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EIJA PIIPPO-SAVOLAINEN

Wheezy Babies - Wheezy Adults?

Asthma, Bronchial Reactivity and Lung Function in Adulthood After Hospitalisation for Bronchiolitis in Early Life

Doctoral dissertation

To be presented by permission of the Faculty of Medicine of the University of Kuopio for public examination in Auditorium, Kuopio University Hospital, on Saturday 9th December 2006, at 12 noon

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ABSTRACT

BACKGROUND: Bronchiolitis, defined as wheezing during respiratory infection in early life, may be the first sign of chronic asthma and may lead to persistent lung function abnormalities. Thus far, available data on long-term outcome until adulthood have almost exclusively been retrospective.

AIMS: The aims of this thesis were to determine the outcome in adulthood for asthma and lung function and the contributing early life factors in subjects with bronchiolitis in infancy.

METHODS: A total of 130 children hospitalised for bronchiolitis or pneumonia at <24 months of age in 1981-82 were recruited for the present study. Baseline clinical and laboratory data were collected on admission and 4-6 weeks later during convalescence. Wheezing history and data on potential predictors for later asthma were prospectively registered until the age of 23 to 35 months. In 2000, at the median age of 19 years, 54 subjects from the bronchiolitis group, 34 from the pneumonia group, and 45 from the control group attended the 18 to 20-year follow-up including clinical investigation, flow-volume spirometry (FVS), methacholine inhalation challenge (MIC), skin prick tests (SPT) to common inhalant allergens and 2-week home peak expiratory monitoring (PEF).

RESULTS: Asthma (by strict and less strict definitions) was present in 30-41% (OR 3.4- 5.5), 15-21% (OR 1.4-2.1) and 11% in the bronchiolitis, pneumonia and control groups, respectively. Undiagnosed asthma comprised of 60% of all asthma cases. The figures for subnormal FVS were 19(36%), 9(27%) and 5(11%), respectively (p=0.02). Bronchial hyper-reactivity (BRH) was present in 52(41%) subjects and positive SPT reactions in 71(55%) subjects.

Among bronchiolitis patients, parental asthma, atopy, recurrence of wheezing and lack of eosinopenic response to infection were early predictors for adult asthma. Early sensitisation to pets and repeated wheezing at <12 months of age predicted BHR in adulthood. Maternal smoking, parental asthma and atopy, onset and recurrence of wheezing at <12 months of age, blood eosinophilia and lack of eosinopenic response to infection were associated with subnormal FVS.

The fifty subjects who hade been hospitalised for bronchiolitis not caused by RSV were characterised by parental history of asthma, wheezing before admission, elevated serum IgE and sensitisation to inhalant allergens. Infection-induced decrease in blood eosinophils was associated with RSV bronchiolitis only. Adult asthma by strict criteria was present in 41% (non-RSV) vs. 18% (RSV;p=0.049), by less strict criteria in 50% vs. 27% (p=0.069), subnormal lung function in 32% vs. 41% (p=0.537) and BHR in 52% vs. 48% (p=1.00).

CONCLUSIONS: This study showed that increased risk for asthma and lung function abnormalities persists into adulthood after hospitalisation for bronchiolitis in early life. Repeated wheezing or wheezing during non-RSV infection, early atopy, lack of eosinopenic response to acute infection and asthma in parents are significant risk factors. Maternal smoking in early childhood caused damage in lung function that persists into adulthood. The considerable number of undiagnosed asthma cases calls for more intensive screening of asthma among young adults.

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Medical Subject Headings: Adult; Asthma/epidemiology; Asthma/aetiology; Bronchiolitis/aetiology; Disease Susceptibility/epidemiology; Follow-up Studies; Hospitalisation; Infant; Respiration; Respiratory Hypersensitivity/epidemiology; Risk Factors

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TIIVISTELMÄ:

TAUSTAA: Lapsuusiän astma alkaa usein jo imeväisiässä virusinfektioon liittyvänä hengitysvaikeutena - bronkioliittina eli ilmatiehyttulehduksena - johon voi liittyä myös myöhempi keuhkojen toiminnan huononeminen. Toistaiseksi maailmalla on julkaistu vain yksi muu imeväisiästä aikuisuuteen jatkunut seuranta varhaislapsuudessa sairastetun bronkioliitin jälkeen.

TAVOITTEET:

Tutkimuksemme tavoite on selvittää varhaislapsuudessaan sairaalahoitoa vaatineen bronkioliitiin sairastaneiden lasten pitkäaikaisennuste aikuisuuteen saakka ja samalla kartoittaa aikuisastman varhaisia riskitekijöitä.

METODIT: Tutkimukseen otettiin alun perin mukaan 130 alle 24 kuukauden ikäisenä bronkioliitin tai keuhkokuumeen vuoksi sairaalahoitoon vuosina 1981-82 joutunutta lasta. Sairaalahoitojakson aikana ja 4-6 viikkoa myöhemmin seurantakäynnillä kartoitettiin taustatiedot ja otettiin laboratoriotutkimuksia. Tämän jälkeen hengenahdistusoireet ja tiedot astman mahdollisista varhaisista riskitekijöistä kirjattiin prospektiivisesti 24-36 kuukauden ikään saakka. Vuonna 2000, 54 bronkioliitin ja 34 pneumonian sairastanutta keskimäärin 19-vuotiasta nuorta aikuista ja heidän 45 tervettä verrokkia osallistuivat 18-20-vuotisseurantatutkimukseen. Tutkimus koostui kliinisesta lääkärintutkimuksesta, virtaus-tilavuus-spirometriasta, metakoliini-inhalaatioaltistuksesta, ihopistokokeista ja koti PEF seurannasta.

TULOKSET: Kaikkiaan 30-41%:lla (OR 3.4-5.5) bronkioliitti- ja 15-21%:lla (OR 1.4-2.1) keuhkokuumepotilaista sekä 11% :lla verrokeista oli astma tai astman kaltainen tila. Yli 60% astmadiagnooseista tehtiin tutkimuskäynnillä. Keuhkojen toimintakokeissa todettiin poikkeavuuksia 36%:lla bronkioliitti- ja 27%:lla pneumoniapotilaista sekä 11%:lla verrokeista (p=0.02). Keuhkoputkien poikkeava supistumistaipumus voitiin osoittaa 52:lla (41%) tutkittavista ja SPT reaktioita 71:llä (55%) nuorella.

Bronkioliittipotilailla vanhemman astma, atopia, toistuva hengitysvaikeus varhaislapsuudessa ja eosinofiilitason pysyminen korkeana infektion aikana ennustivat aikuisiän astmaa. Sen sijaan varhainen allerginen herkistyminen kissalle tai koiralle ja toistuva hengitysvaikeus <12 kk:n iässä liittyivät lisääntyneen keuhkoputkien supistumisherkkyyteen aikuisena. Äidin tupakointi, vanhempien astma tai atopia ja eosinofiilitason infektioaikaisen laskun puuttuminen ennustivat huonontunutta keuhkojen toimintaa aikuisena.

Bronkioliitin aiheuttaja oli respiratory syncytial virus (RSV) 50:llä lapsella ja joku muu virus lopuilla 33:lla.Viimeksi mainituilla todettiin RSV-potilaita useammin vanhemman astma, sairaalahoitoa edeltäneitä hengitysvaikeuskohtauksia, varhain kohonnut S-IgE sekä varhainen herkistyminen hengitysilman allergeeneille. Infektion aiheuttama eosinofiilitason lasku nähtiin vain RSV-bronkioliittilapsilla. Lääkärin toteama astma oli 18%:lla RSV:n ja 41%:lla muiden virusten aiheuttamista bronkioliittitapauksista (p=0.049), kliininen astma 27%:lla vs. 50%:lla (p=0.069), poikkeavuuksia keuhkojen toiminnassa 41%:lla vs.32%:lla (0.537) ja lisääntynyt keuhkoputkien supistumisherkkyys 48%:lla vs. 52%:lla (P=1.00).

JOHTOPÄÄTÖKSET: Tutkimuksemme osoitti astmariskin säilyvän kohonneena aikuisikään saakka varhaislapsuudessa sairaalahoitoa vaatineen ilmatiehyttulehduksen jälkeen. Bronkioliittilasten toistuva tai muun viruksen kuin RSV:n aiheuttamaan infektioon liittyvä hengitysvaikeus, varhainen atopia, infektion aikaisen eosinofiilitason laskun puuttuminen ja vanhempien astma ovat merkittäviä aikuisiän astman riskitekijöitä. Äidin tupakointi varhaislapsuudessa näyttää aiheuttavan aikuisuuteen saakka pysyviä keuhkovaurioita. Diagnosoimattomien ja hoitamattomien astmatapausten huomattava määrä vaatinee jatkossa entistäkin tehokkaampaa astmaoireiden seulontaa nuoruusiällä.

To my family

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My dear children Mira and Mika, for being my children and filling my life with love and joy.

Kuopio, December 2006

Eija Piippo-Savolainen

ABBREVIATIONS

aOR	Adjusted Odds ratio
BHR	Bronchial hyper-reactivity
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
FEV%	FEV1/ FVC
FVS	Flow-volume spirometry
IgE	Immunoglobulin E
LRTI	Lower respiratory tract infection
MEF50	Mid-expiratory flow at 50% of FVC
MEF25	Mid-expiratory flow at 25% of FVC
MIC	Methacholine inhalation challenge
OR	Odds ratio
PD20	Provocative dose of methacholine to produce 20% decrease in FEV1
PEF	Peak expiratory flow
RSV	Respiratory syncytial virus
SPT	Skin prick test

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, which are referred to in the text by their Roman numbers.

I Piippo-Savolainen E, Remes S, Kannisto S, Korhonen K, Korppi M. Asthma and lung function 20 years after wheezing in infancy. Results from a prospective follow-up. Arch Pediatr Adolesc Med 2004; 158: 1070-1076.

II Korppi M, Piippo-Savolainen E, Korhonen K, Remes S. Respiratory morbidity 20 years after RSV infection in infancy. Pediatr Pulmonol 2004; 38: 155-60.

III Piippo-Savolainen E, Korppi M, Korhonen K, Remes S. Adult asthma after non-RSV bronchiolitis in infancy: subgroup analysis of the 20-year prospective follow-up. Pediatr Internat; in press.

IV Piippo-Savolainen E, Remes S, Kannisto S, Korhonen K, Korppi M. Early predictors for adult asthma and lung function abnormalities in infants hospitalized for bronchiolitis. A prospective 18-20 years follow-up. Allergy Asthma Proc; 2006;27:341-349.

V Piippo-Savolainen E, Remes S, Korppi M. Does eosinophilia in wheezing infants predict later asthma? A prospective 18-20 years follow-up. Allergy Asthma Proc; in press.

VI Piippo-Savolainen E, Remes S, Korppi M. Does early exposure or sensitisation to inhaled allergens predict asthma in wheezing infancy. Allergy Asthma Proc; accepted for publication

In addition, the thesis contains supplementary unpublished data.

CONTENTS

1. INTRODUCTION

Bronchiolitis, defined as wheezing during viral respiratory infection in early life, is a common condition (Martinez et al. 1985, Rhodes et al. 2001, Sandin et al.2004, Simpson et al. 2005) leading to hospitalisation in 1-3% of previously healthy infants (Shay et al. 1999, Boyce et al. 2000, Holman et al. 2004, Henderson et al. 2005). Among the various respiratory viruses causing lower respiratory infections, respiratory syncytial virus (RSV) is the single most important virus associated with early childhood wheezing (Rakes et al. 1999, Papadopoulos et al.2002, Jartti et al.2004). In addition, recent investigations have shown that along with RSV, rhinoviruses, enteroviruses and human metapneumoviruses comprise a considerable proportion of bronchiolitis cases (Papadopoulos et al. 2002, Kotaniemi-Syrjänen et al.2003, Jartti et al. 2004, Werno et al. 2004, Xepapadaki et al. 2004, Pitrez et al. 2005, Jacques et al.2006, Garcia-Garcia et al. 2006).

Wheezing during respiratory infection in early life is often the first sign of asthma, continuing with diminishing tendency through school years (Wennergren et al. 1992, Korppi et al. 1993, Wennnergren et al. 1997, Reijonen et al. 2000, Sigurs et al. 2000, Kotaniemi-Syrjänen et al.2002, Sigurs et al. 2002, Taussig et al. 2003, Martinez and Godfrey et al. 2003, Hyvärinen et al.2005b). However, after puberty the risk seems to increase again, and in young adulthood asthma is present in 25-40% of subjects hospitalised for bronchiolitis in early life (Larouche et al. 2000, Gomez et al. 2004, Goksör et al. 2006). In the present cohort, subsequent wheezing after hospitalisation for bronchiolitis was present in 25% at preschool age (Kuikka et al. 1994) and asthma in 15% at the age of 8.5 to 10 years (Korppi et al. 1994) and in 14% at the age of 13 to 16 years (Hyvärinen et al. 2005a).

The persistence of asthma and recurrent wheezing is associated with a family history of asthma (Sears et al. 1996, Sigurs et al. 2005) or atopy (Sears et al. 1996, Goksör et al. 2006), and the presence of atopic dermatitis (Hyvärinen et al. 2005b), elevated serum IgE (Sherrill et al. 1999, Rhodes et al. 2002, Hyvärinen et al. 2005b), or allergic sensitisation in early life. In particular, children who wheeze apart from colds (Castro-Rodriquez et al. 2000) or during respiratory infection not caused by RSV, *e.g.* during rhinovirus infection (Stein et al. 1999a, Hyvärinen et al. 2005b), seem to carry a substantial risk for later asthma and wheezing at least until teen age. In addition, blood

eosinophilia (Martinez et al. 1998, Ehlenfield et al. 2000, Kotaniemi-Syrjänen et al. 2002) and lack of an eosinopenic response during acute infection (Martinez 1998) are related to an increased risk for asthma at least until school age. In contrast, persistently low blood eosinophils (Karakoc et al. 2002) and living on a farm environment (Kilpeläinen et al. 2002) have been associated with a beneficial outcome. Early day-care attendance (Ball et al. 2000, Svanes et al. 2002), number of siblings (Ball et al. 2000, Bodner et al. 2000, Svanes et al. 2002) and early exposure to pets (Remes et al. 2001, Sigurs et al. 2005, Goksör et al. 2006) or pollens (Nilsson et al. 1997, Saitoh et al. 2001, Kihlström et al. 2002) have given controversial results.

Maternal smoking during childhood has been clearly associated with persistently increased risk for wheezing, asthma and abnormalities of lung function in their children in retrospective population-based studies (Strachan et al. 1996a, Strachan et al. 1996b, Gilliland et al. 2001, Upton et al. 2004, Svanes et al. 2004, Jaakkola et al. 2004). If the exposure happens already in utero, deficits in lung function and an increased tendency for wheezing are present already at birth (Young et al. 2000, Lodrup Carlssen et al. 2002) and persist until adulthood (Svanes et al. 2004). Paternal smoking is associated with increased risk for chronic obstructive pulmonary disease in their children as adults, but less evidently with wheezing and impairment in lung function (Svanes et al. 2004). In a prospective post-bronchiolitis study from Sweden, parental smoking in infancy resulted in increased risk for adult asthma in their off-spring, but the effects on lung function in adulthood was not studied (Goksör et al. 2006).

Thus far, there are only two previous studies, both retrospective, on lung function in adulthood after bronchiolitis. Either no association with adulthood lung function (Gomez et al. 2004), or a decrease in FEV1 and FEV1/ FVC values (Larouche et al. 2000) was found. Population-based studies have demonstrated decreased lung function among bronchiolitis patients already in infancy, prior to any wheezing episodes (Young et al. 1995, Turner et al. 2002). This lung function deficit seems to persist at least until 16 years of age (Morgan et al. 2005). These results suggest that wheezing starting in infancy might actually be due to small airway size, causing obstruction with oedema and mucus during an acute LRTI (Martinez et al. 1988, Turner et al. 2002, Martinez and Godfrey 2003, Turner et al. 2004). In addition, viral respiratory infections may also cause structural damage to the airways and induce

alterations in neural regulation of airway tone, leading to subsequent lung function impairment and bronchial reactivity (Gold et al. 1969, Becroft et al. 1971, Wohl et al. 1978, Simoes et al. 1999, Fregonese et al. 2002, Martinez and Godfrey 2003).

In conclusion, bronchiolitis patients form a large and heterogeneous group of children with different characteristics and different long-term outcomes. Additional means are therefore required to distinguish children who are particularly susceptible for subsequent asthma and lung function impairment. In addition to the present study series, there is only one other cohort prospectively followed-up after hospitalisation for bronchiolitis from infancy until adulthood (Wennergren et al. 1992, Wennergren et al. 1997, Goksör et al. 2006).

2. REVIEW OF THE LITERATURE

2.1 What is bronchiolitis?

2.1.1. Definition.

Bronchiolitis is an acute peripheral airway obstruction during viral respiratory infection in early life, usually with no evidence of similar episodes in the past (Kercsmar et al. 2002, Fischer and Boyce 2005). Oedema and mucous trap the small airways and cause the characteristic features of the disease (Fischer and Boyce 2005); breathlessness, prolonged expiration, chest indrawings, inspiratory crackles, audible wheezing and increased respiratory rate, meaning usually hypoxemia (Price et al. 1990, Simoes et al. 1999, Wennergren et al. 2001, Kercsmar et al. 2002, Fischer and Boyce 2005). The severity of infection varies from mild respiratory symptoms treated at home to severe respiratory distress demanding hospitalisation and even artificial ventilation.

However, there is no universally accepted clinical definition for bronchiolitis. In some studies, bronchiolitis has been restricted to respiratory syncytial virus cases (Sigurs et al. 2002, Schauer et al. 2002), or to cases occurring during RSV epidemics only (Shay et al. 1999). Likewise, the age of bronchiolitis patients has been limited to <12 months (Noble et al. 1997, Schauer et al. 2002, Sigurs et al. 2002, Bradley et al. 2005, Sznajder et al. 2005,) or even to <6 months (Welliver et al. 1986), and wheezing episodes during the second years of life have been called as wheezy bronchitis in several studies (Wennergren et al. 1997, Thomsen et al. 2006). However, in clinical follow-up studies, bronchiolitis has usually been defined as respiratory infection associated wheezing in a child <24 months of age, treated either as inpatients or outpatients (Mc Connochie et al. 1985, Wennergren et al. 1992, Reijonen et al. 2000, Larouche et al. 2000, Turner et al. 2002, Gomez et al. 2004). Recurrent wheezing episodes, particularly after 2 years of age, should be considered to be asthma (NAEPP 2002).

2.1.2. Incidence and predictive factors

Approximately one third of all children suffer from wheezing during respiratory infection before their third birthday (Martinez et al. 1995, Rhodes et al. 2001, Sandin et

al. 2004, Simpson et al. 2005), and in 1 to 3% symptoms are severe enough to cause hospitalisation (Shay et al. 1999, Boyce et al. 2000, Kneyber et al. 2000, Holman et al. 2004, Henderson et al. 2005). The causative agent may be any respiratory virus, most often RSV (Wright et al. 1989, Wennergren et al. 1992, Rakes et al. 1999, Papadopoulos et al. 2002, Jartti et al. 2004), and children with pre-existing reduced lung function of small airways are in particular risk for wheezing during respiratory infection (Martinez et al. 1988, Young et al. 2000, Turner et al. 2002). Likewise, male gender (Wennergren et al. 1992), family history of atopy (Young et al. 1995, Camara et al. 2004) passive smoking (Mc Connochie et al. 1989, Young et al. 1995, Stein et al. 1999b, Wright et al. 2001, Murray et al. 2004), short duration of breastfeeding (Wright et al. 2002), frequent contacts with other children (Cardoso et al. 2004, Celedon et al. 1999, Juntti et al. 2003) and chronic underlying illnesses (Boyce et al. 2000) seem to be factors predisposing to bronchiolitis (Taussig et al. 2003, Fischer and Boyce 2005).

2.2. Respiratory viruses

2.2.1. Respiratory syncytial virus (RSV)

RSV is the single most common virus causing lower respiratory tract infection (LRTI) in early childhood. Depending on the age, definition of bronchiolitis and study setting, RSV has comprised 25 to 94% of cases of bronchiolitis requiring hospital treatment (Rakes et al. 1999, Papadopoulos et al. 2002, Jartti et al. 2004, Jacques et al. 2006, Pitrez et al. 2006, Kotaniemi-Syrjänen et al. 2003). Pneumonia may occur together with bronchiolitis, representing a different phase of the infection or a separate clinical entity (Price et al. 2003, Martinez and Godfrey 2003). RSV infection may also present as an upper respiratory infection alone (Heikkinen et al. 1999) or as a laryngeal infection (Castro-Rodriquez et al. 2001). In addition, RSV may cause spells of apnoea as the only symptoms in infants below 2 months of age (Kneyber et al. 1998).

The primary infection usually occurs at the age of 6 weeks to 6 months, and re-infections may occur at any age (Simoes et al. 1999, Wennergren et al. 2001). The infections have seasonal pattern with annual winter and spring epidemics in temperate climate and in rainy season in tropics (Simoes et al. 1999, Wennergren et al. 2001, Jartti et al. 2004). In Finland, RSV epidemics typically occur in two-year cycles, with a

minor epidemic in spring preceding the major epidemic in autumn (Waris et al. 1991, Jartti et al. 2004).

2.2.2. Other viruses

Along with RSV, rhinoviruses and enteroviruses, belonging to picornaviruses (Papadopoulos et al. 2002, Kotaniemi-Syrjänen et al. 2003, Jartti et al. 2004, Jartti et al. 2005, Pitrez et al. 2005, Jacques et al. 2006), and human metapneumovirus (Jartti et al. 2002, Xepapadaki et al. 2004, Jartti et al. 2004, Werno et al. 2004, Jartti et al. 2005, Garcia-Garcia et al. 2006) are the most common causative agents for bronchiolitis among the large variety of respiratory viruses and bacteria comprising lower respiratory infections in early childhood (Jartti et al. 2005). In addition, wheezing may be associated with thus far unknown pathogens, such as human bocavirus, which caused 5.6% of respiratory infections with and without wheezing in 6 to 24 month old Australian children (Sloots et al. 2006).

Bronchiolitis caused by viruses other than RSV is more heterogeneous than RSV bronchiolitis. The causative agents, e.g. rhinoviruses, are less invasive than RSV (Papadopoulos et al. 2002, Kotaniemi-Syrjänen et al. 2003, Xepapadaki et al. 2004, Jartti et al. 2004), and the patients are prone to developing asthma in later childhood (Kotaniemi-Syrjänen et al. 2003).

2.2.2.1. Rhinovirus

Human rhinoviruses cause the majority of common colds at all ages (Mäkelä et al. 1998), comprise 20-30% of bronchiolitis cases needing hospitalisation (Andreoletti et al. 2000, Papadopoulos et al. 2002, Kotaniemi-Syrjänen et al. 2003, Jartti et al. 2005) and commonly induce asthma exacerbations during upper respiratory infections in older children (Rakes et al. 1999).

Rhinovirus bronchiolitis cases occur in early fall and late spring (Jartti et al. 2004), most often outside RSV seasons (Heymann et al. 2004). In comparison to RSV bronchiolitis patients, rhinovirus bronchiolitis patients are older, over 6 months of age (Rakes et al. 1999, Papadopoulos et al. 2002, Korppi et al. 2004), and present more often with blood eosinophilia (Rakes et al. 1999, Korppi et al. 2004) and atopic dermatitis in early life (Korppi et al. 2004). Infants with rhinovirus infection tend to be

hospitalised earlier in their course of disease (Papadopoulos et al. 2002), but present with less hypoxemia than RSV bronchiolitis patients on admission (Korppi et al. 2004).

2.2.2.2. Human metapneumovirus

The newly found human metapneumovirus belongs, like RSV, to the paramyxovirus group and comprises 10-16% of hospitalised bronchiolitis (Jartti et al. 2002, Xepapadaki et al. 2002, Jartti et al. 2004, Garcia-Garcia et al. 2006) cases. Infections typically follow RSV outbreaks in winter or in early spring (Wilson et al. 2004, Jartti et al. 2004, Garcia-Garcia et al. 2006, Foulonge et al. 2006, Mahalingam et al. 2006). Although present also in older children and adults, metapneumovirus infection most often occur in early childhood, at 6 to 12 months of age (Williams et al. 2004, Fischer and Boyce 2005, Garcia-Garcia et al. 2006). Like RSV, metapneumovirus may cause bronchiolitis, pneumonia, croup and spells of apnoea (Xepapadaki et al. 2004, Mahalingan et al. 2006). Respiratory symptoms last for 2 to 3 weeks (Jartti et al. 2002), but in mice, airway obstruction has been demonstrated 2 months and pulmonary inflammation 5 months after infection (Hamelin et al.2006).

2.3. Remodelling and the importance of early diagnosis of asthma

The response of airway epithelium to an acute injury, *e.g.* caused by respiratory viruses (Jartti et al. 2005, Mahalingam et al. 2006) or cytotoxic substances released from eosinophils (Zagai et al. 2004), leads to thickening of subepithelial adventitia, smooth muscle and connective tissue (Coraux et al. 2005) - an irreversible change called remodelling. As a result, the airway wall becomes rigid, and lung function may be impaired permanently (Wilson et al. 2002). However, recurrent wheezing in early childhood can develop also independently from eosinophilic inflammation and reticular basement membrane thickening (Saglani et al. 2005). Evidence from bronchial biopsies suggests that remodelling may occur early, even before any symptoms (Warner 2000).

Therefore, there is a need to find those children who are prone to remodelling and later asthma, and who would benefit from intervention in early life. The factors increasing the risk for remodelling, or the means to prevent it are not known (Warner et al. 2000, Guilbert et al. 2006), but early treatment with anti-histamines (ETAC study

group 1998) and leukotriene receptor antagonists have given promising results (Warner et al.2000).

2.4. Wheezing phenotypes

Wheezing infants and toddlers seem to form a heterogeneous group with different phenotypes and different outcomes (Stein et al. 1997). According to the Tucson and Perth cohort studies, three phenotypes of early wheezers can be distinguished (Table 1). In all, 60% of bronchiolitis patients are transient wheezers with symptoms mainly during respiratory infections and no wheeze after 3 years of age (Taussig et al. 2003).Their lung function is decreased before any wheezing illness and improves by time, although does not catch-up healthy controls at least by the age of 16 years (Taussig et al. 2003, Martinez and Godfrey 2003).

About half of those children, who have persistent wheezing episodes since the age of less than 3 to 6 years become sensitised to local inhalant allergens before school age (Martinez and Godfrey 2003). They are called atopic wheezers (Martinez et al. 1995, Sherrill et al. 1999, Taussig et al. 2003). The first wheezing episode typically takes place during the second or third year of life and is later followed by allergic sensitisation (Martinez and Godfrey 2003). Atopic wheezers typically experience more wheezing episodes and have lower levels of lung function at least until the age of 16 years (Martinez and Godfrey 2003, Taussig et al. 2003).

In contrast, persistent wheezers who do not become sensitised early usually start wheezing before one year of age (Martinez and Godfrey 2003), typically during an RSV infection (Stein et al. 1999a). They subsequently wheeze usually only during respiratory infections, with a decreasing tendency (Halonen et al. 1999). By the age of 13 years, the risk for wheezing is only slightly greater than control children (Stein et al. 1999a), but their lung function remains marginally decreased until the age of 16 years (Morgan et al. 2005).

Table 1. Three phenotypes of early wheezing according to the Tucson and Perth cohort studies.

Wheezing phenotype	Age			
	< 1 year	6 years	11-13 years	16 years
Transient early wheezers (60%)				
Wheeze	+	-	-	-
Abnormal lung function	+	+	+	+
BHR[1]/ PEF variability[2]			-	
Non-atopic persistent wheezers[3] (20%)				
Wheeze	+	+	-	-
Abnormal lung function	-	+	+	+
BHR/ PEF variability	+		-	
Atopic persistent wheezers (20%)				
Wheeze	-	+	+	+
Abnormal lung function	-	+	+	+
BHR/ PEF variability	-	+	+	

[1]Bronchial hyper-reactivity / [2]significant peak expiratory flow variability. [3]Non-atopic persistent wheezers represent children with RSV infection before 3 years of age, with clinical features quite similar to bronchiolitis (Stein 1999a). References: Stein 1997, Stein 1999a, Mochizuki 2000, Palmer 2001, Martinez and Godfrey 2003, Morgan 2005.

2.5. Long-term outcome after bronchiolitis

2.5.1. Wheezing and asthma

Children with wheezing severe enough to need hospital treatment before their second birthday form a group at a particular risk for asthma and other respiratory illnesses in their later life. There are only four prospective follow-up studies after hospitalisation for bronchiolitis, two from Finland and two from Sweden, which have continued until more than 10 years of age (Table 2). Over half of the former bronchiolitis patients suffered from recurrent wheezing episodes at 3 years of age, and 25 to 54% were symptomatic at 4 to 6 years of age (Wennergren et al. 1992, Korppi et

al. 1994, Reijonen et al. 2000). Although the tendency for wheezing decreases over time, still 15 to 30% have asthma during the early school years (Korppi et al. 1994, Wennergren et al. 1997, Sigurs et al. 2002, Kotaniemi-Syrjänen et al. 2002, Kotaniemi-Syrjänen et al. 2003), which is more than the 4 to 10% prevalence of asthma among school children observed in population-based studies in Scandinavian countries (Remes et al. 1996, Norrman et al. 1998).

Some studies in selected patients have suggested that children with respiratory symptoms, at least those with mild symptoms, outgrow their disease by the second decade of life (Balfour-Lynn et al. 1985, Phelan et al. 2002, Rhodes et al. 2002). However, further investigations have revealed that many asymptomatic school children may become symptomatic again in adulthood (Lewis et al. 1995, Sears et al. 2003). Relapsing symptoms seem to be particularly typical for children with severe bronchiolitis needing hospitalisation. About 25 to 40% of these children have asthma in adolescence and 38 to 43% in young adulthood (Table 3). The outcome is better after mild bronchiolitis not requiring hospital treatment. In these children, asthma is present before puberty in 16 to 19%, and in adulthood asthma in 12% (Table 4). However, the figures are higher than those reported for the population overall; in Northern Europe, the prevalence of asthma is about 10% in teen-agers (Norrman et al. 1998) and 3- 8% in adults (Upton et al. 2000, Huurre et al. 2004).

Table 2. Subsequent asthma until school age after hospitalisation for bronchiolitis in early life. Results from four cohorts prospectively followed-up until teen or adult age.

Age (years)	Korppi[1]* 1981-82 N=83	Wennergren[2] 1984-85 N=101	Sigurs[3] 1989-90 N=47	Reijonen[4] 1992-93 N=100
3	58%	-	60%	-
4-6	25%	47%	-	54%
7-10	15%	30%	23%	40%

* Present cohort. References: [1]Korppi 1993, Kuikka 1994, Korppi 1994; [2]Wennergren 1992, Wennergren 1997; [3]Sigurs1995, Sigurs 2000, Sigurs 2002; [4]Reijonen 2000, Kotaniemi-Syrjänen 2002, Kotaniemi-Syrjänen 2003.

Table 3. Bronchiolitis needing hospitalisation in early life: outcome at teenage and adulthood.

Reference	Design	Patients N	Controls N	Age on admission (months)	Age on re-evaluation (years), median (range)	Outcome measure on re-evaluation	Findings on Re-evaluation	OR(95%CI) RR(95%CI) p
Larouche 2000	Retrospective Case-control	42	42	< 18	21 (17-35)	Asthma	38% vs. 12%	p<0.05
						BHR[2]	62% vs.29%	OR 4.1 (NA)
						FEV1 (% pred)	94 vs. 103	p=0.002
						FEV1/FVC (% pred)	80 vs. 87	p<0.0001
Gomez 2004	Retrospective Case-control	71	32	<12	19-24	Asthma	25% vs. 6%	OR 5.09 (1.1-23.47)
						Wheezing	28% vs. 9%	NA
						BHR[2]	61% vs. 29%	OR 3.8 (1.5-9.6)
						PEF ml/s	7,00 vs. 7,95	p=0.02
Sigurs 2005	Prospective Case-control[1]	46	92	< 12 (mean 3.8)	13.4 (13.0-14.0)	Asthma	28% vs. 3%	OR 10.01 (3.4-29.8)
						BHR[2]	6.1 % vs. 4.6%	p=0.047
						FEV1/FVC (%)	85 vs. 88	RR 8.7(2.6-28.9)
						FEF75 (% predicted)	71 vs. 82	p=0.005
Hyvärinen 2005b	Prospective Cohort	81	0	< 24	12.3 (10.9-13.7)	Asthma	40%	NA
Göksor 2006	Prospective Case-control	89	401	< 24	17-20	Asthma	43% vs. 15%	aOR 4.2 (2.5-7.2)

[1] The aetiology of infection was RSV for all patients. [2] Bronchial hyper-reactivity: decrease of FEV1 in dry air challenge. NA means not applicable

Table 4. Bronchiolitis not needing hospitalisation in early life: outcome after ten years of age.

Reference	Design	Bronchiolitis patients N	Controls N	Age on admission (months)	Age on re-evaluation (years)	Outcome Measure	Findings on re-evaluation	OR(95%CI) RR(95%CI) P
Mc Connochie 1985	Case-control Retrospective	25	25	< 24	10.0 (8.2-12.0)	FEF_{25-75} ,% predicted	64% vs. 75%	P=0.04
Mc Connochie 1989	Case-control Retrospective	51	102	< 24	13.5	Wheezing	16% vs. 9%	P=0.10
Rhodes 2001	Prospective,birth cohort with atopic parents	17	43	< 24	22	Asthma	12% vs. 30%	OR 0.3 (0.03-1.7)
Turner 2002	Prospective Cohort	16	162	< 24	11	Wheezing	19% vs. 16%	NS
						FEF25-75 ,% predicted	91% vs. 101%	P=0.03
Toelle 2004	Retrospective community-based cohort	NA	NA	< 24	23-27	Asthma symptoms	NA	OR 1.9 (1.3-2.9)
						Severe asthma	NA	OR 2.4 (1.4-3.9)
Morgan 2005	Prospective,birth cohort transient wheezers[1]	164	425	< 36	16	Wheezing	20% vs. 15%	RR 1.28 (0.97-1.7)
						FEV1/FVC, coefficient	-1.9%	p=0.002
						FEV1, coefficient	-75 ml/s	p=0.02
						FEF25-75, coefficient	-259 ml/s	p<0.001
	persistent wheezers[2]	113	425	< 36	16	Wheezing	50% vs. 15%	RR 3.5 (3.1-4.7)
						FE1/FVC, coefficient	-2.5%	p=0.001
						FEV1, coefficient	-87 ml/s	p=0.03
						FEF25-75, coefficient	-260 ml/s	p=0.03

[1] Wheezing at <3 years of age, but no more after 6 years of age; [2] persistent wheezing from < 3 years onwards.

2.5.2. Bronchial reactivity

Viral respiratory infections increase bronchial reactivity at least transiently (Empey et al. 1987), as originally observed in non-asthmatic adults after an upper respiratory infection (Parker et al. 1965). In non-atopic wheezing children, the tendency for bronchial hyper-reactivity (BHR), whether present at birth (Stick et al. 1990, Chan et al. 1993, Palmer et al. 2001) or induced later by viral infection (Colasurdo et al. 1998), seems to decrease during school years (Burrows et al. 1995) and is assumed to result from alteration in airway neural control (Wennergren et al. 2001, Martinez and Godfrey 2003). In atopic wheezing children, BHR has been suggested to appear after the first wheezing episode (Mochizuki et al. 2000), to persist at least through school age (Burrows et al. 1995), and finally to result in persistent or relapsing wheezing symptoms and even lung function abnormalities at teen age (Sears et al. 1996). Probably, the persistence of BHR is associated with concomitant development of airway remodelling, as documented in adult atopic asthmatics.

2.5.3. Lung function

Airway remodelling (Simoes et al. 1999, Mahalingam et al. 2006) and other persistent changes, such as unilateral hyperlucent lung (Fregonese et al. 2002, Fischer and Boyce 2005), emphysema (Becroft et al. 1971, Newman et al. 1995), atelectasis (Simoes et al. 2005) and even bronchiectasis (Becroft et al. 1971, Fischer and Boyce 2005), have been documented after bronchiolitis in early life. Moreover, pulmonary function seems to remain on a lower level after bronchiolitis through childhood until adult age, reflecting airway remodelling (Tables 3).The deterioration is evident in both large and small airways after severe bronchiolitis treated in hospital, and detectable also after mild bronchiolitis treated at home (Table 4). However, in some studies the smaller size of airways in bronchiolitis patients has been present already at the age of one month, prior to any wheezing episode (Young et al. 1995, Martinez et al. 1998, Turner et al. 2002, Murray et al. 2002), and detectable years after cessation of wheezing (Taussig et al. 2003,Turner et al. 2004).

In population-based studies, adulthood lung function has been persistently decreased in subjects with childhood asthma in comparison with healthy controls (Edwards et al. 2003). Instead, children with wheezy bronchitis but without asthma have normal lung function until 40 years of age but thereafter show a rapid decline

(Edwards et al. 2003). Persistent wheezing from preschool age onwards has resulted in greater, and only partially reversible, airflow reduction in the fourth decade of life (Strachan et al. 1996b).

2.6. Long-term outcome after lower respiratory tract infection in relation to viral aetiology of infection

2.6.1. RSV infections

As seen in Table 5, recurrent wheezing and asthma are common for several years after hospitalisation for RSV bronchiolitis, but then decrease rapidly by pre-school and early school age (Wennergren et al. 1992, Korppi et al. 1993, Kuikka et al. 1994, Korppi et al. 1994, Wennergren et al. 1997, Reijonen et al. 2000, Sigurs et al. 2000, Sigurs et al. 2002, Kotaniemi-Syrjänen et al. 2002, Kotaniemi-Syrjänen 2003). At teen age, asthma prevalence begins a new rise continuing until young adulthood (Table 6). Children who experience a mild RSV LRTI treated at home before 3 years of age have a 3- to 5-fold greater risk of wheezing at six years of age (Taussig et al. 2003), but the risk is no longer increased at the age of 11 to 13 years (Stein et al. 1999a) However, their lung function persists marginally decreased at least until the age of 16 years (Table 6).

Table 5. Subsequent asthma until school age after hospitalisation for RVS infection in early life. Results from four cohorts prospectively followed-up until teen or adult age.

Age (years)	Korppi[1]*	Wennergren[2]	Sigurs[3]	Reijonen[4]
	1981-82	1984-85	1989-90	1992-93
	N=33	N=50	N=47	N=24
3	52%		60%	
4- 6	13%	30%		22%
7- 10	6%	29%	23%	4%

* Present cohort. References: [1]Korppi 1993, Kuikka 1994, Korppi 1994; [2]Wennergren 1992, Wennergren 1997; [3]Sigurs1995, Sigurs 2000, Sigurs 2002; [4]Reijonen 2000, Kotaniemi-Syrjänen 2002, Kotaniemi-Syrjänen 2003.

Table 6. Viral findings in early-life respiratory tract infections in relation to asthma and lung function at teenage and adulthood.

Viral aetiology and type of infection	Reference	Age on re-evaluation (years)	Design	Outcome measure	Findings Present	OR (95%CI) p	Reference category
RSV illness							
RSV LRTI	Stein 1999a	13.5 (SD 0.6)	Prospective	Frequent wheeze	NA	OR 1.4 (0.7-2.6)	No LRTI
		10.9 (SD 0.6)	cohort	Bronchodilator response	NA	OR 2.4(1.0-5.8)	
				Decreased FEV1	NA	p=0.001	
	Guerra 2004	6 to 16.6 (SD0.6)	Prospective cohort	Unremitting[1] wheeze	36% vs. 29%	p for trend=0.013	Remitting wheeze
				Unremitting[1] asthma	30% vs. 29%		Remitting asthma
	Hyvärinen 2005a[2]	13.5-16	Prospective cohort	No wheeze	18%	aOR 0.5(0.1-2.0)	Wheeze ever
				Asthma	8% vs. 16%		Non-RSV LRTI
RSV bronchiolitis requiring hospitalisation	Sigurs 2005	13.4(13.0-14.0)	Prospective case-control	Asthma	28% vs. 3%	OR 10.0(3.4-29.8)	No hospitalisation for bronchiolitis
				BHR[3]	6.1% vs. 4.6%	p=0.047	
				FEV1/FVC (%)	6.1 vs. 4.6	RR 8.7(2.6-28.9)	
				FEF 75 (% predicted)	71 vs. 85 vs. 88	p=0.005	
	Hyvärinen 2005b	12.3 (10.9-13.7)	Prospective cohort	Asthma	20% vs. 52%	OR 0.3 (0.1-0.8)	Non-RSV bronchiolitis
	Goksör 2006	17-22	Prospective cohort	Asthma	48% vs. 41%	aOR 0.4 (0.1-1.4) OR 1.3 (0.5-3.4)	No asthma
Rhinovirus bronchiolitis requiring hospitalisation	Hyvärinen 2005b	12.3 (10.9-13.7)	Prospective cohort	Asthma	58% vs. 34%	OR 2.7 (0.9- 7.9) aOR 1.1 (0.4-4.9)	Non-rhinovirus bronchiolitis
Non-RSV non-parainfluenza LRTI	Stein 1999a	13.5 (SD 0.6)	Prospective cohort	Frequent wheeze	NA	OR 3.1 (1.3-7.6)	No LRTI
LRTI with no detected virus	Stein 1999a	13.5 (SD 0.6)	Prospective cohort	Frequent wheeze	NA	OR 2.1(1.04-4.3)	No LRTI
				Decreased FEV1	NA	p<0.05	

[1] Wheezing or asthma at both 6 and 16 years of age;[2] the present cohort. [3] Bronchial hyper-reactivity: decrease of FEV1 during a dry air challenge. NA designates no data applicable and aOR adjusted odds ratio (95% confidence interval).

2.6.2. Non-RSV bronchiolitis

After bronchiolitis caused by viruses other than RSV, subsequent asthma risk seems to be even higher than after RSV bronchiolitis, remaining elevated until teen age (Table 6). In particular, rhinovirus bronchiolitis is associated with an increased prevalence of asthma at school age, with asthma present in 52 to 58% of patients who had rhinovirus bronchiolitis and in 4 to 20% of patients who had RSV bronchiolitis (Kotaniemi-Syrjänen et al. 2003, Hyvärinen et al. 2005b). There are no follow-up studies on human metapneumovirus, a recently found important trigger for wheezing in early life (Xepapadaki et al. 2004, Jartti et al. 2004, Werno et al. 2004, Garcia-Garcia et al. 2006).

2.7. Early life factors associated with asthma at teenage and in adulthood.

2.7.1. Post-bronchiolitis studies.

There are only five previous post-bronchiolitis cohorts with information available on early predictors for teen age or adult asthma (Table 7). In all these studies, atopy or asthma in family has been a major predictor for wheezing or asthma in adolescence, stressing the role of inheritance in the development of asthma in adulthood. Likewise, female gender, early atopy and early sensitisation to inhaled allergens have been independently associated with an increased risk of asthma until the second decade of life. Among the numerous environmental factors that have been studied, only exposure to passive smoking in infancy and low socioeconomic status have been consistently been risk factors for persisting or relapsing asthma symptoms in adolescence.

2.7.2. Population-based studies

2.7.2.1. Inherited, prenatal and structural factors

In population-based cohort studies, male gender seems to predominate among asthma patients until teenage, but female gender thereafter (Table 8). Again, parental asthma and atopy are the most often reported predictors for adult asthma. In addition, low maternal age, albuminuria, bleeding during pregnancy and reduced lung function at birth predict an increased risk for asthma in adulthood.

Table 7. Early life factors associated with the development of teen age or adult asthma: post-bronchiolitis studies.

Factor	Reference	Outcome measure	OR (95%CI) p
Inheritance			
Parental asthma	Sigurs 2004	Asthma	OR 4.7 (1.6-13.9)
	Hyvärinen 2005b	Asthma	OR 3.4 (0.9-12.2)
Asthma in family	McConnochie 1989	Wheezing	p<0.01
		Asthma	p=0.05
Atopy in family	Goksör 2006	Asthma	OR 2.7 (0.9-7.5)
Gender			
Male	McConnochie 1989	Wheezing	p<0.05
Female	Goksör 2006	Asthma	OR 4.7 (1.8-12.6)
Positive specific serum IgE[1] (> 0.35) against			
Mixt food allergens	Hyvärinen 2005b	Asthma	OR 2.3 (0.8-6.7)
Mixt inhalant allergens	Hyvärinen 2005b	Asthma	OR 11.30(1.89-67.60)
Early atopy			
Serum total IgE	Hyvärinen 2005b	Asthma	OR 3.5 (1.0-13.0)
Atopic dermatitis	Hyvärinen 2005b	Asthma	OR 3.5 (1.0-10.1)
Previous wheezing episodes	Hyvärinen 2005b	Asthma	OR 3.7 (0.9-16.0)
Passive smoking	Goksör 2006	Asthma	OR 3.1 (1.0-9.2)
Maternal smoking	McConnochie 1989	Asthma	OR 2.67, p< 0.01
Low socioeconomic status	McConnochie 1989	Wheezing	p<0.05

[1] Immunoglobulin E

2.7.2.2. Atopic, allergic and immunological factors

As seen in Tables 8 and 9, atopic dermatitis, elevated serum IgE, allergic rhinitis and early allergic sensitisation are factors predicting childhood asthma until 13 years of age, particularly if the child has suffered from wheezing already in early life (Castro-Rodrieguez et al. 2000, Taussig et al. 2003). The association between asthma and sensitisation to food allergens or elevated serum IgE in early childhood remains

significant until adulthood, but has been proven in children of atopic parents only (Rhodes et al. 2002). Instead, the association between sensitisation to inhalant allergens and later asthma has been shown until teen age (Hyvärinen et al. 2005b), but not thereafter. Chronic or invasive early-life infections, such as tuberculosis (von Mutius et al. 2000) and measles (Bodner et al. 2000) have been suggested to protect from later asthma. Instead, pneumonia at the pre-school age is related to increased asthma risk until teen age, but not thereafter (Strachan et al. 1996, Castro-Rodriquez et al. 1999).

2.7.2.3 Early exposure to inhalant allergens

Early exposure to inhalant allergens may lead, depending on the timing and quantity of exposure and on inheritance, to sensitisation with increased risk for allergy and asthma (Kihlström et al. 2002, Guerra et al. 2002, Brussee et al. 2005,) or to tolerance with opposite outcome (Remes et al. 2001). Thus, population-based studies on early exposure to furred pets have given varying results, from increased asthma risk in children with asthma in parents (Sandin et al. 2004) to decreased asthma risk until 13 years of age in children with no asthma in parents (Remes et al. 2001, Sandin et al. 2004). In addition, many studies have found no association at all (Lau et al. 2000, Cullinan et al. 2004). Among children hospitalised for bronchiolitis, early exposure to furred pets has predicted later asthma until pre-school age (Reijonen et al. 2000), but no longer during school age (Kotaniemi-Syrjänen et al. 2002, Sigurs et al. 2005, Hyvärinen et al. 2005b) or in adulthood (Goksör et al. 2006).

Likewise, birth just before or during pollen season is assumed to increase the risk for early sensitisation and later development of allergic disease (Saitoh et al. 2001, Kihlstöm et al. 2002), though a decreased risk for allergic rhinoconjunctivitis by teen age has also been found (Nilsson et al. 1997). Birth month, representing the degree of early exposure to seasonal pollens, predicted allergic asthma at the age of 10 years in a German cohort (Wjst et al. 1992) and allergic rhinitis, but not asthma, in Danish adults (Pedersen et al. 1983).

Table 8. Inherited, prenatal and structural factors associated with the development of teen age or adult asthma in population-based studies.

Factor	Reference	Age on re-evaluation (years)	Design	Outcome measure	OR(95%CI) P
Parental asthma	Sunyer 1997	20-44	Retrospective cohort	Asthma	OR 4.5 (2.5-8.4)
	Sears 1996	18	Prospective from 9 yrs	Asthma	p=0.042
	Sigurs 2005[1]	13	Prospective cohort	Asthma	significant
Parental hay fever	Sears 1996	18	Prospective from 9 yrs	Asthma	p=0.003
Family history if wheezing	Sears 1996	26	Prospective from 9 yrs	Relapsing asthma	OR 1.6 (1.0-2.6)
Lung function (VmaxFRC at 1 month of age)	Turner 2004	11	Prospective cohort	Current wheezing	p=0.03
				Persistent wheezing[2]	p=0.03
Low maternal age (20 vs. 40 years)	Lewis 1995	16	Prospective from 5 yrs, cohort	Persistent wheezing[3]	aOR 2.0 (1.1-3.5)
Albuminuria in mother	Strachan1996a	17-33	Prospective from 7 yrs cohort	Asthma or wheezing	OR 1.6 (1.1-2.3)
Bleeding in pregnancy at <28 weeks	Strachan 1996a	8-16	Prospective from 7 yrs cohort	Asthma or wheezing	3.0(1.3-6.7)
Male gender	Strachan 1996a	8-16	Prospective from 7 yrs, cohort	Asthma or wheezing	OR 1.5 (1.1-1.2)
	Huurre 2004	16	Cross-sectional cohort	Asthma in 3.0% vs. in 2.7%	NA
	Schatz 2004	2-13	Retrospective cohort	Asthma in 65% vs.35%	NA
Female gender	Strachan 1996a	17-33	Prospective from 7 yrs, cohort	Asthma or wheezing	0R 0.8(0.6-1.00)
	Huurre 2004	32	Cross-sectional cohort	Asthma in 4.9% vs. 5.1%	NA
	Schatz 2004	23-64	Retrospective cohort	Asthma in 65% vs. 35%	NA

[1] RSV bronchiolitis cases and controls analysed together; [2] wheezing both at 4-6 and 11 years of age; [3] wheezing both at < 5 and at 16 years of age.

Table 9. Early life atopic, allergic and immunological factors associated with asthma after 10 years of age, population-based studies.

Factor	Reference	Age on re-evaluation (years)	Design	Asthma risk	OR(95%CI) p	Reference category
Allergic sensitisation (SPT[1])						
to food [2] allergens <1 year of age	Rhodes 2001	22	Prospective cohort[3]	Asthma	OR 10.7 (2.1-45.5)	No early sensitisation to food allergens.
to inhalant allergens <2 years of age	Rhodes 2001	22	Prospective cohort[3]	Asthma	OR 7.0 (1.5-55.1) aOR 2.0(NA), p=0.75	No early sensitisation to inhalant allergens.
to *Alternaria Alternata* <6 yrs of age	Halonen 1999	11	Prospective cohort	Asthma	p= 0.003	Wheezing, but not allergic sensitisation at 6 yrs of age.
Elevated serum IgE[4]						
at birth	Stein 1997	11	Prospective cohort	BHR[5]	p=0.07	No BHR
at 9 months of age	Sherrill 1999	11	Prospective cohort	Persistent wheeze	p=0.05	NA
at 3 years of age	Rhodes 2001	22	Prospective cohort[3]	Asthma	p=0.05	No adult asthma
Blood eosinophils >5% at 2 occasions	Karakoc 2002	11	Prospective, birth cohort	Chronic asthma	OR 1.70 (1.2-2.4) for trend	Blood eosinophils <2% in at least 2 occasions
Severe LRTI <5 yrs of age.	Svanes 2002	20-44	Retrospective, cohort	Wheezing	OR 1.9 (1.7-2.1)	No severe LRTI < 5 yrs of age
Pneumonia <3 yrs of age	Castro-Rodriquez 1999	11	Prospective, birth cohort	Asthma in 26% vs. 11% Decreased FEV1 Deceased FEV25-75	2.8 (1.4-5.6) p<0.05 p<0.001	No LRTI No LRTI No LRTI

[1] Skin prick test; [2] milk and hen's egg; [3] cohort of children with parental history of atopy; [4] IgE as continuous variable, [5] BHR in methacholine inhalation challenge

2.7.2.4. Other environmental factors

Despite the vast scientific interest on early life environmental factors with a potential influence on the development of later asthma, only a few factors have been discovered to maintain their influence until teen age or adulthood. Numerous daily child contacts in families and day-care outside home seem to result in less asthma in adolescence and adulthood, although there are also opposite findings. In addition, living in a farm reduces asthma risk at least until young adulthood (Table 10).

2.8. Blood eosinophils in early life as markers for subsequent asthma

Eosinophils are involved in the inflammatory process of airway obstruction and thus contribute to the development of persistent wheezing, asthma and even airway remodelling leading to persistent lung function impairment (Dimova-Yaneva et al. 2003, Zagai et al. 2004). Lack of eosinopenic response during acute viral infection (Martinez et al. 1998), elevated blood eosinophil count in infancy particularly during acute bronchiolitis (Martinez et al. 1998, Ehlenfield et al. 2000), and persistently high blood eosinophil counts (Karakoc et al. 2002) have predicted wheezing and asthma until school age (Table 9). Among bronchiolitis patients treated in hospital, eosinophil count >0.45 x10E9/L before the age of two years has been associated with increased asthma risk at 7 years of age (Kotaniemi-Syrjänen et al. 2002), but no longer at 11-13 years of age (Hyvärinen et al. 2005b). However, the asthma predictive value remained significant until 16 years of age, if eosinophils were elevated before one year of age in children hospitalised for LRTI (Hyvärinen et al. 2005a). In contrast, persistently low (≤2%) eosinophil counts have been associated with beneficial outcome (Karakoc et al. 2002).

2.9. Long term consequences of early exposure to passive smoking

Maternal smoking, particularly if during pregnancy, seems to increase the risk for wheezing during later childhood (Strachan et al. 1996b, Stein et al. 1999b, Jaakkola et al. 2004, Jaakkola et al. 2006). Although the harmful effects seem to decrease with time (Stein et al. 1999b), there is increasing evidence of permanent damage to the airways, manifesting as reduced lung function, increased risk of asthma or wheezing symptoms, which continue until adulthood (Table 11). Lung function deficits are most apparent in the small airways and detectable already at birth if the mother has smoked

Table 10. Early life environmental factors associated with asthma or recurrent wheeze at teen or adult age in population-based studies.

Factor	Reference	Age on re-evaluation (years)	Design	Outcome	OR (95%CI) RR (95%CI) p	Reference category
Siblings						
1 sibling	Ball 2000	6-13	Prospective, birth cohort	Recurrent wheezing	RR 0.9 (0.7-1.0)	No siblings
≥2 siblings	Ball 2000	6-13	Prospective, birth cohort	Recurrent wheezing	RR 0.6 (0.4-1.0)	<2 sibling
	Bodner 2000	34-40	Prospective, case-control	Adult-onset asthma	OR 0.1 (0.03-0.8)	<2 siblings
≥ 4 siblings	Svanes 2002	20-44	Retrospective cohort	Wheezing or shortness of breath	OR 1.12 (1.0-1.4)	<4 siblings
Day-care attendance						
<6 months of age	Ball 2000	6-13	Prospective, birth cohort	Recurrent wheezing	RR 0.4 (0.2-1.0)	No day care at <6 months age
<5 years of age	Svanes 2002	20-44	Retrospective cohort	Wheezing / No siblings	OR 1.5 (1.1-2.0)	No day-care at <5 yrs of age
Exposure to furred pets						
cat/ dog <1 year of age	Hesselmar 1999	12-13	Prospective from 7-9 years of age, cohort	Asthma	p< 0.001	No exposure to cat/ dog at <1yr of age
≥1 indoor dog at birth	Remes 2001	13	Prospective, birth cohort	Low risk of frequent wheezing[1]	p= 0.004	No indoor dogs at birth.
High socioeconomic status	Lewis 1995	16	Prospective from 5 years of age, cohort	Persistent wheezing	OR 2.0 (1.1-3.4)	Low socioeconomic status
Farm environment	Kilpeläinen 2002	18-25	Cross-sectional	Asthma	OR 0.2 (0.1-0.7)	Childhood/ non-farming
	Bråbäck 2004	17-20 (males)	Cross-sectional	Asthma	OR 0.9 (0.8-0.9)	Children/ non-farmers
	Remes 2005	6-13	Cross-sectional	Nocturnal cough	OR 0.5 (0.3-0.8)	Children/ non-farmers

[1]By 13 years of age, the effect was seen in children without parental asthma (p=0.0003), but not in children with parental asthma (p= 0.87).

Table 11. Teen age or adult consequences of early exposure to passive smoking in childhood in population-based studies.

Smoking person	Age of exposure	Reference	Design	Age on re-evaluation (years)	Outcome	aOR (95%CI)
Mother	Pregnancy	Gilliland 2000[3] and 2001[3]	Retrospective cohort	10-16	Asthma, PEF, MMEF	1.2 (1.1-2.9) Decreased
	Pregnancy	Svanes 2004	Retrospective cohort	20-44	Wheezing, COPD[3] FEV1/FVC	1.2 (1.1-1.4) 1.3 (1.1-1.6) Decreased
	Pregnancy and at 16 yrs of age	Strachan 1996a	Prospective birth cohort	17- 33	W, Asthma	1.40 (1.1-1.8)
	Childhood	Gilliland 2000[4] and 2001[4] Upton 2004 Svanes 2004	Prospective cohort Retrospective cohort Retrospective cohort	10-16 45-64, current smokers 20-44	Asthma FVC, FEV1, FEV1/FVC W FVC, FEV1, FEV1/FVC COPD	1.8 (1.1-2.9) Decreased 1.1 (1.0-1.2) Decreased 1.2 (1.1-1.4)
Father	Childhood	Gilliland 2000[4] Svanes 2004	Retrospective cohort Retrospective cohort	10-16 20-44 20-44, men 20-44, women	FEV1, FVC, PEF, MMEF COPD W W	NS 1.1 (1.0-1.3) 1.1 (1.0-1.3) NS
Either parent	Childhood	Svanes 2004	Retrospective cohort	20-44 in men	COPD	1.2 (1.0-1.5)
Environmental	Childhood	Larsson 2001	Postal survey	15-69 never smokers from non-atopic families	Asthma	1.8 (1.3-2.6)

[1] W means wheezing and COPD means chronic obstructive pulmonary disease; [2] FVS means flow-volume spirometry; [3] adjusted for environmental smoking;[4] adjusted for maternal smoking in pregnancy. NA designates not applicable and NS non significant.

during pregnancy (Young et al. 2000, Lodrup Carlssen et al. 2002,Murray et al. 2002). A similar effect has been seen at the end of the first year of life in infants who had been exposed to maternal smoking only postnatally (Dezateux et al. 2001).

The influence of paternal smoking is less evident, but a significant association with an increased prevalence of asthma (Table 10) and increased active smoking in adulthood has been observed (Larsson 2001). Previous post-bronchiolitis studies have failed to demonstrate the long-term harms of early postnatal passive smoking (Sigurs et al. 2000, Reijonen et al. 2000, Kotaniemi-Syrjänen et al. 2002, Sigurs et al. 2005). However, a recent study from Sweden demonstrated a causal relationship between early passive smoking and asthma at school and adult age (Wennergren et al. 1997, Goksör et al. 2006). The harmful effects seem to be mediated via bronchial hyper-reactivity (Hendersson et al. 1995, Goksör et al. 2006) and increased active smoking in young adulthood (Goksör et al. 2006, Larsson et al. 2001).

2.10. Clinical implications

Distinguishing which bronchiolitis patients are at particular risk for permanent wheezing and asthma in later life is essential to prevent airway remodelling and permanent impairment of lung function. Thus, algorithms based on atopic findings in children and asthma in parents have been constructed for clinical use.

The algorithm presented in Table 12 is developed by the Tucson study group. It is based on a large prospective birth cohort study including wheezing children, mainly treated at home, below 3 years of age. The outcome measure in the validation of the selected criteria was asthma at 13 years of age. Loose index – wheezing at <3 years of age and at least one major criterion or two minor criteria – means moderate risk for later asthma. Stringent index – repeated wheezing at <3 years of age and at least one major criterion or two minor criteria – means high risk for later asthma.

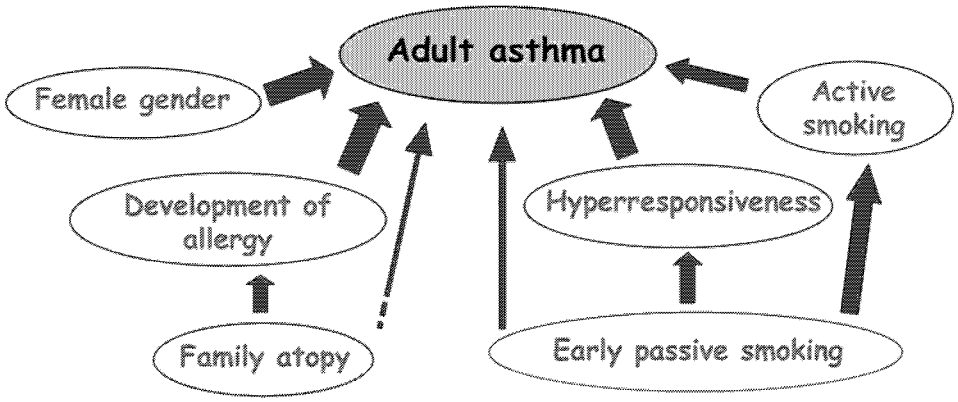
The main results of the recent Swedish prospective case-control post-bronchiolitis study are summarised in Figure 1. The algorithm describes three independent pathways – from family atopy through allergy, from early passive smoking through bronchial hyper-reactivity, and from early passive smoking through later active smoking – leading to adult asthma in subjects hospitalised for bronchiolitis in infancy. In addition, female gender is an independent risk factor for adult asthma.

Table 12. An algorithm to define those wheezing children who are at particular risk for subsequent asthma

Major criteria	Minor criteria
Wheezing at <3 years of age	1. Physician-diagnosed allergic rhinitis
1. Physician-diagnosed asthma in a parent	2. Wheezing apart from colds
2. Physician-diagnosed atopic dermatitis	3. Blood eosinophilia (≥ 4%)

Reference: Castro-Rodriquez 2000.

Figure 1. Pathways leading to adult asthma after hospitalisation for bronchiolitis in early life.



The thick arrows designate significant association in multivariate analyses and the thin arrows in univariate analyses. Reference: Goksör et al. 2006.

3. AIMS OF THE STUDY

The aims of the study were to determine the adulthood outcome in subjects hospitalised for bronchiolitis in early childhood and to assess early life factors predicting adulthood asthma, bronchial hyper-reactivity and lung function abnormalities.

The specific aims were:

1. To asses the occurrence of asthma, wheezing, bronchial hyper-reactivity and lung function abnormalities among young adults hospitalised for bronchiolitis in early life.

2. To compare the characteristics and outcome in adulthood of children hospitalised for bronchiolitis caused and not caused by RSV.

3. To identify factors presenting in early life that are predictive of asthma, bronchial hyper-reactivity and abnormal lung function in adulthood of children requiring hospital treatment for bronchiolitis, with special emphasis on early manifestation of atopy, early life recurrence of wheezing episodes and early exposure or sensitisation to inhaled allergens.

4. To determine the long-term consequences of early exposure to passive smoking in children hospitalised for bronchiolitis in early life.

5. To evaluate the role of blood eosinophils and lack of infection-induced eosinopenic response in early life as markers for adulthood asthma in children hospitalised for bronchiolitis.

4. PATIENTS AND METHODS

4.1. Baseline data on admission in 1981-1982

4.1.1. Participants

Between 1st September 1981 and 31st August 1982, all 130 children younger than 24 months of age (median age 10 months) who were hospitalised for bronchiolitis (n=83) or pneumonia (n=47) in the Department of Paediatrics at Kuopio University Hospital, Kuopio, Finland, were enrolled in the study (Korppi 1986). Three children from the pneumonia group were not included in the analyses until 3 years of age due to inappropriate collection of follow-up data. Thorax-x-ray was taken from all children, and pneumonia was diagnosed radiologically. Bronchiolitis was defined by the presence of tachypnoea, expiratory wheezing or prolonged expirium during lower respiratory infection. Pneumonia patients with expiratory difficulties (n=46) were included in the bronchiolitis group (Korppi et al. 1986, Martinez and Godfrey 2003).

There was an RSV epidemic from 1st October to 31st December 1981 (Korppi et al. 1986). RSV aetiology of infection was identified using antigen assays by radioimmunology for nasopharyngeal aspirates or antibody assays by complement fixation for paired serum samples, in 33 patients with bronchiolitis and in 19 with pneumonia (Korppi et al. 1986). In this thesis, RSV positive cases form RSV group and RSV negative cases the non-RSV group.

The control group consisted of 72 out of 88 newborns without family history of atopy who were originally recruited at birth in 1979-1980 to a birth cohort study and attended a prospective follow-up until 12 months of age (Pöysä et al. 1988, Pöysä et al. 1989a). Only two of the controls had suffered from doctor-diagnosed wheezing episodes (Pöysä et al. 1989a).

4.1.2. Collection of data until 2-3 years of age

Since the index episode of bronchiolitis, the children participated in three control visits before the age of 24 months and in a clinical follow-up study at 20-35 months of age (Korppi et al. 1993). Baseline data were obtained by interviewing the parents on admission. Family history of asthma or allergy was defined by the presence of physician-diagnosed asthma, hay fever or atopic dermatitis in either of the parents

(Kuikka et al. 1994). The children's wheezing episodes were recorded separately for the age periods of 0-12 months and 12-24 months, and if present at least 3 times before 24 months of age (including the index episode), wheezing was classified as repeated (Korppi et al. 1994). The definition was appropriate in 1980's, but the criteria have changed thereafter. The diagnosis of atopic or non-atopic dermatitis was confirmed by a dermatologist in all cases with parent-reported dermatitis (Korppi et al. 1994). Information on pet keeping at home or at day care, breastfeeding, passive smoking, day-care-attendance and number of people in the household was prospectively registered until 30-35 months of age (Korppi et al. 1993).

4.1.3. Exposure to furred pets, pollens and passive smoking

Birth months, classified into three groups (January to April, winter/ spring; May to August, summer; September to December; autumn), represent different exposure patterns to seasonal pollens, viral infections and temperature. A furred pet at home or with the day care family and parental smoking when the child was <24 months old were interpreted to mean early exposure to animal dander or tobacco smoke, respectively. Information on maternal smoking during pregnancy was not collected.

4.1.4. Definition of atopy, exposure, sensitisation and eosinophilia in early life

In this thesis, atopy in early life was defined by elevated total serum immunoglobulin E (IgE) (ALK, Allergologiska Laboratorium, Copenhagen, Denmark) or by the presence of dermatologist-diagnosed atopic dermatitis. Serum IgE was considered as elevated if the concentrations were more than +2SD above the mean for non-atopic Finnish children ($\geq$60 kU/L) (Saarinen 1982) at either of the two measurements at 6-11 and/ or 18-23 months of age (Kuikka 1994). Analyses were also performed at the cut-off level of 150 kU/L, which seems to strongly suggest the development of atopic disease in young children (Kajosaari et al. 1981).

Sensitisation was studied by specific IgE (ALK, Allergologiska Laboratorium, Copenhagen, Denmark) to common inhalant allergens 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) at either occasion was regarded to show sensitisation to that allergen (Paganelli et al. 1998). In addition, the other cut-off concentration (0.70kU/L) proposed by the manufacturer was also explored in the present analyses. The allergens tested

were birch, timothy grass and mugwort pollens, spores of *Cladosporium herbarum*, cat and dog epithelial danders, and two house dust mites, *Dermatophagoides farinae and D. pteronyssimus*.

Blood eosinophils were studied on admission (N=81), that is during acute infection, and during convalescence 4-6 weeks later (N=81), using a counting chamber (Lewis et al. 1975). These determinations were done in both occasions in 79(95%) children. The cell counts were expressed as continuous absolute values and classified into four groups at the cut-off limits of 0.15 x 10E9/L, 0.30 x 10E9/L and 0.45 x 10E9/L. Eosinophilia was defined by >0.30 x 10E9/L, >0.45 x 10E9/L (Eisen et al. 1980, Kotaniemi-Syrjänen et al. 2002) or >0.60 x 10E9/L (Kajosaari et al. 1981) counts.

4.2 Follow-up

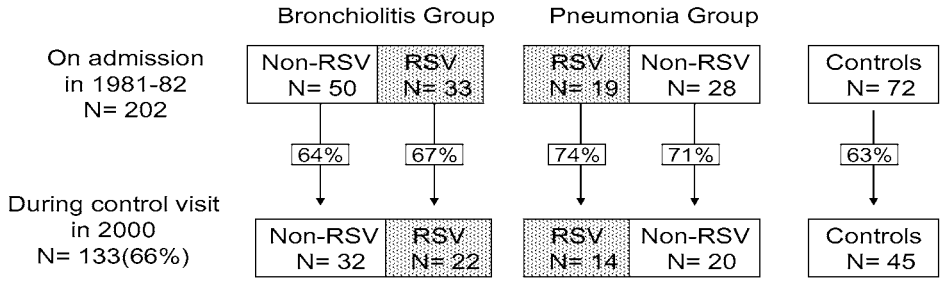
The children with bronchiolitis and pneumonia in infancy were prospectively followed up during clinical control visits at 4.5-6 years (pneumonia cases not included) (Kuikka et al. 1994) and at 8.5-10 years of age (Korppi et al. 1994), and a postal questionnaire study on asthma symptoms and medication was arranged at the age of 13.5-16 years (Hyvärinen et al. 2005a). On each occasion, asthma and allergy status was carefully screened by a questionnaire study and clinical examination (Kuikka et al. 1994, Korppi et al. 1994). Asthma was defined as $\geq$3 wheezing episodes ever in life at the age of 8.5-10 years (Korppi et al. 1984) and physician-treated wheezing episodes within the preceding 12 months at the age of 13.5-16 years (Hyvärinen et al. 2005a).

4.3. Follow-up study at the age of 18- to 20 years in 2000

4.3.1. Participants

Fifty-four subjects (61%), 33 males and 21 females, from the bronchiolitis group attended the follow-up study in 2000, from January to March, at the age of 18 to 21 years (median 19 years). The respective figures were 34(72%), 17 males and 17 females, in the pneumonia group and 45(75%), 25 males and 20 females, in the controls. The index infection was caused by RSV in 41% of bronchiolitis and in 41% of pneumonia patients (Fig. 2). Among the bronchiolitis cases not
by RSV, 10 were hospitalised during the RSV epidemic in the fall 1981.

Figure 2. Attendance to 18-to 20-year follow-up in relation to diagnosis and RSV aetiology of infection.



4.3.2. Collection of follow-up data

Data on the occurrence of respiratory and allergic symptoms, medication and current smoking were obtained by an interview and a written questionnaire. The main focus was in the presence of wheezing episodes and prolonged cough apart from infections during the preceding 12 months, supplemented by information on medication for asthma. Current smoking was defined as regular smoking of at least one cigarette per day.

4.3.3. Methacholine inhalation challenge

Bronchial reactivity was assessed by the MIC test in 127 of the 133 participants. The provocative dose designates the cumulative amount of inhaled methacholine needed to produce a 20% fall (PD20) in FEV1 compared with the baseline value. Methacholine was inhaled using a Spira Electro-2 dosimeter (Respiratory Care Centre, Hämeenlinna, Finland), allowing the calculation of the total amount inhaled by each subject. Lung function by the FVS was measured at the beginning and 1.5 minutes after each methacholine dose. The test was continued until a 20% fall in FEV1 (Hedman et al. 1998, Godfrey et al. 1999, Kiljander et al. 2004), or until a cumulative dose of 4900 μg

of methacholine was reached (Korppi et al. 1994). Bronchial reactivity was classified into four categories by limits similar to those used in the previous phases of the present study: severe (PD20 ≤400), moderate (PD20=401-1600), mild (PD20=1601-4900), and no reactivity (PD20 >4900) (Korppi et al. 1994).

4.3.4. Lung function measurements

The baseline lung function was measured in all 133 participants with a flow-volume pneumotachographic spirometer (FVS) (Medikro, Kuopio, Finland). The measured parameters were FVC (forced vital capacity), FEV1 (forced expiratory volume in one second), FEV% (FEV1/FVC), MEF50 (mid-expiratory flow at 50% of FVC) and MEF25 (mid-expiratory flow at 25% of FVC) (Quanjer et al. 1997). The results are presented as percentages of mean predicted values compared with the gender-specific height-related reference values. The cut-off limits for abnormal results were 80% for FEV1, 88% for FEV%, 62% for MEF50 and 48% for MEF25, obtained from young healthy Finnish adults (Viljanen et al. 1982). The measurements were repeated until the variation of FEV1 in two shape-appropriate curves was less than 5%. The curve with a higher FEV1 was included in the analyses (Quanjer et al. 1997).

4.3.5. Home peak flow monitoring

Two-week home PEF monitoring (Spira PEF meter, Respiratory Care Centre, Hämeenlinna, Finland) was adequately carried out by 110 of the 133 study subjects. The best value of the three consecutive measurements performed twice a day was recorded for the analyses, and the measurements were accepted if the two best results were within 20 L/min. Daily variability was considered significant if PEF morning and evening values varied over 20% in two or more days (Scheffer et al. 1992, Quanjer et al. 1997). During the second week, PEF was measured before and 15 minutes after an inhaled beta-agonist (0.5 mg terbutalin with Turbuhaler, Astra, Södertälje, Sweden) twice a day (Dahl 2000), and an improvement of ≥15% in PEF at least twice was considered significant.

The PEF monitoring was accepted if the test was performed appropriately for 10 days during the 14-day follow-up period, or if the criteria for pathological findings were fulfilled in a shorter time.

4.3.6 Skin prick testing and definition of atopy

SPTs against eight common inhaled allergens in our area (ALK; Allergologiska Laboratorium, Copenhagen, Denmark) were performed in 128 out of the 133 participants. The tested allergens were birch, timothy grass and mugwort pollens, spores of *C. herbarum*, cat and dog epithelial danders, and two house dust mites, *D. farinae and D. pteronyssimus* (Pöysä et al. 1989b). The test result was considered as positive if the average diameter of the weal was 3 mm or more and at least half of that produced by the positive control (Histamine hydrocloride 10 mg/ml) (EAACI 1993), and no reaction to the standardised quality negative control was allowed. Atopy was defined as at least one positive reaction to the 8 tested allergens.

4.3.7. Definition of asthma

Bronchial asthma was defined in two different ways, reflecting the degree of certainty of the diagnosis. For current physician-diagnosed asthma, either ongoing maintenance medication for asthma or the presence of symptoms suggestive of asthma and pathological home PEF monitoring were required. For current clinical asthma, previously diagnosed asthma and asthma-suggestive symptoms during the last 12 months were required; cases with current doctor-diagnosed asthma were included. Wheezing or prolonged (>one month) cough outside infection were accepted as symptoms suggestive of asthma.

4.4. Statistical analyses

The data were analysed using the SPSS 9.0 and 11.0 statistical packages (SPSS Inc. Chicago, IL, USA). In univariate analyses, the chi square test, Fisher's exact test and logistic regression were used for categorical variables, one-way analysis of variance for normally distributed continuous variables and Mann-Whitney U-test for non-normally distributed continuous variables. In addition, Wilcoxon signed rank test was applied for comparisons of two related samples. Logistic regression was performed for adjusted multivariate analyses.

Two-tailed tests were used in all analyses, and the statistical significance was estimated by p values or by odds ratios (OR), adjusted ORs (aOR) and their 95% confidence intervals (CI). The result was considered as statistically significant if the p

value was <0.05, or if the upper or lower limit of 95% CIs of ORs or aORs did not include the value 1.0.

4.5. Ethics

The joint Ethics Committee for Human Research of Kuopio University and Kuopio University Hospital has approved this study, and an informed consent was obtained from all study subjects and from at least one parent.

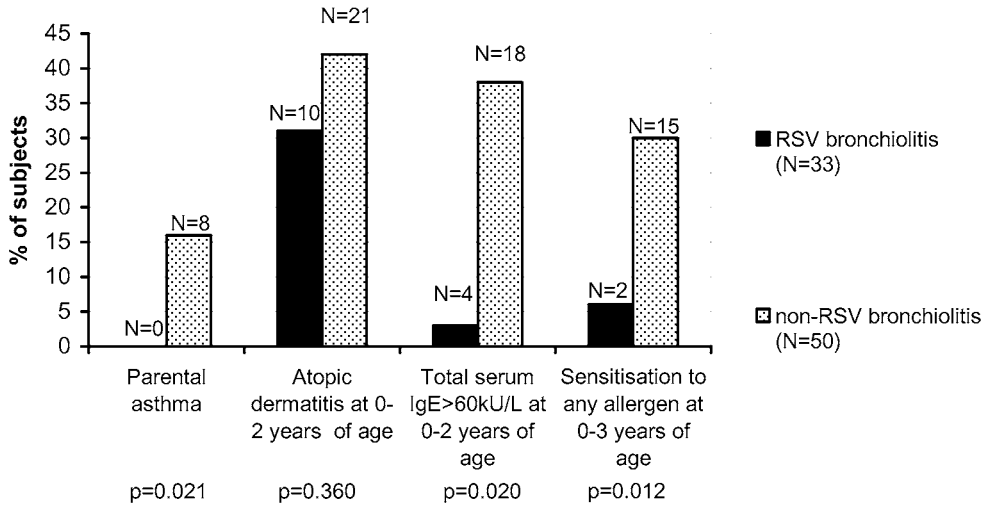
5. RESULTS

5.1. Early life characteristics of bronchiolitis patients in relation to RSV aetiology of infection

5.1.1. Baseline data in bronchiolitis patients (III)

Baseline data on atopy and parental asthma, collected prospectively until 24 months of age, are presented in relation to the RSV and non-RSV aetiology of bronchiolitis in Figure 3. Children with RSV infection were younger than those with non-RSV infection (III); the medians were 6 months (range 1-22) and 13 months (5-23), respectively ($p<0.001$) (unpublished data). In all, 10(46%) non-RSV and 1(5%) RSV bronchiolitis patients reported previous wheezing ($p=0.004$) (III). Parental asthma, elevated total serum IgE and early allergen sensitisation were present more often in the non-RSV group (unpublished data). The groups did not differ in respect with the presence of atopic dermatitis or blood eosinophilia at either cut-off level (unpublished data).

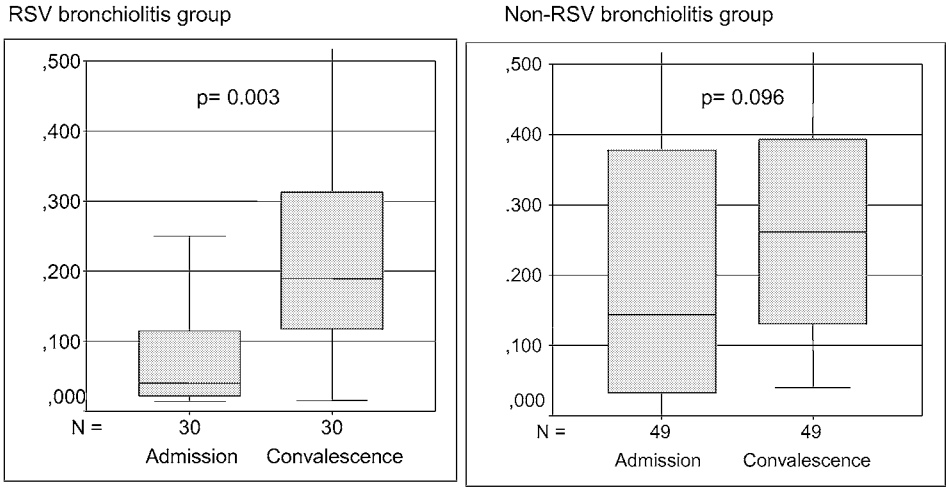
Figure 3. Parental asthma, atopy and allergic sensitisation in early life among 83 children hospitalised for RSV or non-RSV bronchiolitis.



5.1.2. Eosinophil responses during acute bronchiolitis (V)

The median eosinophil count (25-75th percentile) on admission was 0.100 x10E9/L (0.028-0.321) and on convalescence 0.231 x10E9/L (0.119-0.368). Eosinophil counts were significantly lower in RSV than in non-RSV bronchiolitis patients on admission, but not during convalescence (Fig. 4). Correspondingly, the eosinophil count decreased significantly only during bronchiolitis induced by RSV (Fig. 4).

Figure 4. Blood eosinophils on admission and on convalescence within RSV and non-RSV bronchiolitis groups, presented by box-plot graphics, including medians, 25th-75th percentiles and ranges.



p= 0.027 between RSV and non-RSV groups on admission.

5.2. Outcome in young adulthood - comparison of bronchiolitis, pneumonia and control groups (I)

5.2.1 Asthma (I)

At the median age of 19 years, asthma was present, depending on the definition, in 30-41% of those who had been hospitalised for bronchiolitis. Thus, their risk for adult asthma was 3-4 times higher than in the controls, among whom asthma was present in 11-12%. In contrast, after hospitalisation for pneumonia, the prevalence of asthma was similar to controls (Fig. 5). Ten patients were receiving maintenance medication for

asthma at the study visit. A new diagnosis of asthma, based on pathological home PEF monitoring in symptomatic participants, was made in 16 cases (Fig. 6).

Figure 5. Asthma in 88 young adults who were hospitalised for bronchiolitis or pneumonia in early life, and in 45 controls.

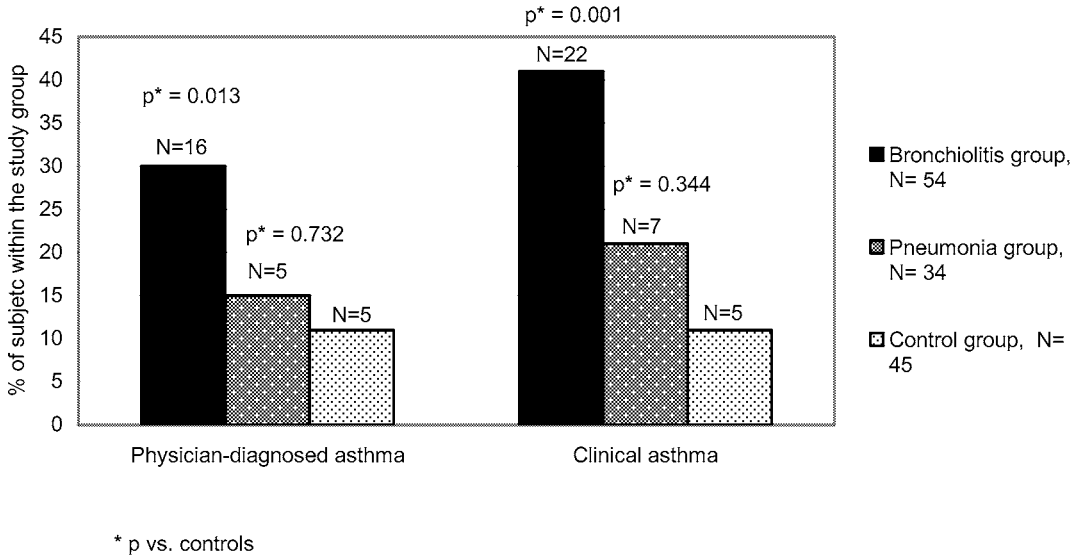
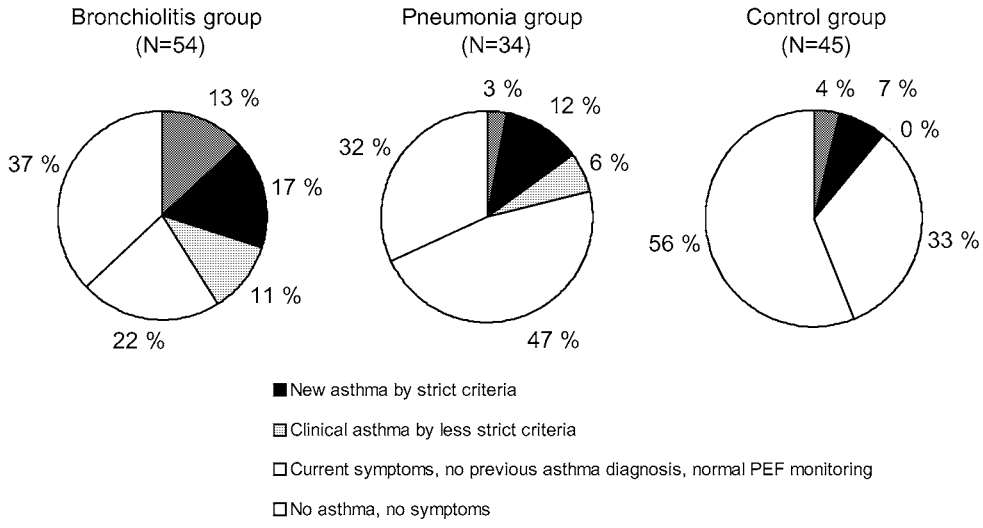


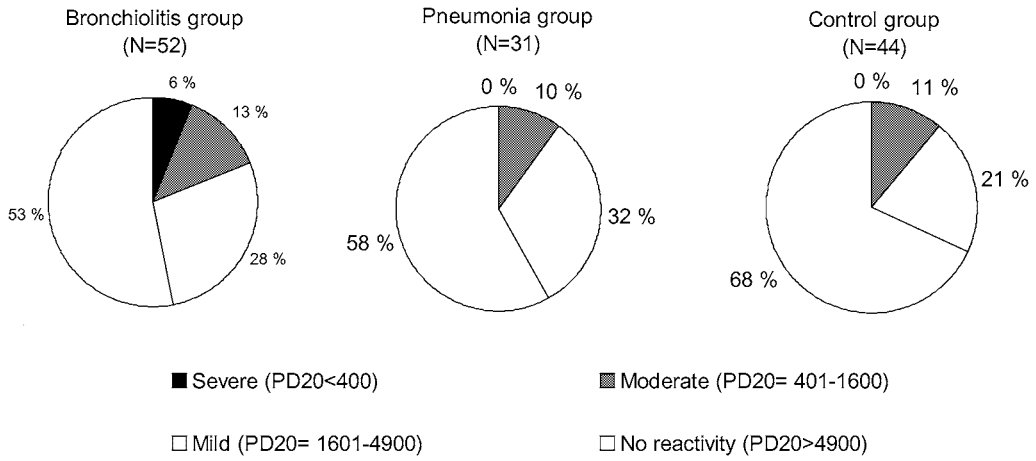
Figure 6. Asthma medication and symptoms in 88 young adults hospitalised for bronchiolitis or pneumonia in early life, and in 45 controls.



5.2.2. Bronchial reactivity (I)

Measurable bronchial reactivity (PD20 ≤ 4900) was demonstrated in 52 (41%) participants, with no significant differences between the groups at any level (Fig. 7). Severe hyper-reactivity (PD20 ≤400) was observed in only three cases, all belonging to the bronchiolitis group. Among the 16 new asthma cases, bronchial reactivity was present in 9 out of 13 participants with MIC results available (unpublished data).

Figure 7. Results of the methacholine inhalation challenge in 83 young adults hospitalised for bronchiolitis or pneumonia in early life, and in 44 controls.



There were no statistically significant differences between the groups at any level of bronchial reactivity.

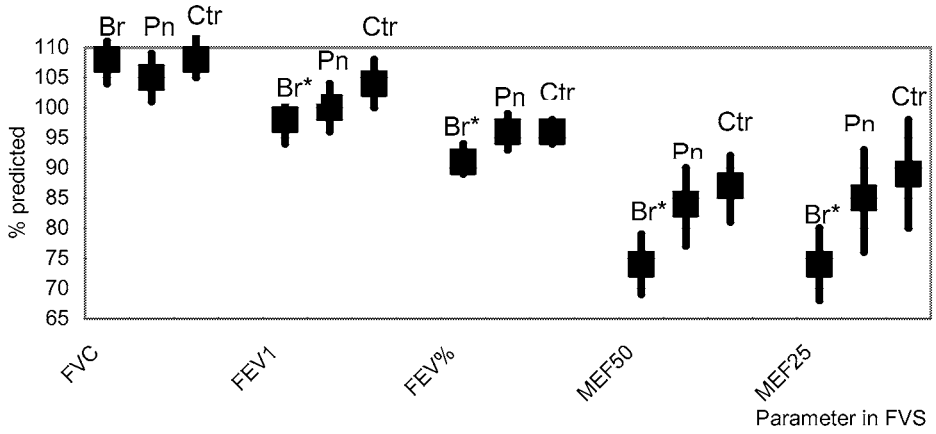
5.2.3. Lung function (I)

In FVS, the mean values (% predicted) were normal, and even the lower limits of the 95% confidence intervals were normal in all groups (Fig. 8). However, all the four expiratory flow variables; FEV1, FEV%, MEF50, MEF25, were significantly lower among the bronchiolitis group vs. the control group.

Abnormal results were observed significantly more often in the bronchiolitis group (at least one in 36%) than in the controls (11%). The difference was most obvious in abnormal MEF50 and MEF25 values (Fig. 9). Ten (71%) out of 14 new asthma cases

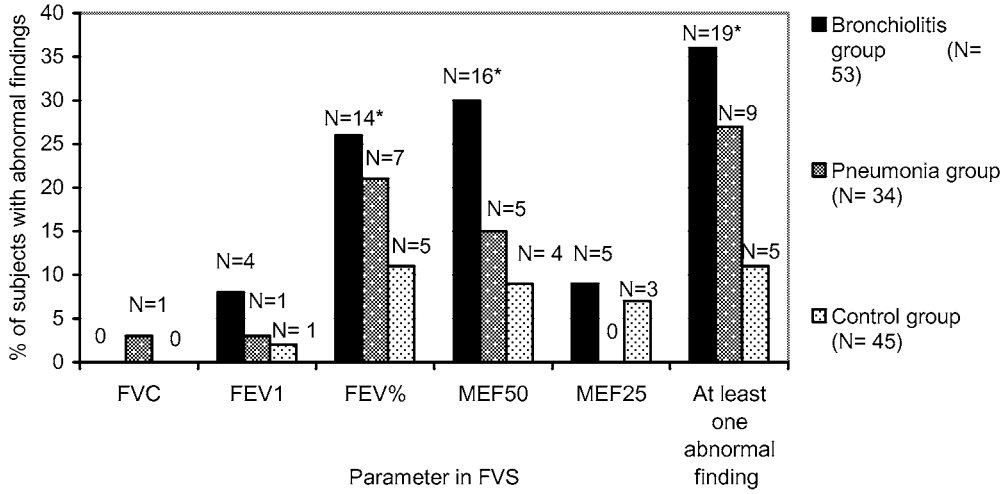
who attended the FVS had at least one abnormal result. FEV% and MEF 50 were the most sensitive indices for new asthma (unpublished data).

Figure 8. Lung function results in FVS, presented in % of predicted (mean; 95% confidence intervals) among 132 study subjects.



Br = Bronchiolitis group (N=53); Pn = pneumonia group (N=34); Ctr = control group (N=45).* p<0.05 vs. control group, ** p<0.05 vs. pneumonia and control groups.

Figure 9. Numbers of cases with abnormal results in FVS, among 87 young adult hospitalised for bronchiolitis or pneumonia in early life, and in 45 controls.



* p<0.05 vs. controls. The cut-off limit for an abnormal result in FVS was 80% of predicted for FEV1, 88% for FEV%, 62% for MEF 50 and 48% for MEF25.

5.2.4. Atopy in adulthood (I)

Current atopy, defined by at least one positive reaction in SPTs, was present in 71(55%) of the 128 study subjects tested. There was no significant difference between bronchiolitis, pneumonia and control groups. Among them, 50(70%) suffered from current allergic rhinitis or conjunctivitis ($p<0.0001$). In all, 64 subjects reported symptoms of allergic rhinitis (N=56) or conjunctivitis (N=47) during the preceding year.

Atopy was associated with asthma, which was present in 25-31% of atopic and in 11-12% of non-atopic subjects ($p= 0.021$, physician-diagnosed asthma; $p=0.008$, clinical asthma). Likewise, both measurable bronchial reactivity (51% vs. 30%, $p=0.011$) and abnormal lung function (31% vs. 16%, $p=0.061$) were detected more often among atopic than non-atopic young adults. All bronchiolitis patients who had blood eosinophil count >0.600 x10E9/L (N=5) or allergen-specific IgE >0.70 kU/L (N=8) at <24 months of age had atopy in adulthood.

5.3. Comparison of outcome in adulthood in children hospitalised for RSV and non-RSV bronchiolitis (III)

Among the bronchiolitis patients, RSV aetiology of infection was detected in 22 cases, and 32 were RSV negative. To form two virologically pure subgroups, the 10 RSV-negative cases that occurred during the epidemic were excluded from the analyses. Thus, the study group consisted of 22 RSV bronchiolitis cases and 22 non-RSV bronchiolitis cases.

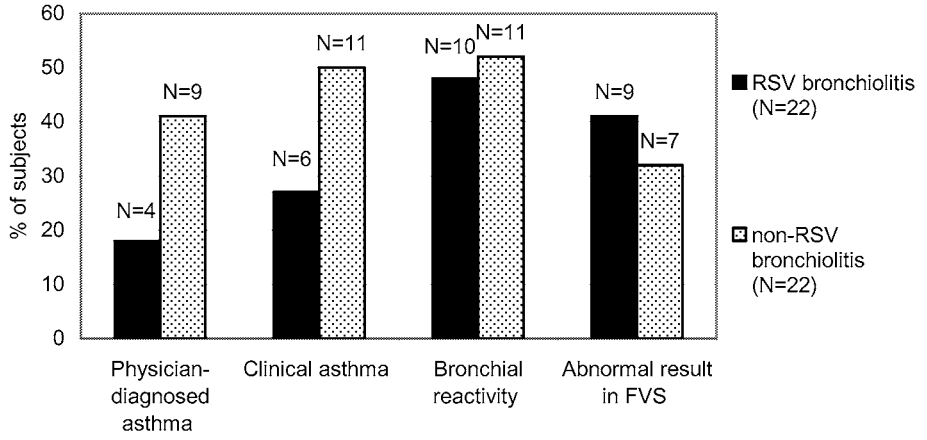
As seen in Figure 10, asthma was two times more common among non-RSV than among RSV bronchiolitis patients in adulthood, but the difference did not reach statistical significance. No differences were found in bronchial reactivity and in spirometry.

5.4. Outcome in adulthood after hospitalisation for RSV lower respiratory infection (II)

In all, 36 attendants had been hospitalised for RSV bronchiolitis or RSV pneumonia in early life. Among them, 17 to 22% had asthma and 45% had measurable bronchial reactivity in adulthood. The results did not differ significantly from the corresponding figures, 11% and 32%, in the control group. In FVS, the air flow parameters were on average within normal limits, but the values were significantly lower and abnormal

results were found more often among RSV LRTI patients than in controls (Table 12). At least one abnormal result was found in 16(44%) index subjects, compared with 11% in the controls (p<0.010).

Figure 10. Outcome in adulthood for 44 children hospitalised for RSV or non-RSV bronchiolitis in early childhood.



There were no statistically significant differences between the RSV and non-RSV groups. Bronchial reactivity designates PD20≤ 4900 μg in the MIC. Abnormal result in FVS means at least abnormal finding, see Fig 9.

Table 12. Lung function in FVS, presented in % predicted, in 35 subjects hospitalised for RSV lower respiratory tract infection in early childhood, in comparison with 45 healthy controls.

Parameter in FVS (% predicted)	Mean (95%CI)	p vs. controls	Number of abnormal results	p vs. controls
FVC	109(100-111)	0.924	0	NC
FEV1	100(95-105)	0.176	1 (3%)	1.000
FEV%	92(90-95)	0.044	12 (34%)	0.015
MEF50	78(71-85)	0.092	11 (31%)	0.019
MEF25	76(68-84)	0.031	2 (6%)	0.031

The cut-off limit for an abnormal result was 80% of predicted value for FEV1, 88% for FEV%, 62% for MEF 50 and 48% for MEF25. For the results of the control group, see Fig. 8 and 9. NC designates not possible to calculate.

5.5. Early predictive factors for adult asthma in children hospitalised for bronchiolitis

5.5.1. Atopy and atopy in parents (IV)

Asthma, but not atopy, in either parent predicted asthma in their children (Table 12). Likewise, early manifestation of atopy, defined as the presence of atopic dermatitis or elevated (>60kU/L) total serum IgE before the age of 2 years, was a significant predictor for adult asthma. However, no such association between asthma and either factor alone was observed (Table 13).

Table 13. Family history of asthma or atopy, and atopy in children in early life in relation to adulthood asthma in 52 young adults with appropriate data available.

Baseline data until 24 months of age	Physician-diagnosed asthma N=15	p vs. no asthma	Clinical asthma N=21	p vs. no asthma	No asthma N=16
Parental atopy[1]	3	0.750	6	0.797	8
Parental asthma	5	0.017	6	0.025	1
Atopic dermatitis[1]	7	0.163	11	0.055	8
Total serum IgE >60kU/L	7	0.243	9	0.306	9
Total serum IgE >150 kU/L	1	1.00	2	1.00	3
Atopic dermatitis[1] or total serum IgE >60kU/L	11	0.063	16	0.023	13

[1] Only physician-diagnosed cases included.

5.5.2 Wheezing history (IV)

As seen in Table 14, over two thirds of the participants had suffered from repeated wheezing (≥ 2 episodes) before the age of 12 months, and carried an increased risk for asthma by both criteria as adults. In contrast, age on admission, gender or the onset or recurrence of wheezing during the first year of life, were not associated with an increased risk of asthma in adulthood. There were 7 subjects with asthma in parents, and all had experienced repeated wheezing in early life. In subgroup analyses, early repeated wheezing was predictive for adult asthma by both criteria if either of the

parents had asthma, but only by the less strict criteria if there was no asthma in parents (unpublished data).

Table 14. Adulthood asthma in relation to wheezing history in early life in 52 subjects hospitalised for bronchiolitis in early life.

Wheezing symptoms	Physician-diagnosed asthma N=15	p vs. no asthma	Clinical asthma N=21	p vs. no asthma	No asthma N= 16
First wheezing episode <12 months of age	10	0.886	15	0.603	20
Repeated wheezing at the age of					
0-11 months	6	0.084	10	0.018	5
12-23 months	10	0.081	15	0.024	12
0-23 months	13	0.046	19	0.013	23

5.5.3. Sensitisation and exposure to inhalant allergens (VI)

Every third participant had been exposed to furred pets and 25% were sensitised to inhalant allergens before the age of 36 months. No association was observed between birth season, early allergen exposure or sensitisation and subsequent asthma in adulthood (Table 15). Eight children showed serum allergen specific IgE > 0.70kU/L to any allergen, and 5 of them had asthma by either criteria (NS).

5.5.4. Environmental factors (IV)

Over half (54%) of the children were breastfed longer than 4 months, 38% attended day care outside the home, and 33% lived in household with ≥4 inhabitants. These characteristics had no relation to outcome in adulthood.

Table 15. Early exposure and sensitisation to inhalant allergens in relation to adulthood asthma in 54 young adults hospitalised for bronchiolitis in early life.

Data on allergen exposure or sensitisation until 36 months of age.	Physician-diagnosed asthma N=16	p vs. no asthma	Clinical asthma N=22	p vs. no asthma	No asthma
Birth season					
winter to spring	7	0.407[1]	9	0.311[1]	10
summer	6		9		10
Autumn	3		4		12
Exposure to cats or dogs[2]	3	0.492	5	0.543	12
Specific IgE ≥0.35kU/L					
to cat or dog dander[2]	3	0.676	3	1.000	4
to seasonal pollens[3]	4	0.208	6	0.140	3
to any tested allergen	6	0.289	8	0.213	6

[1] p between 3 seasons. [2] One subject was both sensitised and exposed to pets, and exclusion of this case from the analysis did not change the results. [3] Timothy, birch and mugwort pollens.

5.6 Early life factors in relation to adulthood lung function among children hospitalised for bronchiolitis in early life (IV)

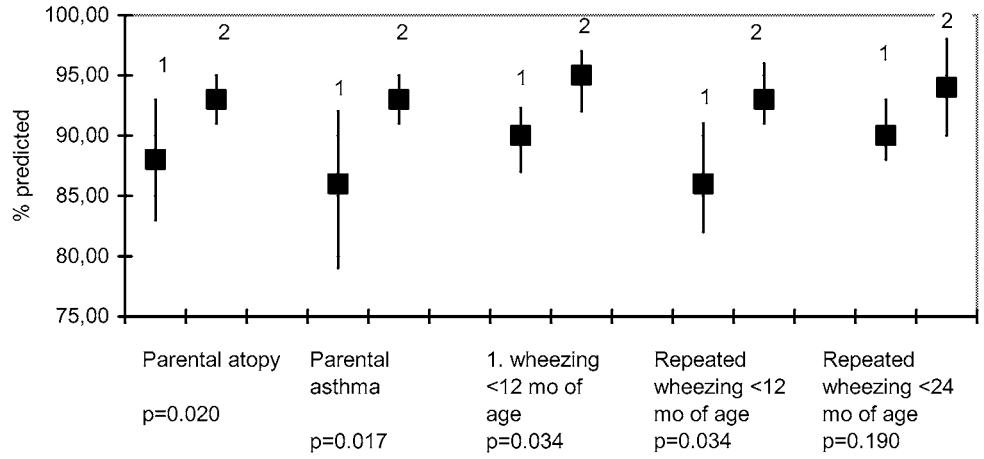
5.6.1. Bronchial reactivity (IV)

Gender, age on admission, first-year onset of wheezing, parental asthma, elevated total serum IgE or atopic dermatitis in early life and the environmental factors assessed in the study were not significantly associated with bronchial reactivity in adulthood. In contrast, repeated wheezing episodes before 12 months of age predicted bronchial hyper-reactivity in adulthood (p=0.031). BHR (PD20≤4900μg) was present in adulthood in 86% of those sensitised to pets and in 78% of those sensitised to pollens in early life, vs. 61% of those with no such sensitisation (NS; unpublished data).

5.6.2. Flow -volume spirometry (IV)

When lung function parameters were analyzed as continuous variables, parental asthma was associated with lower values in all obstruction indices (FEV1, FEV%, MEF50 and MEF25); the onset of wheezing at 0-11 months of age with lower values in FEV%; repeated wheezing at 0-11 months of age with lower values in FEV%, MEF50 and MEF25; and repeated wheezing at 0-23 months of age with lower values in MEF50 (Figure 11). None of the tested risk factors was significantly associated with FVC in adulthood.

Figure 11. Early-life factors in relation to FEV%, presented in % of predicted (mean, 95% confidence intervals) among 52 young adults hospitalised for bronchiolitis in early life.



1= risk factor present ; 2= risk factor not present

Table 16. Lung function abnormalities in relation to parental asthma or atopy, and early onset of wheezing history in 52 young adults hospitalised for bronchiolitis in early life.

Risk factor	All N=52	FEV1 N=4	FEV% N=14	MEF50 N=16	MEF25 N=5	≥1 abnormal results N= 19
Parental atopy	14	2/ 3 p=0.186	7/ 13 p=0.029	8/ 15 p=0.016	3/ 4 p=0.06	9/ 18 p=0.013
Parental asthma	7	2/ 3 p=0.048	4/ 13 p=0.065	5/ 15 p=0.02	2/ 4 p=0.089	5/ 18 p=0.052
First wheezing episode <12 months of age	35	3 p=1.00	13 p=0.021	13 p=0.207	5 p=0.159	14 p=0.058
Repeated wheezing at the age of						
0-11 months	15	2 p=0.569	7 p=1.00	8 p=0.044	4 p=0.021	8 p=0.115
12-23 months	27	2 p=1.00	7 p=1.00	10 p=0.376	4 p=0.352	10 p=0.938
0-23 months	36	4 p=0.299	10 p=1.00	13 p=0.331	5 p=0.300	14 p=0.599

Data on parental asthma or atopy was available in 50 subjects. The cut-off limit for an abnormal result in FVS result was 80% of predicted value for FEV1, 88% for FEV%, 62% for MEF 50 and 48% for MEF25. Statistical significance: p vs. cases with the corresponding risk factor not present.

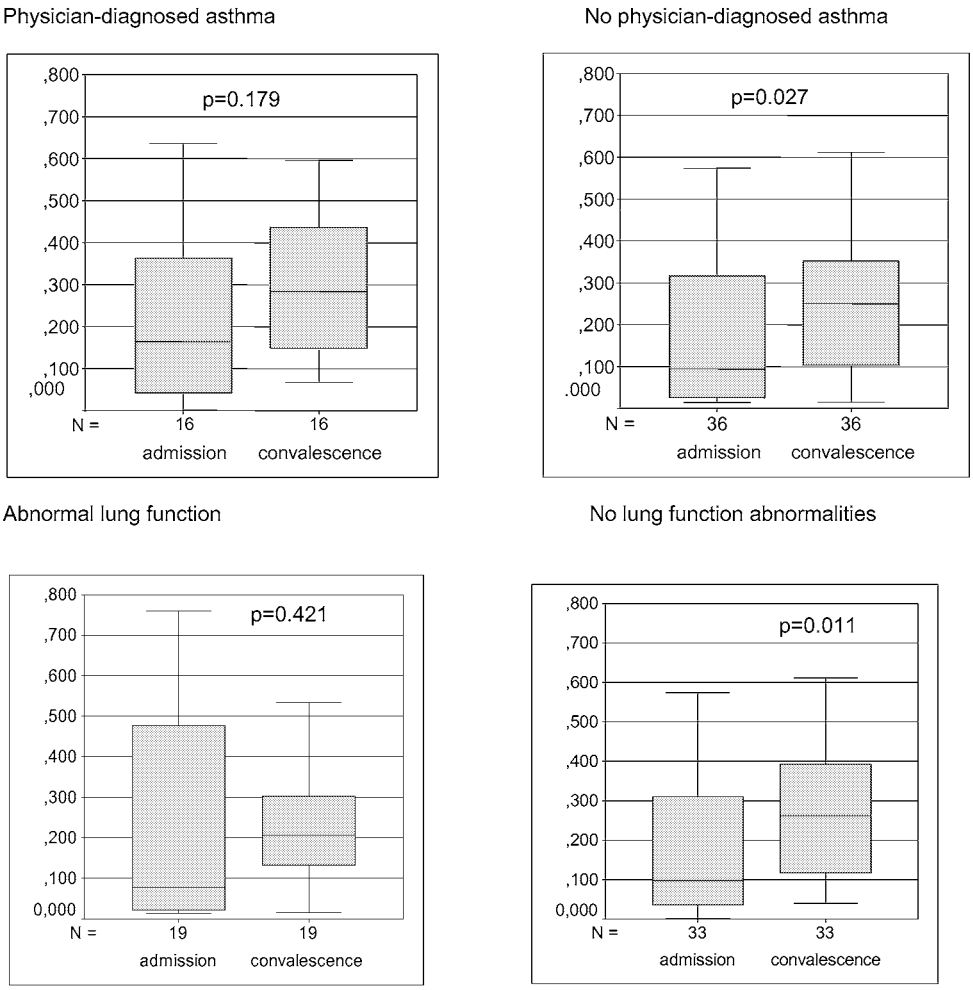
5.7. Blood eosinophils as markers for adulthood outcome in bronchiolitis patients (V)

Neither blood eosinophils on admission nor during convalescence were related to adult hyper-reactivity or asthma by either definition. In contrast, abnormal lung function was seen in 6 of 7 children with blood eosinophil count >0.450 x 10E9/L on admission vs. 13/ 46 children with lower eosinophil count (p=0.006). Eosinophils were >0.600 x 10E9/L on admission in 3 children and all of them had lung function abnormalities in adulthood.

Eosinophils decreased significantly (>0.070 x10E9/L; 75th percentile for decrease) during acute bronchiolitis among those who did not have physician-diagnosed asthma

(p=0.027) nor lung function abnormalities (p=0.011, unpublished data) as adults (Fig. 12). No such an eosinopenic response was seen among participants with asthma by either criteria, bronchial reactivity at any level, or any lung function abnormality. The association between the lack of eosinopenic response and lung function abnormalities was present in RSV patients only.

Figure 12. Blood eosinophils on admission and on convalescence, presented by box-plot graphics including medians, 25-75th percentiles and ranges in relation to asthma and lung function abnormalities in adulthood.



Blood eosinophils are expressed as cells x10E9/ L.

When blood eosinophils obtained on admission and on convalescence were analysed as combined, low eosinophil count (< 0.150 x10E9/L) on both occasions was observed in 19 children. Eleven of them were followed until adulthood, and none had physician-diagnosed asthma (p= 0.039) and only 3(27%) had clinical asthma (p=0.493). Blood eosinophilia, estimated at cut-off levels 0.300 x 10E9/L (n=25/83) and 0.450 x 10E9/L (n=20/83) was not significantly associated with BHR, lung function abnormalities, or adult asthma by either definition (unpublished data). Eosinophils were >0.600 x 10E9/L in five children. Two of them had current physician-diagnosed (NS) and three had clinical asthma in adulthood (NS). Measurable bronchial reactivity was present in all 5 participants (p=0.051) and abnormal lung function in 3 (NS).

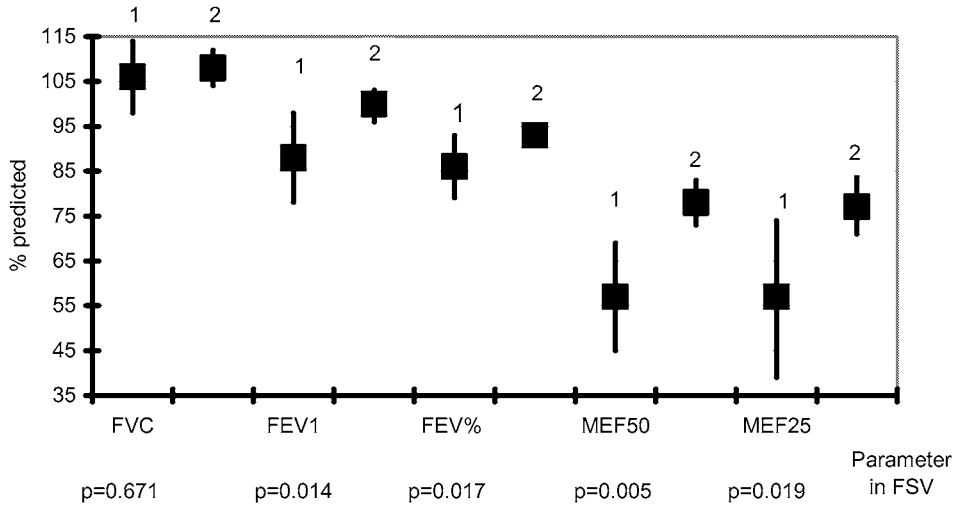
5.8. Consequences in adulthood of early exposure to passive smoking among children hospitalised for bronchiolitis in early life (IV)

In all, 15(29%) mothers and 24(46%) fathers had smoked when their child was below 24 months of age. Maternal, but not paternal, smoking resulted in lower level of lung function (Fig. 13) and a 4-fold (95%CI 1.2-14.3) risk for abnormalities in FVS. The difference was most evident in small airways, as 53% of smoking and 22% of non-smoking mothers' children had a decreased MEF50 (p=0.041). Both parents smoked in 11 cases, and 10 of their off-springs achieved at least one abnormal result in FVS in adulthood (p=0.012, unpublished data).

All 15 mothers had started smoking before their child was 6 months old, and only 2 of the smoking mothers had asthma. The risks for abnormal lung function remained significant when analysed specifically for maternal smoking at the ages of <6 months and <12 months. Data on smoking during pregnancy was not available.

There were 29(56%) participants who had at least one parent who smoked, but no association was found with current smoking, asthma or bronchial reactivity in adulthood. However, all 5 participants who smoked more than 20 cigarettes a day came from smoking families.

Figure 13. FVS results, presented in % predicted (mean; 95% confidence interval), in relation to exposure to maternal smoking at the age of 0-2 years among 52 young adults hospitalised for bronchiolitis in early life.



1 = mother smoked; 2 = mother did not smoke

5.9. Results of multivariate analyses.

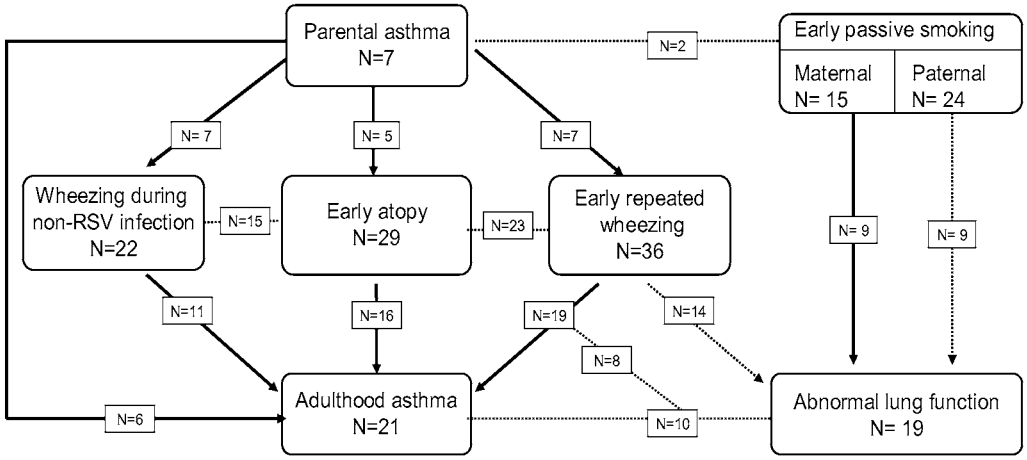
The results of the final multivariate analyses performed by logistic regression and adjusted for gender, age on admission, and current smoking, are presented in Figure 14. Wheezing during respiratory infection not induced by RSV (aOR 4.5; 95%CI 0.9-22.6), repeated wheezing episodes (aOR 8.2;95%CI 1.5-43.7) and atopy (aOR 5.6; 95%CI 1.5-21.8) in early childhood were significant predictors for adult asthma. When the analyses were continued by adding all the three factors as covariates in the same logistic regression model, only repeated wheezing in early life remained as an independent predictor for adult asthma (aOR 7.0; 95%CI 1.1- 45.1).

The combination of all three risk factors was present in 13 subjects, and 8(62%) of them had asthma in adulthood. The risk was 5-fold, compared to those 10(29%) bronchiolitis patients without such a risk factor combination (aOR= 5,3; 95%CI 1.2-23.9). Parental asthma was significantly related to all three asthma predictive factors and therefore, finally also to adult asthma. Only 2 of the 7 asthmatic parents had smoked when their child was below two years of age.

Lung function abnormalities were present in 10 asthma patients, and 8 of them had experienced repeated wheezing episodes in early life. In adjusted logistic regression,

maternal smoking during the first 24 months of the child predicted independently abnormal lung function in adulthood (aOR 4.2; 95%CI 1.1-15.6), but paternal smoking did not (aOR 0.9; 95%CI 0.3-3.0). In further adjustments with paternal smoking, maternal smoking remained as an independent predictor for adulthood lung function abnormalities (aOR 9.5; 95%CI 1.7-52.2).

Figure 14. Multivariate analyses by logistic regression: early predictive factors for adult asthma among 52 subjects hospitalised for bronchiolitis in early life.



Continuous arrows designate statistically significant associations. Numbers on arrows and lines demonstrate the numbers of subjects with both factors present.

6. DISCUSSION

6.1. Design of the study

This clinical study was a prospective 18- to 20-year follow-up of children hospitalised for bronchiolitis or pneumonia at the age of 0-23 months during a surveillance period of 12 months in 1981-1982. Data on possible early predictors for asthma were prospectively registered until 24 months of age by 6 months periods. Three clinical follow-up studies were arranged at the ages of 2-3 (Korppi et al. 1993), 4.5-6 (Kuikka et al. 1994) and 8.5-10 years (Korppi et al. 1994). In addition, a postal questionnaire study on asthma and allergy status was carried out at 13.5-16 years of age (Hyvärinen et al. 2005a). The present phase of the study was performed in 2000, when the study subjects were 18.5 to 20 years old.

6.1.1. The study population

The study cohort of the present thesis represents a selected population of bronchiolitis patients with a major risk for subsequent wheezing and asthma (Martinez et al. 1999). In concordance with previous reports, that 1 to 3% of young children require hospital treatment for bronchiolitis (Rakes et al. 1999, Boyce et al. 2000, Kneyber et al. 2000, Henderson et al. 2005, Holman et al. 2004, Shay et al. 1999), the bronchiolitis patients of the present thesis formed 1.0 to 1.5% of the <24-month old population in the study area.

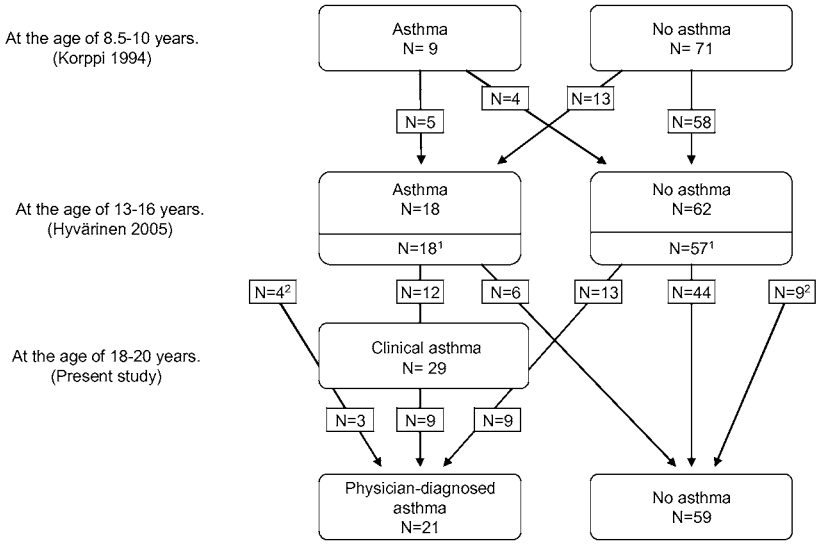
The original study design did not include healthy control children, but pneumonia patients formed a non-wheezing control group for bronchiolitis cases through childhood. In the present study in adulthood, the subjects from a prospective atopy prevention study, started at birth in 1979-1980, formed the control group (Pöysä et al. 1988). The cases and controls were about the same age, and they came from the same population and the same geographical area. Only two controls had wheezed in early life, and neither was hospitalised. Thus, the study design offered a possibility to compare former bronchiolitis patients not only with controls with no early hospitalisation or wheezing, but also with subjects who were hospitalised for non-wheezing lower respiratory infection in early life.

6.1.2 Definition and persistence of asthma

The diagnosis of physician-diagnosed asthma was rather strict, and was assessed according to the national guidelines for good clinical practice in our country (Finnish Society for Pulmonologists 2000). Because bronchial asthma is a fluctuating condition with a risk of under-diagnosis without sufficient follow-up (Zhang et al. 2002), less strict asthma criteria were constructed based on current asthma symptoms and whether an asthma diagnosis had ever been made previously.

The long-term follow-up of the present cohort confirmed the fluctuating nature of asthma also in children and adolescents. From 8.5-10 to 13.5-16 years of age, 44% of asthma cases improved and 56% persisted (Hyvärinen et al. 2005a). The results were close to the 48% persistence of wheezing between 8 to 13 years found in a retrospective post-bronchiolitis study from the USA (Mc Connochie et al. 1989). The respective figures between 13.5-16 and 18-20 years were 33% and 67% in the present study (Figure 15).

Figure 15. The persistence of asthma from 8 to 20 years of age among 80 subjects hospitalised for bronchiolitis or pneumonia in early life.



[1] Number of subjects attending to the follow-up both at 13-16 years and at 18-20 years of age;
[2] Number of subjects attending to the follow-up at 18-20 years, but not at 13-16 years of age.

6.1.3. Comparable studies

Thus far, only one comparable post-bronchiolitis follow-up study, continuing from infancy until adulthood, has been published (Wennergren et al. 1992, Wennergren et al. 1997, Goksör et al. 2006). Also in the prospective study from Gothenburg, Sweden, the design was initially non-controlled (Wennergren et al. 1992, Wennergren et al. 1997), but in the follow-up at the age of 17-20 years, population-based controls without any earlier systematic follow-up were available (Goksör et al. 2006). In addition, two prospective post-bronchiolitis follow-up studies have continued until teen-age: a controlled study after RSV bronchiolitis at <12 months of age from Borås, Sweden (Sigurs et al. 1995, Sigurs et al. 2000, Sigurs et al. 2005), and a non-controlled study after mainly RSV and rhinovirus bronchiolitis at <24 months of age from Kuopio, Finland (Reijonen et al. 2000, Kotaniemi-Syrjänen et al. 2002, Hyvärinen et al. 2005b). In addition, adulthood lung function after hospitalisation for bronchiolitis in early life has been evaluated in two recent retrospective studies (Larouche et al. 2000, Gomez et al. 2004).

6.2. Prevalence of asthma and wheezing symptoms in adulthood.

6.2.1. Comparison with population-based studies.

In population-based studies, the prevalence of asthma has been 3 to 7% among young Finnish adults (Kotaniemi et al. 2002, Huurre et al. 2004, Latvala et al. 2005). An additional 19 to 23% have transient symptoms suggestive of asthma (Lindström et al. 2001, Pallasaho et al. 2005). Thus, the figures are similar to the 10-22% in the controls of our study. The present asthma prevalences, 30-41% after bronchiolitis and 15-21% after pneumonia, are high, but compatible with the 38-43% prevalence of adult asthma reported in other post-bronchiolitis studies (Larouche et al. 2000, Goksör et al. 2006). The present results, in line with recent data from Sweden (Goksör et al. 2006), show that asthma often relapses in young adults who have wheezed in early life.

In all, 62% of the strict asthma diagnoses were made during the study visit. In addition, there were 8(6%) potential asthma cases with less strict asthma criteria. Our findings suggest that there are a considerable number of under-diagnosed and untreated asthma cases among young adults. In accordance, undiagnosed asthma comprised about one third of all 54 asthma cases among 495 school children aged 12-

15 years in a recent cross-sectional study from Denmark (Sierstedt et al. 1998). In that study, asthma diagnosis was based on a combination of respiratory symptoms and a pathological result in lung function, home PEF monitoring, or methacholine inhalation challenge. The cut-off level for bronchial hyper-reactivity was not reported. In the present study, severe hyper-reactivity was rare, suggesting that at least a proportion of asthma cases may actually have a mild disease with episodic symptoms. On the other hand, all patients with a new asthma diagnosis showed pathological results during home PEF monitoring as an objective measure of bronchial lability.

6.2. 2. Comparison with post-bronchiolitis studies

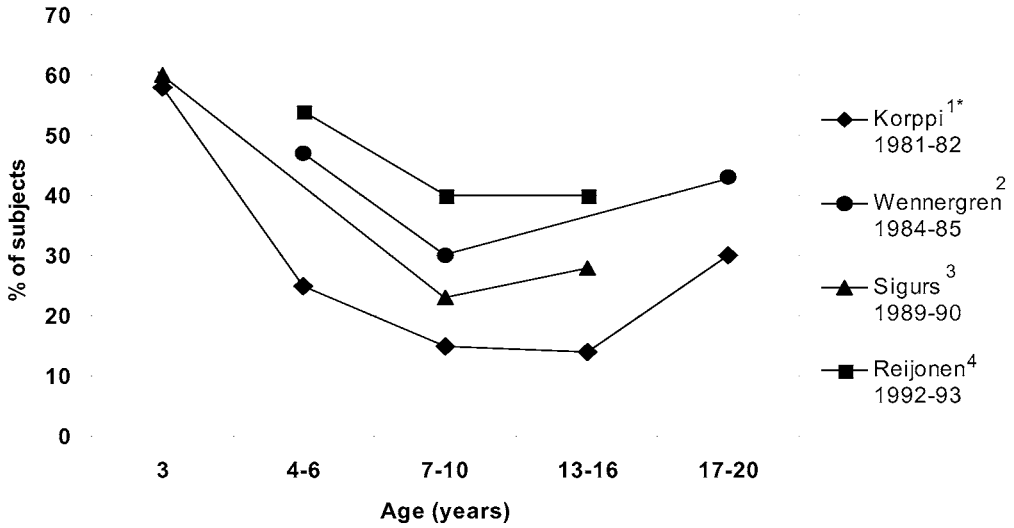
In the present study, asthma risk remained elevated, although with diminishing tendency through school age after hospitalisation for bronchiolitis in early life, as seen also in previous post-bronchiolitis studies (Sly et al. 1989, Wennergren et al. 2001, Kotaniemi-Syrjänen et al. 2002, Sigurs et al. 2001, Taussig et al. 2003). However, asthma prevalence began to increase again at puberty and by the end of the second decade of life, over third of former bronchiolitis patients had at least mild asthma. A similar pattern has been observed in all the four prospective post-bronchiolitis studies continuing at least until teen age, as demonstrated in Figure 16.

Through childhood, the asthma prevalence was lowest in the present cohort (Korppi 1982-83) and highest in the later Finnish cohort (Reijonen et al. 1992-93) reflecting the increase of paediatric asthma observed in all developed countries during the last decades (Upton et al. 2000, Akinbami et al. 2002, Latvala et al. 2005). In Eastern Finland, this increase began later than in most European countries, with a prevalence of asthma at school age of 0.6% in 1980 (Pöysä et al. 1991) and 4.0% in 1994 (Remes et al. 1996). The differences may also, at least partly, derive from different diagnostic criteria applied in the studies. In the study from Gothenburg, Sweden, (Wennergren et al. 1984-85), asthma was classified as severe, moderate and mild according to the frequency of wheezing episodes (Wennergren et al. 1992, Wennergren et al. 1997, Goksör et al. 2006). At least mild asthma was present in 43% at the age of 17 to 20 years (Goksör et al. 2006), which corresponded well to the 41% prevalence of adult asthma by less strict criteria in the present thesis. Likewise, severe to moderate asthma was compatible with physician-diagnosed asthma in the present study. The prevalences of asthma of 14%, 10 % and 14% at preschool, early school and adult age

in the Gothenburg study (Wennergren et al. 1992, Wennergren et al. 1997, Goksör et al. 2006) were rather similar to the figures of the present cohort, as seen in Figure 16.

In the other Swedish cohort, asthma was defined as the occurrence of ≥3 physician-diagnosed wheezing episodes (Korppi et al. 1994, Sigurs et al. 1995, Sigurs et al. 2000). The definition was identical in the present study until school age. Thus, asthma prevalences were quite similar in the two studies.

Figure 16. Prevalence of asthma during childhood after hospitalisation for bronchiolitis at <24 months of age. The four prospective follow-up studies continuing until teen-age or longer are included.



present thesis; [2]Wennergren 1992, Wennergren 1997, Goksör 2006; [3]Reijonen 2000, Kotaniemi-Syrjänen 2002, Hyvärinen 2005; [4]Sigurs 1995, Sigurs 2000, Sigurs 2002, Sigurs 2005. In the present cohort, the figures by strict asthma criteria are presented for 13-16 and 17-20 years of age.

6.3. Bronchial reactivity in adulthood after hospitalisation for bronchiolitis in early life

In the present study, at least mild bronchial reactivity was common, and no association between hospitalisation for bronchiolitis and adulthood BHR was observed. Our results differ from previous studies indicating that the risk for BHR is elevated for several years after bronchiolitis (Pullen et al. 1982, Kattan et al. 1999). The results in methacholine inhalation challenge may be partly interpreted by asthma medication. In this study, 7 of the 10 patients receiving maintenance medication for asthma came

from the bronchiolitis group, and inhaled corticosteroids decrease methacholine responsiveness (Gyllfors et al. 2006).

In line with the earlier observations from the Tucson study until teenage (Taussig et al. 2003, Martinez and Godfrey 2003), BHR was present more often in adulthood than in non-sensitised subjects if the subjects had been sensitised to pets in early life. However, the result did not reach statistical significance due to the small number of sensitised participants. In addition, the persistence of BHR and asthma until adulthood was strongly associated with the concurrent development of atopy, a relationship previously established in school-aged children from 9 to 15 years of age (Burrows et al. 1995). In the present cohort, neither atopy nor BHR in adulthood were related to hospitalisation for bronchiolitis or pneumonia in early life, opposite to two previous retrospective post-bronchiolitis studies (Larouche et al. 2000, Gomez et al. 2004).

6.4. Lung function in adulthood after hospitalisation for bronchiolitis in early life

Thus far, there are only two previous, retrospective, studies on the adulthood lung function after bronchiolitis indicating either no association with lung function in adulthood (Gomez et al. 2004) or a decrease in FEV1 and FEV1/ FC´VC values (Larouche et al. 2000). In the present study, the risk for abnormal lung function was 4-fold among former bronchiolitis patients. Former bronchiolitis patients also had lower FEV1, FEV%, MEF50 an MEF25 than in the controls regardless of the asthma status. The results are in line with previous findings from two population-based studies that bronchiolitis patients have reduced lung function until 11 to 16 years of age irrespective of wheezing symptoms (Turner et al. 2004, Morgan et al. 2005).

Parental asthma or atopy and onset or recurrence of wheezing episodes below one year of age were significantly associated with lung function impairment in adulthood. In accordance, parental atopy and recurrent wheezing in infancy were related to significantly diminished lung function at the age of one year in a cohort study from Manchester, UK, (Murray et al. 2002). Thus, our results give support to the idea of congenitally lower size of airways predisposing to breathing difficulties already at a very early age (Martinez et al. 1988, Young et al. 1995, Dezateux et al. 1997, Turner et al. 2002, Murray et al. 2002). In addition, blood eosinophilia during acute infection and lack of an eosinopenic response to acute infection were significant predictors for

abnormal lung function in adulthood, perhaps due to the promotion of remodelling by eosinophils (Zagai et al. 2004).

6.5. Adulthood outcome in relation to viral aetiology of lower respiratory tract infection

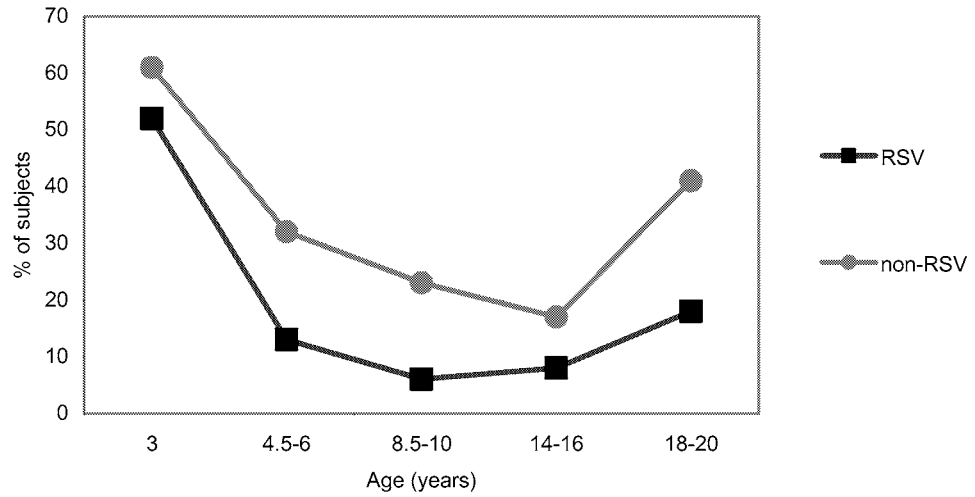
6.5.1. Comparison of RSV and non-RSV bronchiolitis patients

In the present study, RSV was the most common causative agent for bronchiolitis, present in 40% of the cases. Other viruses or *Mycoplasma pneumoniae* were detected in 15% (Korppi et al. 1986). Thus, the numbers of other detected respiratory viruses were too small to allow for stratified analyses. Therefore, a combined non-RSV bronchiolitis group was constructed.

On the study entry, 25 years ago, there were no means to detect recently found bronchiolitis causing viruses, such as human metapneumovirus, rhinovirus or enteroviruses (Kotaniemi-Syrjänen et al. 2002, Papadopoulos et al. 2002, Jartti et al. 2004, Xepapadaki et al. 2004). Thus, many of the 35% of bronchiolitis cases with no viral findings in the present study may have been caused by these viruses. Typical features for non-RSV bronchiolitis patients were, compared with RSV bronchiolitis cases, the presence of asthma in parents, older age on admission, early atopy, lack of eosinopenic response and early sensitisation to inhaled allergens – all factors known to be associated with later asthma (Martinez 1998, Castro-Rodriguez 2000). Because the non-RSV bronchiolitis patients had also more often experienced previous wheezing episodes prior to hospitalisation, they might actually have had asthma already on admission.

As seen in Figure 17, the risk for adulthood asthma was, in accordance with earlier studies until teen age (Stein 1999, Kotaniemi-Syrjänen 2003, Hyvärinen 2005b), clearly higher after hospitalisation for non-RSV than for RSV bronchiolitis. In adulthood, the difference was even clearer than at earlier ages. Thus, early wheezing induced by viruses other than RSV seems to reveal those individuals who are susceptible to asthma in later life.

Figure 17. Prevalence of asthma during childhood and early adlulthood after hospitalisation for RSV bronchiolitis at <2 years of age, compared with bronchiolitis induced by other viruses.



References: Korppi 1993, Kuikka 1994, Korppi1994, Hyvärinen 2005a, and data of the present thesis. The strict asthma criteria were used for 14-16-year and 18-20-year figures.

6.5.2. RSV lower respiratory tract infection

In prospective follow-up studies, children with RSV induced bronchiolitis and pneumonia in early life have presented with a lowered level of lung function at least until 11-13 years of age (Stein et al. 1999a, Sigurs et al. 2005). Our results extend these observations until adulthood, because FEV% and all MEF indices were significantly lower among subjects hospitalised for RSV bronchiolitis or pneumonia than among healthy controls. However, RSV infection showed no association with adult asthma, in line with the results of the Tucson study that followed children until 13 years of age (Stein et al. 1999a).

Thus, RSV is a highly invasive virus may cause transiently elevated risk for wheezing and even baby asthma, but does not increase the risk of asthma in children with no susceptibility to asthma in adulthood (Stein et al. 1999a). However, our findings, along with others (Stein et al. 1999a, Castro-Rodriguez et al. 1999), suggest that RSV may induce persistent deficits in lung function. These deficits may lead to further deterioration of lung function and even to COPD in middle age (Edwards et al. 2003).

6.6. Prediction of outcome in adulthood in children hospitalised for bronchiolitis in early life

In the present study several factors in early life were evaluated as potential predictors for adult asthma and lung function abnormalities. Data on these potential risk factors were prospectively registered by 6-month periods until 24 months of age, which allowed the estimation of the influence of different factors in relation to the time and age points. Possibly due to large number of confounding factors present during childhood, most early life environmental factors, like the number of people in the household, day-care attendance and breastfeeding, had no influence on adulthood outcome in this selected cohort of children, although some of these have been significant predictors for adult asthma in population-based studies (Bodner et al. 2000, Svanes et al. 2002).

6.6.1. Early wheezing history, atopy and parental history of asthma.

Among all of the analysed factors, parental asthma, early atopy, repeated wheezing and wheezing during non-RSV infection were the only independent predictors for adulthood asthma after hospitalisation for bronchiolitis in early life. All factors were associated with each other, which, in accordance with earlier studies (Mc Connochie et al. 1989, Castro-Rodriquez et al. 2000, Hyvärinen et al. 2005, Sigurs et al. 2005, Goksör et al. 2006), stresses the important role of inheritance in the development of persistent asthma. The results of this thesis extend the impact of the Tucson childhood asthma predictive index until adulthood, at least for the major criteria of asthma, which are asthma in parents and repeated wheezing or atopic dermatitis in the children (Castro-Rodriquez et al. 2000, see Table 11). In this thesis, early atopy was defined by either atopic dermatitis (Martinez et al. 1995, Castro-Rodriquez et al. 2000, Hyvärinen et al. 2005b) or elevated IgE (Stein et al. 1997, Sherrill et al. 1999, Rhodes et al. 2001, Hyvärinen et al. 2005b) before 2 years of age. Neither alone, probably due to insufficient statistical power, was predictive for adult asthma.

6.6.2. Early sensitisation to inhalant allergens

In the present study, early sensitisation to inhalant allergens, defined by the detection of allergen-specific IgE before the age of 36 months, was rare and had no association with adulthood asthma. Accordingly, only a minority of the future persistent atopic

wheezers from the Tucson study showed a positive allergic reaction to inhalant allergens before the age of two years (Martinez and Godfrey 2003). In fact, IgE against inhalant allergens normally becomes detectable in serum months or even years after the first exposure, and early sensitisation to these allergens predicts recurrent wheezing and asthma in later childhood (Reijonen et al. 2000, Kotaniemi-Syrjänen et al. 2002, Martinez and Godfrey 2003, Hyvärinen et al. 2005b).

In the only previous study concerning allergic sensitisation in early life and asthma in adulthood, skin prick test reactivity to food allergens during the first year of life predicted asthma in adulthood in children of atopic parents. A similar association was seen for inhalant allergens, but in adjusted multivariate analyses, only sensitisation to food allergens remained as an independent risk factor (Rhodes et al. 2002).

In the present study, early sensitisation to pets predicted bronchial hyper-reactivity in adulthood, suggesting that the statistical association with adult asthma might be lost due to the small number of asthma patients or numerous confounding factors present during the 18 to 20 year follow-up.

6.6.3 Early exposure to inhalant allergens

In the present study, no association between early exposure to pets or pollens and asthma in adulthood was found, in line with the recent post-bronchiolitis follow-up from Sweden (Goksör et al. 2006). In population-based studies, the association has been dependent on the parental history of asthma (Remes et al. 2001, Sandin et al. 2004) and the age on the onset of wheezing (Sandin et al. 2004).

Likewise, we found no association between the season of birth and adulthood asthma, and thus our results do not support the assumption that early exposure to seasonal pollens might influence the pattern of allergic sensitisation and further development of allergic diseases and asthma (Wjst et al. 1992, Nilsson et al. 1997, Saitoh et al. 2001, Kihlström et al. 2002) – not at least among children who have been hospitalised for bronchiolitis in early life.

Unfortunately, the small size of the present cohort did not allow any stratified analyses according to parental asthma or age during the first wheezing episode. It is also probable that the association of early exposure to pets (or other environmental factors) may be different in a general population and in selected patient populations,

such as our study population, which included patients hospitalised for bronchiolitis in infancy.

6.7. Blood eosinophils as markers for adulthood outcome in children hospitalised for bronchiolitis in early life

No association between eosinophilia at any cut-off level in infancy and adult asthma was observed in the present study. The result is in accordance with the only previous post-bronchiolitis study on blood eosinophils in early life and asthma at teen age (Hyvärinen et al. 2005b) In contrast, high eosinophils during acute bronchiolitis predicted abnormal lung function in adulthood, in line with the idea that blood eosinophilia may enhance airway remodelling and lead to persistently impaired lung function (Zagai et al. 2004). In addition, our results extend into adulthood the previous findings that early childhood eosinophilia is associated with the development of atopy in later childhood (Kajosaari et al. 1981, Borres et al. 1995).

An eosinopenic response to acute bronchiolitis was seen only in RSV bronchiolitis patients who, on average, had a favourable outcome in adulthood. In addition, lack of an eosinopenic response to acute bronchiolitis was a significant predictor for adult asthma and abnormal lung function, in accordance with the findings from the Tucson study until 6 years of age (Martinez 1998). Persistently low eosinophils were related to lower asthma risk, as observed earlier in children followed until the age of 11 years (Karakoc et al. 2002).

6.8. Outcome in adulthood after early exposure to passive smoking among children hospitalised for bronchiolitis in early life

In our country, 30% of men and 20% of women are current smokers (Heloma et al. 2004, Giskes et al. 2004). Moreover, the trend is increasing in women. Thus, a considerable proportion of young children are exposed to passive smoking in early life. Parental, particularly maternal, smoking is related to an increased risk for wheezing and asthma (Strachan et al. 1996, Wennergren et al. 1997, Stein et al. 1999, Dezateux et al. 2001, Gilliland et al. 2001, Larsson et al. 2001, Svanes et al. 2004, Jaakkola et al. 2004, Goksör et al. 2006) in their off-springs from early childhood until adulthood. However, no such association was found in the present study. This is perhaps due to

the small number of smoking mothers and low prevalence of asthma among smoking parents, which may have influenced the results.

On the other hand, maternal smoking in early life was an independent risk factor for lung function abnormalities in adulthood. In population-based retrospective studies, maternal smoking, especially if during pregnancy, has been convincingly associated with lung function deterioration in their off-springs from infancy (Young et al. 2000, Gilliland et al. 2000, Dezateux et al. 2001, et al. Lodrup Carlsen 2002, Murray et al. 2002, Jaakkola et al. 2006) until middle age (Upton et al. 2004, Svanes et al. 2004). In the present study, no information on maternal smoking during pregnancy was available, but all smoking mothers had smoked already during the first six months after delivery. Therefore, the exposure probably had taken place already in pregnancy

6.9. Methodological aspects

6.9.1 Strengths

The main strength of the present thesis is the long prospective follow-up time from infancy until young adulthood. On admission, the viral aetiology of infection was defined mainly by antigen detection, which was at that time a new technique available in a few research laboratories only. The RSV and non-RSV groups were constructed to be as pure as possible for case-control comparison. All RSV cases were microbiologically confirmed, and the non-RSV cases were hospitalised at a time when there were no or only occasional RSV cases in the population.

Serum total IgE and allergen specific IgE were measured twice before 36 months of age, which allowed for the evaluation of early atopy and sensitisation as predictors for later asthma. In addition, blood eosinophils were counted twice, both during and outside wheezing associated infections, during the age period from less than 6 to 24 months, which has been considered as a critical time for the development of allergy and asthma. Thus, the material allowed evaluation of both eosinophil counts and infection-induced changes in eosinophils as predictors for later wheezing and asthma. Eosinophils were counted as absolute values, rather than as percentages of total leukocytes, which increase the accuracy of the measurements and the comparability between different measurements.

Parental history of asthma and atopy were screened on admission, and atopy, wheezing episodes and environmental factors of the children were prospectively registered at 6 months periods until 24 months of age, which allowed versatile analyses on early life factors and their association with asthma in later life.

At the median age of 19 years, asthma symptoms were carefully screened by a structured questionnaire supplemented by interview, and lung function, bronchial reactivity and lability were carefully assessed by flow volume spirometry, methacholine inhalation challenge and home PEF monitoring. The study was controlled and blinded, since the clinical examination and diagnostic decisions were made without knowledge of the early life data.

6.9.2. Weaknesses

The main shortcoming of the present study is the small number of participants, which did not allow for subgroup analyses, *e.g.* for specific analyses of high or low eosinophil counts or stratified virus-specific analyses. The original bronchiolitis group consisted of 83 infants, and the power of the study was further decreased by drop-outs (33%), and further by the necessity of using multivariate analyses to control for confounding factors.

The drop-outs had, based on the questionnaire data available, less wheezing during the preceding 12 months, but no differences were seen in asthma medication or cough symptoms between the participants and drop-outs. In addition, the proportions of drop-outs were similar in all three study groups. Thus, the confounding effect caused by drop-outs is not likely to alter the main finding of the study, that the risk for asthma and abnormal lung function remain elevated into adulthood after hospitalisation for bronchiolitis in early life.

The selected control group, recruited from non-atopic families, may have influenced the results, but *e.g.* the prevalence of asthma among them did not differ from the figures in population-based studies in our country (Kotaniemi et al. 2002, Huurre et al. 2004).

The lack of population-based control group in the analyses on possible early predictors for asthma is a clear limitation in the present thesis. However, a control group without early-life wheezing was not considered to be a necessity, because our primary aim was to clarify if there are any means to identify wheezing infants who are

at a particularly high risk for subsequent asthma. In addition, the lack of skin prick tests in early life and allergen-specific IgE measurements to food antigens weaken the estimation of the role of early sensitisation. The numerous confounding factors during the 18- to 20-year surveillance period also make reliable estimation of early life risk factors difficult. Therefore, final analyses were performed using multivariate models.

7. SUMMARY AND CONCLUSIONS

1. In the present study, 30-41% of subjects who were hospitalised for bronchiolitis in infancy had asthma in adulthood. Although their asthma risk decreased during childhood, a rapid increase was seen during adolescence. Finally, at the age of 18 to 20 years, the risk was 3- to 4-fold greater than same-aged controls with no hospitalisation for lower respiratory tract infection in early life. Thus, the increased risk for asthma persists at least until young adulthood after hospitalisation for bronchiolitis in early life.

2. Over half of the present cohort of young adults had suffered from symptoms presumptive of asthma during the preceding year. However, only 14% of them were receiving ongoing maintenance medication for asthma. In home PEF monitoring, a diagnostic result for asthma was discovered in 22% of symptomatic study subjects. Thus, undiagnosed and untreated asthma was common, comprising 62% of all asthma cases.

3. Parental asthma, wheezing during respiratory infection not caused by RSV, atopy and repeated wheezing in early life were significant predictors for adult asthma among children hospitalised for bronchiolitis in early life. Children with a combination of these three factors formed a subgroup of bronchiolitis patients with a particularly high risk for asthma in later life.

4. A high eosinophil count during acute infection predicted lung function abnormalities and the lack of an eosinopenic response to acute bronchiolitis predicted both asthma and lung function impairment in adulthood. Instead, persistently low blood eosinophils during the first two years of life were associated with a favourable outcome. Thus, our results stress the role of blood eosinophils as markers of persistent asthma and lung function impairment in wheezing infants.

5. Wheezing during RSV and non-RSV infection proved to be different entities with different outcomes. Children with non-RSV bronchiolitis more often had asthma-related characteristics, *e.g.* parental asthma, early atopy, early sensitisation to inhalant

allergens and lack of eosinopenic response to acute bronchiolitis. In later life, they more often had asthma than RSV bronchiolitis patients. Thus, wheezing during respiratory infection not caused by RSV seems to reveal those infants who are susceptible for subsequent asthma in later life.

In contrast, children with a single wheezing episode-associated respiratory infection caused by RSV seem to grow out of a tendency for wheezing by young adulthood, at least if no atopy develops. However, patients with RSV bronchiolitis requiring treatment in hospital may represent a subgroup with an increased risk for COPD in middle or old age, because their lung function was significantly deteriorated already in early adulthood.

6. Maternal, but not paternal, smoking in early life was associated with a lower level of lung function and increased risk for abnormal lung function in young adulthood. Evidently, maternal smoking during pregnancy and early childhood causes long-term deterioration of lung function in their offspring.

8. RECOMMENDATIONS/ CLINICAL IMPLICATIONS

1. As the risk for asthma seems to increase again during or after teen age in former bronchiolitis patients, they should be encouraged to avoid other risk factors for asthma, such as smoking and overweight (Guerra et al. 2004).

2. Screening of symptoms and risk factors for asthma in the school health care system, preferably supplemented with lung function measurements, are recommended for detection of untreated asthma among adolescents and teenagers with a history of early childhood wheezing.

3. Because wheezing induced by RSV and by other viruses have different characteristics and different outcomes in later life, identification of RSV cases, e.g. by antigen detection tests, is recommended for all bronchiolitis cases, at least if treatment in hospital is indicated.

4. Wheezing infants who have a history of parental asthma, early atopy, or wheezing during respiratory infection not caused by RSV carry an increased risk for asthma through childhood into adulthood. For these children, careful follow-up and anti-inflammatory treatment should be considered at an early age, at least from the second wheezing episode requiring hospital treatment onwards.

5. Blood eosinophils should be measured both during and outside acute respiratory infection in wheezing infants, at least if hospital treatment is required. If eosinophils are high or if no eosinopenic response to acute infection is seen, early intervention with anti-inflammatory medication should be considered, with the intent of preventing remodelling and persistent deterioration of lung function. However, there are no studies indicating the preventive effect of such a medication. Likewise, no reference values are available for the normal eosinopenic response to an acute respiratory infection.

6. Because especially maternal smoking impairs lung function in their offspring, mothers should be encouraged to avoid smoking during pregnancy. Both parents should also be discouraged from smoking while their children are small to avoid

respiratory impairment, particularly if the child has wheezed or if there is family history of asthma or allergy.

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ORIGINAL PUBLICATIONS I-VI

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