even more common in normal weight subjects than in the overweight in Group 1981-1982 and in Group 1992-1993 study subjects, even though statistical significance was not reached.

In a Finnish prospective cohort study which examined both children and adults, asthma was associated with increasing BMI and prior excessive weight gain, but not earlier than at 24 - 39 years of age (Jartti et al. 2009b). In Group 1981-1982, the study subjects were only at the lower level of the observed age window, and thus the association between overweight and asthma may appear later in life. In the Finnish cohort study, no association was found between obesity-related biomarkers and asthma and allergy (Jartti et al. 2009b). There is increasing evidence from adult studies suggesting that obesity-related asthma is a distinct asthma phenotype, appearing from age of 12 - 17 years onwards (Lessard et al. 2008, Lang et al. 2011, Wenzel et al. 2013).

Most studies, independently from the design, have failed to reveal any association between overweight or obesity and allergic diseases or atopic sensitization (Jarvis et al. 2002, Ma et al. 2010), and in contrast to expectations, underweight has actually been associated with atopic sensitization (Van Gysel et al. 2009) and allergic rhinitis (Kusunoki et al. 2008) at school age. In some studies, the association between excessive weight gain and allergy has been gender-dependent, being present only in girls in their teenage years or in young women (Schachter et al. 2003, Hancox et al. 2005). In the 1992-1993 cohort of the present study, the results were negative for both females and males. In the 1981-1982 cohort, current atopy was strongly associated with asthma but not with current overweight or obesity. In a Finnish study of 18- to 25- year-old young adults, the risk of asthma increased linearly with BMI in men but not in women, and the risk of allergic rhinoconjunctivitis and atopic dermatitis increased linearly with BMI in women but not in men, perhaps indicating that different and gender-related effects body fat has on asthma and atopic disease (Kilpeläinen et al. 2006).

6.5 METHODOLOGICAL ASPECTS

6.5.1 Strengths of the study

Group 1981-1982

The main strength of the present study is the long prospective follow-up from infancy to the median age of 27 years. In fact, this present study is the longest prospective follow-up thus far published after bronchiolitis in infancy. The participation rate, 76 %, was good for a

prospective study lasting over 25 years. In infancy, the basic data were registered prospectively and carefully during their hospitalization as well as at the two control visits, including at that time advanced viral antigen determinations. The definitions of asthma were rather stringent being based on current medication, current symptoms and doctor-made asthma diagnoses either within the recent 24 months (doctor-diagnosed asthma) or earlier (self-reported asthma). Thus, the diagnosis was never based on respiratory symptoms alone since these are known to be nonspecific in obese patients (Sin et al. 2002) as well as in smokers (Kjaergaard et al. 2011). Atopic constitution and both passive and active smoking are factors significantly predisposing to both early-life wheezing and later asthma (Goksör et al. 2006, Goksör et al. 2007, Piippo-Savolainen and Korppi 2008, Piippo-Savolainen and Korppi 2009), as was seen also in the present study with the association between current allergic rhinitis and current smoking. Therefore, current smoking and current allergic rhinitis were included as covariates in the logistic regression model, and early childhood wheezing proved to be, a significant risk factor for asthma in adulthood independently from allergy and smoking.

Group 1992-1993

The main strengths of the present study are the long-term prospective follow-up time from infancy until the median age of 16.5 years and the use of matched population controls born in the same area as the former bronchiolitis patients. In addition, RSV and rhinovirus etiology of bronchiolitis had been evaluated in infancy, making it possible to conduct separate analyses for the outcomes after bronchiolitis induced by either RSV or rhinovirus. About 70% of the study subjects attended remained as participants even though the study lasted as long as 15.5 years.

6.5.2 Shortcomings of the study

Group 1981-1982

Especially, the main shortcomings of the present study are the small number of the subjects, study subjects with asthma and asthma-like symptoms at adulthood. The confidence intervals for both current doctor-diagnosed and self-reported asthma were rather large, and thus the results need to be interpreted with caution. In particular, this concerns the results of the subgroup analyses. It was not possible to conduct certain subgroup analyses, for example, to examine the severity or etiology of bronchiolitis.

The data were collected only by postal questionnaire. In addition, the in-house questionnaire was not validated, though largely used in many other phases of the study for both cohorts. The data obtained from interview and clinical studies are more reliable, but especially in clinical studies, the numbers of drop-outs are usually greater and the number of the controls must be limited.

When assessing the outcome after bronchiolitis, or after other infections in infancy, the results are highly dependent on the numbers of the controls and on how they have been selected. An important question is whether, when studying the outcome after early-life infection one should use, healthy controls, healthy population-based controls, non-selected population-based controls, controls with the same clinical presentation (but different etiologies), controls with the same etiology (but different presentations), or available population data from epidemiological surveys. The present study used two different controls, highly selected controls from nonatopic families with no infantile bronchiolitis prospectively followed-up from birth, with a 46 % attendance ratio, and nonselected, age- and gender-matched controls from the same area with no prospective follow-up data available, with a 37 % response ratio. The questionnaires were sent with the intention of obtaining by a 1:4 patient–control ratio, and in analyses, appropriate controls were included for women at 1:2 and for men at 1:1.65 patient–control ratio. Though the number of the

controls followed prospectively from birth was clearly under-powered in many of the analyses, the analyses gave surprisingly similar results with both control groups.

Unexpectedly, asthma by all definitions was even more common in normal weight individuals than in overweight subjects. Thus, the low statistical power of the study is not the main reason for the negative results concerning the association between asthma prevalence and overweight.

Group 1992-1993

The small number of the cases is also the main shortcoming of this part of the study, leading to the risk of under-powered analyses. In addition, the participation of the controls was so uneven, prohibiting conducting more powerful case-control analyses. Thus, the finding that non-RSV and rhinovirus bronchiolitis in infancy associated significantly with self-reported asthma but not with doctor-diagnosed asthma, may be due to the fact that non-RSV and rhinovirus bronchiolitis predispose only to mild asthma, or perhaps it is simply due the under-powering of the study, i.e. there was an insufficient number of doctor-diagnosed asthma cases. The present study was a questionnaire study which carries a risk of under-estimating the number of doctor-diagnosed diseases and over-estimating the number of symptom-based diseases. The present study was an in-house questionnaire study which was not validated, though largely used in many other phases of the study for both cohorts.

The negative results of the present study i.e. the lack of any association between asthma and obesity must be interpreted with caution. Due to the small number of bronchiolitis cases and the rarity of asthma in controls, the study may have been under-powered to detect some true albeit minor differences between overweight and normal weight adolescents. The high dropout rates, 37.5 % in cases and 61 % in controls of those invited to take part in the present study, may bias the results. On the other hand, the rate of doctor-diagnosed asthma in controls (5.3 %) was virtually identical to the rate of self-reported doctor-diagnosed asthma (3 – 5 %) in the population (Huurre et al. 2004). There may be a risk of understating the body weight in questionnaire studies, but in a validation study, self-reported weight and height correlated well with measured weight and height (Hu et al. 2004). One reason for the negative results of the present study may be the highly selected study group. In these subjects, being overweight or obese may be a less important risk factor than other factors, for example, heredity, viral disease or smoke exposure in early childhood.

7 Conclusions

The aims of the present study were to evaluate the outcome in adolescence and adulthood in subjects who had been hospitalized for bronchiolitis in early childhood, and to compare that with selected controls and non-selected population controls, in an attempt to identify potential early-life risk factors for adulthood asthma and to assess the role of overweight and obesity on the prevalence of asthma.

The main conclusions that can be drawn from this present study are:

1. After hospitalization for wheezing at age less than two years, depending on the definition, 30-64 % of the subjects were suffering from asthma in adolescence and 20–41 % in adulthood. The risk was 4- to 6-fold greater than that of similar aged selected controls and non-selected population controls with not hospitalized for lower respiratory tract infection in their early lives. In the former bronchiolitis groups, there were also more wheezing symptoms. Thus, the increased asthma risk in early-life wheezers appeared to continue until at least 27 years of age.

2. In adolescence, the asthma risk seemed to be increased both if the individual had suffered bronchiolitis due to either RSV or rhinovirus in infancy. Non-RSV and rhinovirus bronchiolitis had a greater impact on the risk of self-reported asthma but not of doctor-diagnosed asthma than RSV bronchiolitis. RSV hospitalization in infancy seemed to increase, independently from several confounding factors like allergy, smoking and overweight, with the asthma risk being more than 10-fold in adulthood, but it was not a risk factor for allergic rhinitis or conjunctivitis.

3. It seems that there is no association with overweight and obesity versus asthma or allergy in adolescence and in adulthood if an individual had had to be hospitalized for bronchiolitis in infancy.

4. Atopic dermatitis in infancy was the only independently significant early life predictor of doctor-diagnosed asthma in adolescence but not any longer in adulthood after hospitalization for bronchiolitis in infancy. Instead, other early-life risk factors, like maternal smoking in pregnancy, passive smoking during infancy, blood eosinophilia in infancy, or positive allergen-specific IgE at less than 24 months of age, exerted no influence on asthma risk in adolescence and adulthood.

The present study has shown that hospitalization for bronchiolitis in infancy is a significant risk factor for asthma in adolescence and adulthood.

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APPENDICES

KYSELYKAAVAKE

ORIGINAL PUBLICATIONS (I-V)

BRONKIOLIITIN ENNUSTE JA GENETIIKKA (BEG)

KYS, Lastenklinikka

KYSELYKAAVAKE

Nimi: _____ Tutk.nro _____

Sosiaaliturvatunnus: _____-_____

1. HENGENAHDISTUSOIREET

Ympyröi sopiva vaihtoehto.	**Ei**	**Kyllä**
Onko Sinulla ollut hengitysvaikeuksia etenkin uloshengitykseen liittyen viimeisen 12 kuukauden aikana?	0	1

*Jos vastasit **Ei**, siirry kohtaan 2. Jos vastasit **Kyllä**, vastaa alla oleviin kysymyksiin.*

Ympyröi sopiva vaihtoehto.	**Ei**	**Kyllä**
Onko hengitysvaikeuksia esiintynyt enemmän kuin kerran edeltävän 12 kk aikana?	0	1
Onko hengitysvaikeuksia esiintynyt vilustumisen yhteydessä?	0	1
Onko hengitysvaikeuksia esiintynyt liittyen siitepöly-ja/tai eläinaltistukseen?	0	1
Onko hengitysvaikeuksia esiintynyt rasituksessa?	0	1
Onko hengitysvaikeuksia esiintynyt jossain muussa tilanteessa? **Kyllä-vastauksessa tilanteen kuvaus:**	0	1

2. YSKÄOIREET

Ympyröi sopiva vaihtoehto.	**Ei**	**Kyllä**
Onko Sinulla ollut pitkäaikaista (vähintään 4 viikkoa kestänyttä) yskää muulloin kuin hengitystieinfektion eli flunssan aikana viimeisen 12 kuukauden aikana?	0	1
Onko Sinulla esiintynyt toistuvaa yöyskää muulloin kuin hengitystieinfektion eli flunssan aikana viimeisen 12 kk aikana?	0	1

3. ASTMADIAGNOOSI

Ympyröi sopiva vaihtoehto.	**Ei**	**Kyllä**
Onko lääkäri todennut Sinulla astmaa viimeisen 12 kuukauden aikana? Kyllä-vastauksessa terveyskeskuksen/sairaalan/palvelun tuottajan nimi ja sijainti:	0	1
Onko lääkäri todennut Sinulla astmaa viimeisen 24 kuukauden aikana? Kyllä-vastauksessa terveyskeskuksen/sairaalan/palvelun tuottajan nimi ja sijainti:	0	1
Onko lääkäri todennut Sinulla koskaan astmaa? Kyllä-vastauksessa terveyskeskuksen/sairaalan/palvelun tuottajan nimi ja sijainti:	0	1

4. ASTMALÄÄKITYS

Ympyröikää sopiva vaihtoehto.	**Ei**	**Kyllä**
Onko Sinulla ollut säännöllisessä käytössä jokin astman hoitava lääke (esim. Pulmicort, Flixotide, Beclomet , Seretide, Symbicort, Singulair) **viimeisen 12 kuukauden aikana?**	0	1
Onko Sinulla koskaan ollut säännöllisessä käytössä astman hoitavaa lääkettä?	0	1

Ympyröi sopiva vaihtoehto.	**Ei**	**Kyllä**
Onko Sinulla ollut käytössä jokin keuhkoputkia avaava lääke (esim. Bricanyl, Serevent, Ventoline, Airomir) **viimeisen 12 kuukauden aikana? Kyllä-vastauksessa lääkkeen tarve, ympyröi sopivin vaihtoehto:** **päivittäin viikoittain kuukausittain harvemmin**	0	1
Onko Sinulla koskaan ollut käytössä keuhkoputkia avaavaa lääkettä?	0	1

5. NUHAOIREET

Ympyröi sopiva vaihtoehto.	**Ei**	**Kyllä**
Onko Sinulla ollut aivastelua, vetistä nuhaa tai nenän tukkoisuutta muulloin kuin vilustumisen yhteydessä viimeisen 12 kuukauden aikana?	0	1

*Jos vastasit **Ei**, siirry kohtaan 6. Jos vastasit **Kyllä**, vastaa alla oleviin kysymyksiin.*

Ympyröi sopiva vaihtoehto.	**Ei**	**Kyllä**
Onko aivastelua, vetistä nuhaa tai nenän tukkoisuutta esiintynyt vuodenaikoihin liittyen? Kyllä-vastauksessa ympyröi oikeat vaihtoehdot: tammi-. helmi-, maalis-, huhti-, touko-, kesä, heinä-, elo-, syys-, loka-, marras-, joulukuussa	0	1
Onko aivastelua, vetistä nuhaa tai nenän tukkoisuutta esiintynyt eläinkontakteihin liittyen?	0	1
Onko aivastelua, vetistä nuhaa tai nenän tukkoisuutta esiintynyt jossain muussa tilanteessa? Kyllä-vastauksessa tilanteen kuvaus:	0	1

6. SILMÄOIREET

Ympyröi sopiva vaihtoehto.	**Ei**	**Kyllä**
Onko Sinulla ollut silmien kutinaa, punoitusta tai vetistystä muulloin kuin vilustumisen yhteydessä viimeisen 12 kuukauden aikana?	0	1

*Jos vastasit edellisen sivun kysymykseen **Ei**, siirry kohtaan 7. Jos vastasit **Kyllä**, vastaa alla oleviin kysymyksiin.*

Ympyröi sopiva vaihtoehto.	**Ei**	**Kyllä**
Onko silmien kutinaa, vetistystä tai punoitusta esiintynyt vuodenaikoihin liittyen? Kyllä-vastauksessa ympyröi oikeat vaihtoehdot: tammi-. helmi-, maalis-, huhti-, touko-, kesä, heinä-, elo-, syys-, loka-, marras-, joulukuussa	0	1
Onko silmien kutinaa, vetistystä tai punoitusta esiintynyt eläinkontakteihin liittyen?	0	1
Onko silmien kutinaa, vetistystä tai punoitusta esiintynyt jossain muussa tilanteessa? Kyllä-vastauksessa tilanteen kuvaus:	0	1

7. IHO-OIREET

Ympyröikää sopiva vaihtoehto.	**Ei**	**Kyllä**
Onko Sinulla ollut kutisevaa ihottumaa viimeisen 12 kuukauden aikana?	0	1

*Jos vastasit **Ei**, siirry kohtaan 8. Jos vastasit **Kyllä**, vastaa alla olevaan kysymykseen.*

Ympyröi sopiva vaihtoehto.	**Ei**	**Kyllä**
Onko kutisevaa ihottumaa esiintynyt nilkkojen etupuolella tai pakaroiden alapuolella, kaulan, korvien tai silmien alueella tai kyynär- tai polvitaipeissa?	0	1

8. SUKULAISTEN ASTMA

Ympyröi sopiva vaihtoehto.	**Ei**	**Kyllä**
Onko lääkäri koskaan todennut äidilläsi astmaa?	0	1
Onko lääkäri koskaan todennut isälläsi astmaa?	0	1
Onko lääkäri koskaan todennut sisaruksillasi astmaa?	0	1
Onko lääkäri koskaan todennut lapsillasi astmaa?	0	1

9. TUPAKOINTI

Ympyröi sopiva vaihtoehto.	**Ei**	**Kyllä**
Tupakoitko tällä hetkellä? **Kyllä-vastauksessa savukkeiden lukumäärä/vrk:**	0	1

10. PAINOINDEKSI

Paino	
Pituus	

Marja Ruotsalainen

Do Wheezing Infants Grow Up to be Asthmatic Adults?

Asthma Prevalence in Relation to Early-Life and Current Risk Factors

Bronchiolitis is the most frequent infectious disease in infancy. It is known that if bronchiolitis require hospitalization, it is a major risk factor for subsequent wheezing and asthma. This study investigated the prevalence of asthma and allergy and the role of overweight on the prevalence of asthma after hospitalization for bronchiolitis in infancy. The increased asthma risk in children with early-life wheezing symptoms continues until at least 27 years of age.

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