Young children often contract respiratory infections. Bronchiolitis, a viral respiratory infection associated with the development of asthma, is one of the most common hospitalisation reasons in young children. However, there is a lack of information on how to prevent these diseases. This thesis addresses factors associated with frequent respiratory infections and the development of asthma during early childhood to assist in developing preventive strategies for these common childhood diseases.
PREDICTIVE FACTORS FOR RESPIRATORY INFECTIONS AND POST-BRONCHIOLITIS ASTHMA IN EARLY CHILDHOOD
Eija Bergroth

PREDICTIVE FACTORS FOR RESPIRATORY INFECTIONS AND POST-BRONCHIOLITIS ASTHMA IN EARLY CHILDHOOD

To be presented by permission of the Faculty of Health Sciences, University of Eastern Finland for public examination in MS301 Auditorium, Kuopio on September 4th 2020, at 12 o’clock noon

Publications of the University of Eastern Finland
Dissertations in Health Sciences
No 556

University of Eastern Finland
Kuopio
2020
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ABSTRACT

Young children often contract respiratory tract infections (RTIs). Bronchiolitis, a viral RTI associated with the development of asthma, is one of the most common hospitalisation reasons in young children. However, there is a lack of information on how to prevent these common childhood diseases. This thesis addresses factors associated with frequent respiratory infections and the development of asthma during early childhood to assist in developing preventive strategies for these common childhood diseases.

Children of mothers from rural environments in Austria, Finland, Germany, and Switzerland were studied. Their mothers participated in the birth cohort study ‘Protection against Allergy–Study in Rural Environments’ (PASTURE, for which \( n \) was 550) or its Finnish extension, ‘Lapsuuden kasvuympäristö ja allergiat’ study (LUKAS, for which \( n \) was 397), including mothers from suburban areas. The children were born from September 2002 to May 2005. Their respiratory symptom and infection frequencies and contact with dogs and cats during their first year were collected in weekly diaries. Cord blood (CB) samples were obtained after each child’s delivery and stimulated with a phorbol ester and ionomycin combination (P/I) for 24 hours. Interleukin (IL)-5, IL-10, tumour necrosis factor (TNF)-\( \alpha \) and interferon (IFN)-\( \gamma \) production were determined using enzyme-linked immunosorbent assays (ELISAs). Multivariable models were done with generalised estimating equations (GEEs) and Poisson regression analyses. Higher CB IL-5 and IFN-\( \gamma \) production were associated with lower numbers of weeks with middle ear infections. A positive association occurred between TNF-\( \alpha \) production and such ear infections. Children with dogs were healthier, i.e., had fewer symptoms and infections, than children with no dogs. The former had less frequent ear infections and needed fewer antibiotics than the latter.

Associations between the viral aetiology of bronchiolitis and the future use of asthma medication were examined. Altogether, 408 children hospitalised for bronchiolitis at younger than two years old were enrolled in a three centre–follow up
study in Finland from 1 November to 31 March, from 2008 to 2010. Viruses were
detected with polymerase chain reactions (PCRs) in nasopharyngeal aspirates. The
children’s parents were interviewed during the hospitalisations. At follow-up
periods of 12 months (for which n was 365) and 48 months (for which n was 349), a
structured questionnaire was given on asthma medication used on the children.
Binary logistic and Cox regression analyses followed. At both follow-ups, the use of
asthma control medication was prevalent in children who had rhinovirus (RV)
bronchiolitis, followed by children negative for respiratory syncytial virus (RSV) and
RV. Such medication was used the least among the RSV-positive children. The results
were similar when the times from when the children contracted bronchiolitis to when
the children began medication were compared. The results were also similar for RV-
C (associated with asthma control medication use), and especially if a child had an
atopic eczema history and had a fever at the time of their hospitalisation.

The functional statuses of adaptive immunities may be different at birth for
children who will or will not develop respiratory infections during early childhood.
However, having dogs while a child is in their infancy might benefit the child’s early
immune development. Children with RV-C might be a feasible target for future
asthma prevention studies.

National Library of Medicine Classification: QW 568, WC 505, WF 553, WQ 210, WS 285,
WV 232
Medical Subject Headings: Asthma; Bronchiolitis; Child; Dogs; Enzyme-Linked
Immunosorbent Assay; Cytokines; Fetal Blood; Follow-up Studies; IL10 protein, human;
Interleukin-5; Interleukin-10; Infant; Pets; Otitis Media; Respiratory Tract Infections;
Respiratory Syncytial Viruses; Rhinovirus; Risk Factors
Bergroth, Eija
Hengitysteinfektioiden ja bronkioliitin jälkeisen astman ennustekäytö varhaislapsuudessa
Kuopio: Itä-Suomen yliopisto
Publications of the University of Eastern Finland
Dissertations in Health Sciences 556. 2020, 128 s.
ISBN: 978-952-61-3338-6 (nid.)
ISSNL: 1798-5706
ISSN: 1798-5706
ISBN: 978-952-61-3339-3 (PDF)
ISSN: 1798-5714 (PDF)

TIIVISTELMÄ


vähemmän korvatulehdusja ja tarvitsivat harvemmin antibiootteja kuin lapset perheissä, joissa ei ollut koiraa.


Hankitun immunitetin toiminta voi olla erilaista jo syntyessä lapsilla, jotka sairastavat paljon ja jotka sairastavat vähän hengitystieinfektiöitä varhaislapsuudessa. Koirakontaktit saattavat edistää vastuskyvyn kehittymistä. Lisäksi lapset, joilla todetaan tyyppi C rinoviruksen aiheuttama bronkioliitti, voivat olla mahdollinen kohderyhmä tutkimuksille, joissa pyritään löytämään keinoja astman ehkäisyyn.
To my family
ACKNOWLEDGEMENTS

This work was carried out from 2008 to 2020 in the Department of Paediatrics of Kuopio University Hospital and in the Institute of Clinical Medicine by the Faculty of Health Sciences of the University of Eastern Finland in Kuopio.

This study was financially supported by Kalle and Kerttu Viik’s Fund, the Foundation for Pediatric Research, the Kuopio University Foundation, Kuopio University Hospital and the University of Eastern Finland, which are sincerely acknowledged.

I express my deepest gratitude to all my supervisors. It has been a privilege to work with and learn from you. I am grateful to my primary supervisor, Docent Sami Remes, MD, PhD, for his calm encouragement and advice throughout this process. I also want to warmly thank my other supervisors: Professor Leea Keski-Nisula, MD, PhD, for her enthusiasm and guidance, especially at the beginning of this project when I knew nothing of statistical analysis or scientific writing; Professor Matti Korppi, MD, PhD, for the knowledge and experience he has shared and Docent Eija Piippo-Savalainen, MD, PhD, for her support throughout the years.

I wish to thank the official reviewers of my thesis, Professor Marjukka Mäkelä, MD, PhD and Docent Anna Kaarinen Kukkonen, MD, PhD, for their constructive criticisms and comments, which have helped to improve this work.

I want to express my appreciation to Professor Raimo Voutilainen, MD, PhD, Professor Jarmo Jääskeläinen MD, PhD, Professor Marjo Renko MD, PhD and Docent Pekka Riikonen, MD, PhD, for their help during this process. I thank former Head of the Department of Paediatrics Docent Mikko Perkkiö, MD, PhD, for allowing me to combine clinical and research work at Kuopio University Hospital. I am also sincerely grateful to Chief of Paediatrics Juhani Lehtola, MD, from the Central Finland Health District, for enabling the same in my current position.

The members of my thesis committee – Docent Tarja Heiskanen-Kosma, MD, PhD and Mari Ylönen, MD, PhD – are warmly thanked for their encouragement.

I am deeply grateful to Professor Juha Pekkanen, MD, PhD, for allowing me to work alongside experts at the Centre of Health and Welfare in Kuopio, for the use of data from the PASTURE and LUKAS projects for my thesis, and also for his expert insights and straightforward comments on the work. I am obliged to Docent Marjut Roponen, PhD, for helping me to make more sense of the cytokine data. I also want to thank Anne Karvonen, PhD, for always helping me whenever needed, Timo Kauppinen, MSc, for his help with the diary data and Pekka Tiittanen, MSc, for his valuable advice with statistical modelling. I warmly thank Professor Erika von Mutius, MD, MSc, all the other co-authors and the people in the PASTURE and LUKAS study groups.

I express my sincere gratitude to Docent Tuomas Jartti, MD, PhD, for his help with and enthusiasm towards the MARC-30 Finland project and critiques of my analyses and writing, which I have learnt a lot from. I sincerely thank my co-authors
Matilda Aakula, MD, for collecting the four-year follow-up data and analysing it together with me, and Varpu Elenius, MD, PhD, for her help and encouragement with this work. Tero Vahlberg, MSc, is thanked for his statistical assistance. I also wish to thank the people who have worked with the original MARC 30 project at the EMNet. I am especially grateful to Professor Carlos A. Camargo Jr., MD, DrPH, for his vision and advice with our work. My thanks also go to co-authors Professors James Gern, MD, PhD and Tony Piedra, MD, for constructive comments on my writing. In addition, I want to thank all the other co-authors and people who have taken part in collecting the MARC-30 Finland data. Finally, I owe special thanks to Anneli Paloranta, RN, for her dedicated work with this project.

I wish to thank the personnel in the administrations of the Department of Paediatrics in Kuopio University Hospital, the University of Eastern Finland and the Central Finland Healthcare District who have helped me during this project.

I warmly thank all my colleagues in Kuopio and Jyväskylä. I am especially grateful to those of you who have shared your thoughts with me while working on your own theses.

I am deeply grateful to all the study children and their families for making this work possible.

I want to thank all my friends and relatives for the great and valuable times spent together.

I owe everything to my parents Kyllikki and Pekka; they have always supported and loved me unconditionally. Kiitos! I also thank my in-laws Salme and Ilpo and their families. I am grateful to my brother Jouni and his wife Annukka for their friendship.

Finally, my boys, you mean the world to me. I wish to express my heartfelt gratitude to my dear husband, Teemu. Without his support and patience, this thesis would never have been completed. I am so grateful, happy and proud of our children Tobias and Johannes. You are the love of my life!

Jyväskylä, February 2020

Eija Bergroth
LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:


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*shared first authorship
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## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>aHR</td>
<td>Adjusted hazard ratio</td>
</tr>
<tr>
<td>aOR</td>
<td>Adjusted odds ratio</td>
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<tr>
<td>aRR</td>
<td>Adjusted relative risk</td>
</tr>
<tr>
<td>CB</td>
<td>Cord blood</td>
</tr>
<tr>
<td>CDHR3</td>
<td>Cell surface protein Cahderin-related family member 3</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>COAST</td>
<td>Childhood Origins of Asthma Study</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
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<td>HMPV</td>
<td>Human metapneumovirus</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>IFN</td>
<td>Interferon</td>
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<tr>
<td>Ig</td>
<td>Immunoglobulin</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>LPS</td>
<td>Lipopolysaccharide</td>
</tr>
<tr>
<td>MARC</td>
<td>Multicenter Airway Research Collaboration</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger ribonucleic acid</td>
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<tr>
<td>OM</td>
<td>Otitis media</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PASTURE</td>
<td>Protection against Allergy – Study in Rural Environments</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PHA</td>
<td>Phytohaemagglutinin</td>
</tr>
<tr>
<td>P/I</td>
<td>Phorbol ester and ionomycin</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>RSV</td>
<td>Respiratory syncytial virus</td>
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<tr>
<td>RTI</td>
<td>Respiratory tract infection</td>
</tr>
<tr>
<td>RV</td>
<td>Rhinovirus</td>
</tr>
<tr>
<td>SEB</td>
<td>Staphylococcal enterotoxin B</td>
</tr>
<tr>
<td>Th</td>
<td>T-helper cell</td>
</tr>
<tr>
<td>TLR</td>
<td>Toll-like receptor</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
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## GLOSSARY OF TERMS

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Asthma control medication</td>
<td>An inhaled corticosteroid or leukotriene receptor antagonist</td>
</tr>
<tr>
<td>Cytokine</td>
<td>Proteins that act as mediators in both innate and adaptive immune reactions</td>
</tr>
<tr>
<td>Immune system</td>
<td>The organs, tissues, cells and molecules that work together to provide immunity</td>
</tr>
<tr>
<td>Infancy</td>
<td>The period from a child’s birth to their first birthday</td>
</tr>
<tr>
<td>Toll-like receptor</td>
<td>Pattern-recognition receptors that are on the surfaces of many cells, recognise different pathogen-associated molecular patterns and activate pathways that promote inflammation and resistance to infections</td>
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</table>
When a child is born, almost everything around them is new and unfamiliar. They have a lifelong journey with, and sometimes a battle against, foreign entities in the world. However, this journey begins long before the child’s birth. Many things the mother encounters during her pregnancy, and even during her entire life, shape the infant’s immune system (Ege et al., 2008; Hornsby et al., 2018; Keski-Nisula et al., 2010; Noakes et al., 2006; Pfefferle et al., 2010). The child’s final passage into the world, i.e., their birth mode, also matters (Keski-Nisula et al., 2010; Wampach et al., 2018). It involves differences in levels of cytokines, the messengers of cells, in the child’s CB, and variations in these levels are associated with the development of, for example, wheezing and eczema (Tadaki et al., 2009; Wood et al., 2011). However, it is not well known whether variations in cytokine levels during birth also affect children’s risks of contracting infections.

Various things in one’s environment may affect one’s immune system. Newborn babies, and later, small children, encounter many microbes and allergens novel to them. Their bodies should know how and to what extent they should react to these invaders, but occasionally, challenges occur, and diseases develop. One may posit that this is a result of genes. It is possible; however, the human genome has not changed as much or as rapidly as it should have if it were the main cause of, for example, increases in many atopic and autoimmune disease incidences in past decades (Law, Morris, Wald, Luczynska, & Burney, 2005; Molodecky et al., 2012). Thus, there must be an environmental factor that affects the way humans, and human genes, present themselves (Yang, Lozupone, & Schwartz, 2017). One may question whether it is pollutants, moulds, other children, foods or even animals that make a difference. Indeed, many people have pets in their living environments. There have been studies on the effects of pets on health, especially on allergies and asthma, although final conclusions on these influences are not yet clear (Bufford et al., 2008; Lodge et al., 2012; Nafstad, Magnus, Gaarder, & Jaakkola, 2001; Ownby, Johnson, & Peterson, 2002).

The human body’s battles against harmful microbes are not always successful, at least not immediately. Respiratory infections are inevitable in life and more so in early childhood. They often present themselves as the flu, but more serious forms of infections also occur, such as bronchiolitis. Further, during the first year, 93% of children present coughing or wheezing at least once, and up to 50% of children present coughing or wheezing during more than four weeks (Latzin et al., 2007). Some children are later diagnosed with asthma after contracting viral bronchiolitis or after presenting a wheezing illness in infancy (Carroll et al., 2009; Henderson et al., 2005; Jackson et al., 2008). It is unclear which occurred first: asthma or bronchiolitis.

Addressing factors associated with frequent RTIs and the development of asthma during early childhood could assist in developing preventive strategies for these common childhood diseases. This thesis evaluates the effects of early immunological profiles, i.e., CB cytokine levels, and pet contact on the frequencies of RTIs and their symptoms in
infants. In addition, this thesis examines associations between the viral aetiology of bronchiolitis and the use of asthma control medication in early childhood.
2 LITERATURE REVIEW

2.1 RESPIRATORY TRACT INFECTIONS AND THEIR SYMPTOMS IN EARLY CHILDHOOD

RTIs are common throughout childhood, especially during the first few years of life (Chen & Kirk, 2014; Dowell et al., 2017); hence, they are a cause of a great stress to children and their families, and they are a financial burden on society as a whole. Respiratory conditions constitute almost half of general practitioners’ child consultations, and nearly 70% of children are brought to visit general practitioners because of respiratory problems during their first year (Dowell et al., 2017). The majority of cases are flu or common cold-like illnesses; a child may present a fever, rhinitis, a sore throat or a mild cough. However, such a case may also be a more serious, life-threatening disease with wheezing or an obstructive cough. RTIs are typically caused by a virus, and RV is the most common pathogen in general (Kusel et al., 2006; Regamey et al., 2008; van der Zalm et al., 2009), while RSV contributes specifically to cases of lower RTIs (Shi et al., 2017). However, several bacteria also cause respiratory infections, e.g., pneumonia or otitis media (OM), often as coinfections with or complications of viral infections (Chonmaitree et al., 2016; Honkinen, Lahti, Österback, Ruuskanen, & Waris, 2012).

2.1.1 Frequency

The frequency of RTIs within the first year of life varies from three to six episodes (Grüber et al., 2008; Kusel, De Klerk, Holt, Landau, & Sly, 2007; von Linstow et al., 2008). In a recent Finnish study, it was found that the median annual number of days children had RTIs was 44.2 per child during the first two years of each child’s life (Toivonen et al., 2016). Another study found that rhinitis was the most common manifestation of RTI, with 2.3 episodes annually during the first and second years of life (Grüber et al., 2008). In an Australian survey, it was found that 46.3% of children four years old or younger had suffered from acute RTIs during the past four weeks at the time of the survey; the highest yearly incidence was 6.5 cases per person among boys (Chen & Kirk, 2014). However, it should be noted that there are substantial global variations in the frequencies of RTIs. E.g., incidences of lower RTIs are around 28.7 episodes per 1,000 children under five years of age in Western Europe, compared to 38.8 episodes in high-income regions of North America, 58.2 episodes in sub-Saharan Africa and 81.2 episodes in Eastern Europe (Troeger et al., 2018).

2.1.2 Factors associated with frequency and severity

Various factors affect RTI frequency and severity. Some factors are associated with each child’s immunological properties, while other factors are associated with microbes and environments. Immunological properties include, among other factors, genetic variations in the functions of each child’s immune system, young ages and possible comorbid
conditions, such as cardiopulmonary or neurological problems. Microbes are associated with the maturation of children’s adaptive immunities and environments affect the probability a child may encounter pathological microbes.

The presence of older siblings and early entrance into day care are examples of such risk factors for RTIs (Goetghebuer, Kwiatkowski, Thomson, & Hull, 2004; Grüber et al., 2008; Kusel, De Klerk, Holt, Landau, & Sly, 2007; Sun & Sundell, 2011; Toivonen et al., 2016; von Linstow et al., 2008). Further, the probability a parent will stay at home to take care of a child differs significantly by country, even among western countries. This may explain some of the aforementioned variations seen in the frequencies of RTIs, as may other factors. Breastfeeding, especially when exclusive, might protect against infections (Goetghebuer, Kwiatkowski, Thomson, & Hull, 2004; Quigley, Kelly, & Sacker, 2007), and the use of raw cow’s milk in early life can reduce a child’s risk of respiratory infections (Loss et al., 2015). In addition, a maternal history of asthma, parental smoking and mould in living environments might impact a child’s susceptibility to infections and respiratory illness symptoms (Biagini et al., 2006; Goetghebuer, Kwiatkowski, Thomson, & Hull, 2004; Håberg, Stigum, Nystad, & Nafstad, 2007).

Recent studies have shown that not only postnatal but also prenatal conditions affect the frequencies and natures of respiratory symptoms and infections. For example, maternal smoking during pregnancy (Koehoorn et al., 2008; Latzin et al., 2007) increases a child’s risk of presenting respiratory illness symptoms during their early years, independent of postnatal smoking (Håberg, Stigum, Nystad, & Nafstad, 2007). This is of interest, as smoking during pregnancy has also been linked to impaired neonatal toll-like receptor (TLR)-mediated immune responses (Noakes et al., 2006). In addition, there have been reports on the effects of prenatal exposure to different environmental toxins, e.g., polychlorinated biphenyls, dioxins and organochlorines, on incidences of RTIs in early life (Stølevik et al., 2013; Sunyer et al., 2010). Finally, season of birth may be associated with RTI frequency and severity as it may affect the age and maturation stage of a child’s immune system when children encounter peak RTI season. Birth season may also affect maternal, and thus foetal, concentrations of antibodies against respiratory viruses (Stensballe et al., 2009).

2.2 MIDDLE EAR INFECTIONS

The middle ear infection, or OM, is a spectrum of diseases ranging from OM that is acute or with effusion to OM that is chronically suppurative or adhesive (Rovers, 2008). Finnish Current Care Guidelines define acute OM as a sudden onset—short term infection in the middle ear in the presence of effusion and visual signs of inflammation of the tympanic membrane. The simultaneous onset of one or more signs or symptoms of systemic or middle ear inflammation, such as rhinitis, a cough, a sore throat, otalgia, otorrhea, hearing loss, a fever or irritability belong to the clinical picture for OM (Acute otitis media: Current Care Guidelines, 2017). However, in OM with effusion, a patient may present fluid in the middle ear without the above signs or symptoms of acute infection (Rovers, 2008).
2.2.1 Frequency during the first years of life

OM is one of the most common infections during early childhood. It is among the leading causes of both the use of antibiotics and the need for surgical intervention at such an age (Freid, Makuc, & Rooks, 1998; Rovers, Schilder, Zielhuis, & Rosenfeld, 2004). It is also a relatively common complication of upper RTIs (Revai et al., 2007), and as children frequently contract RTIs during their first year, incidences of OM are high. Nearly 40 years ago, it was reported that 50% of Finnish children had experienced at least one OM episode by their third birthday, and incidences were highest (75.5%) among infants 6–11 months old (Pukander, Karma, & Sipilä, 1982). Indeed, in a more recent Finnish study, it was found that 64% of children had experienced acute OM during their first two years (Toivonen et al., 2016). In contrast, in a recent Dutch birth cohort study, it was found that 32.8% of children had experienced at least one parent-reported symptomatic OM episode during their first year, with incidences at 569 episodes per 1,000 children each year (Prins-van Ginkel et al., 2017). Among European children two years old or younger, incidences of doctor-diagnosed acute OM were 299 per 1,000 children each year (Liese et al., 2014).

Overall, studies from different continents have found that by the time children reach their first birthday, 23 to 40 percent will have had at least one acute OM episode, with the incidence varying from 499–569 episodes per 1,000 children each year (Gribben, Salkeld, Hoare, & Jones, 2012; Jacobson et al., 2008; Kaur, Morris, & Pichichero, 2017; Ladomenou, Kafatos, Tselentis, & Galanakis, 2010; Prins-van Ginkel et al., 2017). OM is most common during the first year of life (Gribben, Salkeld, Hoare, & Jones, 2012), especially among infants aged six months to one year (Kaur, Morris, & Pichichero, 2017; Revai et al., 2007).

2.2.2 Factors associated with frequency

A child’s susceptibility to OM is determined by multiple factors associated with the individual’s immunological properties and microbial load, which can cause OM (Rovers, 2008). As aforementioned, younger children experience respiratory infections and OM more often than older children; this is likely due to the younger children having weaker immune responses (Rovers, Schilder, Zielhuis, & Rosenfeld, 2004). Naturally, human genes affect the way the human immune system functions; for example, monozygotic twins have more similar rates and symptoms of OM than dizygotic twins (Casselbrant et al., 1999; Rovers, Haggard, Cannon, Koeppen-Schomerus, & Plomin, 2002). There may also be a link between atopy and OM (Kaur, Morris, & Pichichero, 2017; Oh & Kim, 2016). Known environmental risk factors for the condition are older siblings and early day care attendance (Kaur, Morris, & Pichichero, 2017; Prins-van Ginkel et al., 2017), which relate to viral and bacterial loads (Rovers, 2008). Other risk factors are a lack of breastfeeding (Kaur, Morris, & Pichichero, 2017; Ladomenou, Kafatos, Tselentis, & Galanakis, 2010) and an exposure to tobacco smoke (Håberg et al., 2010), although some studies have not found these factors to be associated with risks of OM (Ladomenou, Kafatos, Tselentis, & Galanakis, 2010; Prins-van Ginkel et al., 2017).

It has been considered that general incidences of OM have decreased slightly, as the pneumococcal conjugate vaccine has been added to the national vaccination programs of many countries (Gisselsson-Solen, 2017; Palmu, Rinta-Kokko, Nohynek, Nuorti, &
In addition, the general treatment practices for OM have changed in past decades. The Finnish national guidelines recommend that treatment be administered if a patient presents the aforementioned criteria for acute OM, especially if the patient is younger than two years of age, their tympanic membrane is bulging or leaking and their OM is bilateral (Acute otitis media: Current Care Guidelines, 2017). However, for milder cases, an observational strategy is now acceptable and even recommended (Venekamp, Sanders, Glasziou, Del Mar, & Rovers, 2015), and this may have produced some fluctuations in the reported incidences of OM.

2.3 BRONCHIOLITIS

Bronchiolitis is a lower RTI that affects the smallest airways: bronchioles. The main findings are oedema, the necrosis of epithelial cells, and increased secretions of mucus (Aherne, Bird, Court, Gardner, & McQuillin, 1970; Ralston et al., 2014). These findings may vary depending on the viral aetiology of the disease. For example, among the two most common aetiologic agents of bronchiolitis, RSV causes more extensive damage to airways than RV (Rossi & Colin, 2015).

Clinically, bronchiolitis is a disease of young children, and it typically begins with rhinitis, followed by coughing, a fever, tachypnea, hyperinflation, chest retractions, widespread crackles or wheezing (Meissner, 2016; Smyth & Openshaw, 2006). The history of these symptoms and the clinical findings are the bases for bronchiolitis diagnoses—laboratory tests and radiographic studies are rarely needed (Ralston et al., 2014). Treatments are symptomatic and may include the suctioning of secretions, oxygen administration, nasogastric or intravenous fluid therapy and respiratory support with a high-flow nasal cannula or continuous positive airway pressure (Ralston et al., 2014; Sinha, McBride, Smith, & Fernandes, 2015; Tapiainen et al., 2016). However, the severity of the disease varies from mild with home-treated symptoms to severe respiratory distress with intensive care.

2.3.1 Definition

Although clinical diagnoses of bronchiolitis are straightforward, definitions of the disease vary by clinician and researcher (Fernandes et al., 2016). For example, the upper age limit of patients may vary from 12 (Carroll et al., 2009; Midulla et al., 2012; Mikalsen, Halvorsen, & Øymar, 2012) to 24 months old (Calvo et al., 2010; Valkonen, Waris, Ruohola, Ruuskanen, & Heikkinen, 2009), and in one study, the age limit was set to six months old (Koponen, Helminen, Paassila, Luukkaala, & Korppi, 2012). The American Academy of Paediatrics’ clinical guidelines for the treatment of bronchiolitis concern children from one to 23 months of age (Ralston et al., 2014), but the Finnish Current Care Guidelines concern children up to 12 months of age (Lower respiratory tract infections in children: Current Care Guidelines, 2014).

Definitions regarding the inclusion of children with histories of wheezing episodes vary; it is also contested whether wheezing is an essential criterion for diagnosis (Baraldi et al., 2014; Friedman, Rieder, & Walton, 2014; Ralston et al., 2014; Tapiainen et al., 2016). Hence, terms such as ‘bronchiolitis’, ‘virus-associated wheezing illness’ and ‘acute lower...
respiratory tract illness’ may or may not refer to the same disease. This complicates interpretations and comparisons of different studies.

2.3.2 Prevalence

In previous studies, it was found that 18 to 32 percent of children have had wheezing illnesses or acute lower respiratory tract illnesses during their first year, and 9 to 17 percent of the children experienced such illnesses during their second year (Matricardi et al., 2008; Taussig et al., 2003). In another study, when a focus was placed on RSV infections, the rate of bronchiolitis was 18% during the first year of life (Carroll et al., 2009). Further, one study found that incidences of acute RSV-induced lower RTIs among children younger than six months old varied from 66.1 cases per 1,000 children in industrialised countries to 82.5 cases per 1,000 children in non-industrialised countries (Shi et al., 2017). However, less data collected from higher income countries and yearly seasonal variations in incidences of RSV infections may have affected the results (Shi et al., 2017).

Overall, one to five percent of children with bronchiolitis need hospitalisation. Consequently, it is one of the leading causes of hospital treatment among infants (Carroll et al., 2009; Hall et al., 2009; Hasegawa, Tsugawa, Brown, Mansbach, & Camargo, 2013; Shay et al., 1999; Skirrow et al., 2019; Stockman, Curns, Anderson, & Fischer-Langley, 2012). In particular, infants younger than two months of age, prematurely born children and children born with congenital heart diseases, neurological problems or immunological deficits are vulnerable to severe forms of bronchiolitis (Hall et al., 2009; Hall et al., 2013; Purcell & Fergie, 2004; Stockman, Curns, Anderson, & Fischer-Langley, 2012).

2.3.3 Viral aetiologies

Today, with the modern technology, one can determine the viral aetiologies of early life wheezing episodes and bronchiolitis in 90 to 100 percent of the cases (Jackson et al., 2008; Mansbach et al, 2012; Turunen et al., 2014).

2.3.3.1 Respiratory syncytial virus

RSV is a single-stranded enveloped ribonucleic acid (RNA) virus that has two major antigenic groups, A and B (Jartti & Gern, 2017). It typically produces annual epidemics of varying severity (Haynes et al., 2013), with peaks every two to four years depending on region (Cangiano et al., 2016; Valkonen, Waris, Ruohola, Ruuskanen, & Heikkinen, 2009). Novel diagnostic techniques have identified new microbes that may cause bronchiolitis; however, the illness’s typical cause is RSV. Thus, the virus is the most commonly diagnosed pathogen, especially during the first year of life. It causes 32 to 83 percent of bronchiolitis cases during the first year of life and 42 to 72 percent of bronchiolitis cases by the second year of life. Further, incidences of RSV have been found to increase particularly in studies in which the proportion of infants younger than six months of age
has been high (Calvo et al., 2010; Cangiano et al., 2016; Jartti, Lehtinen, Vuorinen, & Ruuskanen, 2009; Mansbach et al., 2012; Ricart et al., 2013; Skjerven et al., 2016).

2.3.3.2 Rhinovirus

RV is an RNA virus with tremendous genetic variability; it has over 160 different genotypes (Jartti & Gern, 2017). It also has three species classifications: A, B and C (McIntyre, Knowles, & Simmonds, 2013). Of these, RV-A and RV-C produce more severe diseases than RV-B (Lee et al., 2012; Turunen, Jartti, Bochkov, Gern, & Vuorinen, 2016). In previous bronchiolitis reports, RV-C was found in more than half of the cases reported; it was followed by RV-A, which had a 10 to 20 percent prevalence. RV-B was only rarely detected (Skjerven et al., 2016; Turunen, Jartti, Bochkov, Gern, & Vuorinen, 2016). Numbers of RV diagnoses increased as PCR analyses became more common, because RV-C did not grow in traditional cell cultures (Arden, McErlean, Nissen, Sloots, & Mackay, 2006).

RV emerges as a particularly important aetiological agent of bronchiolitis during the second year of life; during the first year of life, 6 to 34 percent of children with bronchiolitis have RV infections, and it has been found in 17 to 35 percent of cases during the first two years of life (Calvo et al., 2010; Cangiano et al., 2016; Jartti, Lehtinen, Vuorinen, & Ruuskanen, 2009; Mansbach et al., 2012; Ricart et al., 2013; Skjerven et al., 2016). However, in high-risk populations of children with atopic parents, proportions of lower RTIs induced by RV might be higher during the first year of life (Kusel, et al., 2006). In general, RV-induced wheezing episodes that lead to hospitalisation are associated with atopic characteristics (Jartti et al., 2010; Turunen et al., 2014).

2.3.3.3 Other viruses

RSV and RV account for 75 to 85 percent of bronchiolitis cases (Cangiano et al., 2016; Jartti, Lehtinen, Vuorinen, & Ruuskanen, 2009; Mansbach et al., 2012), but many other viruses can cause bronchiolitis and early life viral wheezing illnesses as well. The most common causes of them are the human bocaviruses, parainfluenza viruses, coronavirus, adenoviruses, influenza viruses, enteroviruses and human metapneumovirus (hMPV) (Calvo et al., 2010; Ricart et al., 2013).

2.3.3.4 Coinfections

Multiple viruses can be detected simultaneously in a substantial proportion of children with bronchiolitis, i.e., in one- to two-thirds of cases (Jartti et al., 2009; Mansbach et al., 2012; Skjerven et al., 2016). In a Spanish study of infants younger than 12 months old with bronchiolitis, RSV was found in 71% of the infants, RV was found in 30% of the infants, human bocavirus was found in 29% of the infants and hMPV was in 6% of the infants, but only 45%, 32%, 14% and 46% of the cases, respectively, were single infections (Ricart et al., 2013). Another report from the same country investigated children younger than 24 months old who had bronchiolitis. It found that the illness was caused by RSV in 53% of the children, RV in 17% of the children, human bocavirus in 11% of the children,
adenovirus in 8% of the children and hMPV in 4% of the children. Further, 70%, 38%, 33%, 11% and 85%, respectively, were single virus infections (Calvo et al., 2010).

The clinical significance of an individual virus is difficult to assess if it is primarily found in multiple virus infections and is rarely detected in general. In many studies, coinfections have been associated with more severe diseases than single infections, whether disease severity was defined by higher severity indexes, longer hospital stays or higher risks of relapse (Hasegawa et al., 2014; Mansbach et al., 2012; Midulla et al., 2010). However, contradictory results have been presented (Calvo et al., 2010; Martin, Kuypers, Wald, & Englund, 2012; Skjerven et al., 2016). The detection of more than one virus during bronchiolitis may not necessarily be reflected in the illness’s clinical picture (Petrarca et al., 2008; Yan et al., 2017), because it matters which viruses are detected together (Mansbach et al., 2012).

### 2.3.3.5 Viral genomic loads

The number of viruses causing a lower RTI can be measured using nasal or tracheal samples. Because intubation and direct tracheal suctions are not needed often, nasopharyngeal aspirate samples are the most common way of obtaining information on an amount of microbes. Nasopharyngeal aspirate samples have been shown to resemble specimens collected from the lower respiratory tract, at least in regard to RSV (Malley et al., 2000). After samples are collected, viral genomic loads are further analysed using reverse-transcription PCRs for the majority of cases (Gerna et al., 2009; Hasegawa et al., 2015; Nenna et al., 2015).

RSV loads in samples collected from young children with respiratory infections have been found to correlate with disease severities (Buckingham, Bush, & Devincenzo, 2000; El Saleeby, Bush, Harrison, Aitken, & DeVincenzo, 2011; Fodha et al., 2007; Hasegawa et al., 2015; Houben et al., 2010; Scagnolari et al., 2012; Skjerven et al., 2016; Zhou et al., 2015). For example, during the 30th Multicentre Airway Research Collaboration (MARC-30), RSV genomic loads in samples collected from patients with bronchiolitis were associated with longer patient hospitalisations and increased risks of intensive care use (Hasegawa et al., 2015).

RV loads in samples collected from patients with respiratory infections have been associated with RV viremia, which has been found to be related to severe diseases (Esposito et al., 2014). For example, RV loads have been associated with severe diseases in children older than 12 months of age, although the association has been found to be opposite among children younger than 12 months old (Takeyama et al., 2012). In addition, increases in RV-A loads have been associated with severe diseases in children younger than 24 months old, although it should be noted that this has not been found to occur with RV-C (Xiao et al., 2015).

Many studies have not found associations between RSV (Jansen et al., 2010; Jartti, Hasegawa, Mansbach, Piedra, & Camargo, 2015; Wright et al., 2002; Yan et al., 2017) or RV (Jansen et al., 2010; Jartti et al., 2015) loads and disease severities or short-term outcomes. Further, there have been only a few reports on the effects of viral loads other than RSV and RV. No associations have been found between hMPV loads and disease
severities during acute lower RTIs (Yan et al., 2017). However, in children younger than 12 months old, hMPV loads have been found to correlate with the durations of oxygen therapy and lengths of hospital stays for bronchiolitis, though no correlations have been found with other markers of disease severities (Ricart et al., 2013).

### 2.4 POST-BRONCHIOBLITIS RESPIRATORY SYMPTOMS

Bronchiolitis and viral wheezing illnesses during early life have been associated with later respiratory symptoms and the development of asthma, one of the most prevalent chronic diseases of childhood (Carroll et al., 2009). A recent British study concluded that almost 22% of children who were previously admitted to hospital for bronchiolitis had further respiratory hospital admissions by the age of five, compared to only 8% of children who were not admitted to hospital for bronchiolitis (Skirrow et al., 2019). Pathologically, asthma (Figure 1) is characterised by chronic airway inflammation (Krawiec et al., 2001; van den Toorn et al., 2001), followed by airway wall remodelling (Payne et al., 2003; van den Toorn et al., 2001) and hyper-responsiveness. These symptoms lead to smooth muscle contractions, mucus secretions, oedemas and further obstructions (Arakawa et al., 2017).

![Figure 1. The pathophysiology of asthma. This figure is a modification of a figure by Arakawa et al. (2017).](image)

Various factors, both genetic and environmental, contribute to airway inflammation; bronchiolitis is affected by environments, which can contain allergens, tobacco smoke and air pollutants. Among children with early wheezing illnesses, RV infections, the severities of their diseases and their atopic characteristics can be important risk factors for the development of asthma (Carroll et al., 2009; Rubner et al., 2017). Although many effectors of this process may be known, the exact interplay between the effectors is not yet entirely clear.
2.4.1 Definitions and diagnoses of asthma in early childhood

Many infants and preschool-aged children experience wheezing or coughing recurrently during viral infections, but some have bronchial symptoms outside infections as well. Many children ‘outgrow’ their asthma or bronchial hyper-responsiveness by school age, but some have full spectrums of atopic diseases (Henderson et al., 2008; Martinez et al., 1995). Hence, childhood asthma is not a single entity, but a collection of illnesses with different genetic backgrounds and environmental triggers. It may not be appropriate to diagnose it as asthma before patients reach school age (Brand et al., 2008). Nonetheless, children with asthmatic symptoms in early childhood are often classified into groups based on the natures of their diseases (Table 1). A child’s classification may be mutable or may be done retrospectively (Schultz et al., 2010; Wonderen et al., 2016).

Table 1. Suggested classification criteria for wheezing among infants and preschool-aged children.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Temporal patterns of wheezing</td>
<td></td>
</tr>
<tr>
<td>1) Multiple-trigger wheezing</td>
<td>Wheezing with exacerbations and symptoms between episodes</td>
</tr>
<tr>
<td>2) Episodic wheezing</td>
<td>Wheezing during discrete time periods, often associated with viral infections</td>
</tr>
<tr>
<td>Durations of wheezing</td>
<td></td>
</tr>
<tr>
<td>1) Transient wheezing</td>
<td>Wheezing during the first three years of life, with no wheezing after the age of six years</td>
</tr>
<tr>
<td>2) Persistent wheezing</td>
<td>Wheezing during the first three years of life that continues after the age of six years</td>
</tr>
<tr>
<td>3) Late-onset wheezing</td>
<td>Wheezing after the first three years of life that continues after the age of six years</td>
</tr>
<tr>
<td>Durations, temporal patterns,</td>
<td></td>
</tr>
<tr>
<td>and atopic associations of</td>
<td></td>
</tr>
<tr>
<td>wheezing</td>
<td></td>
</tr>
<tr>
<td>1) Transient early wheezing</td>
<td>Wheezing during the first two to three years of life, with no wheezing after the age of three</td>
</tr>
<tr>
<td>2) Nonatopic wheezing</td>
<td>Wheezing triggered by a viral infection that tends to remit later in childhood</td>
</tr>
<tr>
<td>3) IgE-associated wheezing</td>
<td>Wheezing associated with clinical manifestations of atopy, blood eosinophilia, a high total</td>
</tr>
<tr>
<td></td>
<td>IgE, IgE-mediated sensitisations to foods or inhaled allergens in childhood and parental histories of asthma</td>
</tr>
<tr>
<td>4) Severe intermittent wheezing</td>
<td>Infrequent acute wheezing episodes associated with atopy and minimal morbidities when respiratory tract illnesses are not present</td>
</tr>
</tbody>
</table>

IgE, immunoglobulin E.


Young children are often incapable of performing any tests that are commonly available for evaluating lung function, airway inflammation or bronchial hyper-responsiveness. Thus, diagnoses are typically based on histories of atopy and breathing difficulties; these histories are used with clinical findings and, if possible, test results to assess atopy or allergies. If criteria are met (Table 2), treatment trials with inhaled corticosteroids can begin (Papadopoulos et al., 2012). Hence, needs for asthma-controlling medications relate to recurrences and severities of respiratory symptoms after bronchiolitis occurs. Diagnoses should be based on evidence of decreased lung function. This evidence should be noted when a child is able to perform specific tests, such as impulse oscillometry or spirometry tests. This is typically possible when the patient is about preschool age (Zapletal & Chalupová, 2003).
Table 2. Recommendations for the initiation criteria of asthma control therapy for young children with recurrent wheezing episodes, based on the Asthma Predictive Index and Finnish Current Care Guidelines (Asthma: Current Care Guidelines, 2012; Castro-Rodríguez, Holberg, Wright, & Martinez, 2000; Guilbert et al., 2004).

<table>
<thead>
<tr>
<th><strong>Asthma Control Therapy for young children</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended if</strong></td>
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<tr>
<td>• at least three episodes of wheezing lasting more than one day and affecting sleep occurred in the past year</td>
</tr>
<tr>
<td>• and one of the following is present: parental history of physician’s diagnosis of asthma, physician’s diagnosis of atopic dermatitis or sensitisation to aeroallergens</td>
</tr>
<tr>
<td>• or two of the following are present: IgE-mediated sensitisations to foods, wheezing when colds are not present or eosinophilia ≥ 4% or 0.4 x 10^9/l.</td>
</tr>
<tr>
<td><strong>Considered if</strong></td>
</tr>
<tr>
<td>• symptomatic treatment was required more than two days a week for more than four weeks,</td>
</tr>
<tr>
<td>• two exacerbations required systemic corticosteroids within six months or</td>
</tr>
<tr>
<td>• there are periods or seasons of previously documented risks.</td>
</tr>
</tbody>
</table>

*IgE*, immunoglobulin E.

### 2.4.2 Wheezing and asthma prevalences in early childhood

Several birth cohort and post-bronchiolitis/early life viral wheezing illness follow-up studies conducted around the world have focused on the development of asthma.

#### 2.4.2.1 Studies in Finland

Figures as low as 10% for recurrent wheezing during the first post-bronchiolitis year were reported in a retrospective study conducted in Turku (Valkonen et al., 2009). This figure seems low, because in follow-up studies in Turku and Kuopio, 29 to 40 percent of children with viral wheezing illnesses or bronchiolitis in their early years had asthma at school age; 91% of the children with asthma diagnoses also used continuous asthma medication (Kotaniemi-Syrjänen, Reijonen, Korhonen, & Korppi, 2002; Lukkarinen et al., 2017). Further, atopic and nonatopic asthma were equally common (Lukkarinen et al., 2017). In a post-bronchiolitis Tampere follow-up study in infants younger than six months of age at the times of their diagnoses, 27% of the patients had asthma by school age (Koponen, Helminen, Paassilta, Luukkaala, & Korppi, 2012).

In an analysis of asthma-medication reimbursement data from 2012 to 2013, incidences of asthma in children four years old or younger were around 0.5% among boys and 0.3% among girls, with age-specific prevalences of roughly 1% and 0.5%, respectively (Kankaanranta, Tuomisto, & Ilmarinen, 2017). The children were entitled to reimbursements if regular asthma control medications needed to be administered for longer than six months. Hence, some children with episodic and intermittent types of asthma may not have been included in the analysis.

#### 2.4.2.2 International studies

Recurrent wheezing is common in early childhood, especially with respiratory infections. A EuroPreval birth cohort study showed 13.5% and 7.8% prevalences of wheezing in
patients’ first and second years of life, respectively, and 3.1% of patients presented recurrent wheezing. However, great variations in figures have been found across Europe with roughly northwestern to southeastern decreasing gradients (Selby et al., 2018). In the Tucson Children’s Respiratory Study, prevalences of wheezing with lower respiratory tract illnesses were 32%, 17% and 12% during patients’ first, second, and third years of life, respectively (Taussig et al., 2003). In the Netherlands, almost 29% of children were found to have had at least one wheezing episode each during their first year, and close to 15% were reported to have had recurrent wheezing (Visser, Garcia-Marcos, Eggink, & Brand, 2010). Further, among two-year-old children in Norway, the prevalence of wheezing was found to be 26% and the prevalence of asthma was found to be 7% in the general population (Smidesang et al., 2010).

In regards to study subjects, by the time children reached early school age, 48% of the children in the Tucson Children’s Respiratory Study and 65% of Australian children with high risks for atopy had had at least one wheezing episode (Kusel et al., 2007; Martinez et al., 1995), and 11% of children in North American studies had been diagnosed with asthma (Carroll et al., 2009; Dell et al., 2010), with a slightly higher proportion of 15 to 28 percent with asthma diagnoses found in high-risk atopic children on different continents (Bønnelykke, Vissing, Sevelsted, Johnston, & Bisgaard, 2015; Jackson et al., 2008; Kusel et al., 2007). The Tucson Children’s Respiratory Study found that 20% of children had had transient wheezing, 15% of children had had late-onset wheezing and 14% of children had persistent wheezing at the age of six years (Martinez et al., 1995). Further, phase three of the International Study of Asthma and Allergies in Childhood found the global prevalences of current wheezing and symptoms of severe asthma to be 11.5% and 4.9%, respectively, among six-to-seven-year-old children (Lai et al., 2009).

In an Italian cohort, within a year after contracting bronchiolitis in infancy, 53% of children had had new episodes of breathing difficulties (Midulla et al., 2012), and after three years, 40% of children had presented recurrent wheezing (Midulla et al., 2014). Nearly a third (31%) of preschool asthma diagnoses were among former bronchiolitis patients in a retrospective birth cohort study of more than 90,000 children conducted in the USA (Carroll et al., 2009).

### 2.4.3 Effects of viral aetiologies

The viral aetiologies of bronchiolitis and viral wheezing illnesses are significant when determining patients’ risks of developing asthma in the future, whether as markers, which indicate children are developing chronic airway diseases, or as factors that initiate the development of such diseases. There is evidence that the severities of original viral wheezing illnesses are associated with patients’ future risks of experiencing recurrent wheezing and asthma (Carroll et al., 2009; Lemanske Jr. et al., 2005; Midulla et al., 2012). However, it could be that numbers of respiratory episodes, not particular viral triggers, or even wheezing, determine later developments of asthma (Bønnelykke, Vissing, Sevelsted, Johnston, & Bisgaard, 2015; Skytt, Bønnelykke, & Bisgaard, 2012).

Table 3 summarises the results of follow-up studies that have evaluated the effects of the viral aetiologies of bronchiolitis and viral wheezing illnesses on the prevalences of
asthma in early childhood. It shows that RV infections are stronger risk factors of subsequent wheezing or developments of asthma than RSV infections (Table 3). However, it also shows variations in the inclusion criteria used in studies.

Table 3. The development of asthma or recurrent wheezing by school age in follow-up studies of bronchiolitis and early life viral wheezing illnesses.

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Inclusion diagnosis or symptom</th>
<th>Age</th>
<th>Outcome, age (year)</th>
<th>Viral aetiology and prevalence of outcome (%)</th>
<th>RV</th>
<th>RSV</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth cohort studies of children with high risks of asthma or atopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copenhagen, Denmark⁵</td>
<td>Respiratory episode of three days</td>
<td>1 month – 3 years</td>
<td>Asthma, 7</td>
<td>Not a viral aetiology, but the number of episodes was significant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wisconsin, USA⁶</td>
<td>Viral wheezing illness</td>
<td>≤ 3 years</td>
<td>Wheezing, 2–3</td>
<td>1st year wheezing: 65% 48% 49%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1st year wheezing: 47% 27% 24%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2nd year wheezing: 46% 26% 22%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>78%</td>
<td></td>
<td></td>
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<tr>
<td>Perth, Australia⁷</td>
<td>Wheezing</td>
<td>&lt; 1 year</td>
<td>Asthma, 5</td>
<td>RV +/- RSV associated with asthma, only among children with early atopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up studies after early life wheezing illnesses</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Kuopio, Finland⁸</td>
<td>RTI-related wheezing</td>
<td>1–23 months</td>
<td>Asthma, 7</td>
<td>64% 10% 25%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rome, Italy⁹</td>
<td>Bronchiolitis</td>
<td>&lt; 1 year</td>
<td>Recurrent wheezing, 1 year later</td>
<td>80% 43%</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Recurrent wheezing, 3 years later</td>
<td>60%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soma, Japan¹</td>
<td>Lower RTI with wheezing</td>
<td>≤ 3 years</td>
<td>Subsequent wheezing, 3 years later</td>
<td>82% 44% 52%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tampere, Finland¹</td>
<td>Bronchiolitis</td>
<td>&lt; 6 months</td>
<td>Asthma, 5–7</td>
<td>14% 8% Non-RSV in general 24%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turku, Finland¹</td>
<td>1st viral wheezing episode</td>
<td>3–35 months</td>
<td>Recurrent wheezing, 1 year later</td>
<td>Treated with prednisolone: 28% 63%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo: 50% 17% 46%</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Asthma, 8 34% 14% 35%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atopic: 25% 6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonatopic: 9% 9% 35%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RSV, respiratory syncytial virus; RTI, respiratory tract infection; RV, rhinovirus.
2.4.3.1 Respiratory syncytial virus

Children hospitalised for RSV-induced wheezing illnesses or bronchiolitis in early childhood are at risk of developing asthma (Henderson et al., 2005; Ruotsalainen, Hyvärinen, Piippo-Savolainen, & Korppi, 2013). During their first post-bronchiolitis year, 17 to 43 percent of children experience a new wheezing episode (Lehtinen et al., 2007; Midulla et al., 2012). Further, 38%, 43% and 76% of children with high risks of atopy, who present with RSV-induced outpatient wheezing illnesses during their first, second and third years of life, respectively, have asthma at the age of six years (Jackson et al., 2008). Associations between severe early life RSV infections and developments of asthma may also continue up to adulthood (Backman, Piippo-Savolainen, Olikainen, Koskela, & Korppi, 2014; Sigurs et al., 2010). However, non-RSV bronchiolitis may indicate a greater risk of recurrent wheezing and asthma in childhood than RSV bronchiolitis (Lehtinen et al., 2007; Valkonen, Waris, Ruohola, Ruuskanen, & Heikkinen, 2009). RSV causes damage to airway epithelia through direct viral effects and through inducing acute inflammation (Rossi & Colin, 2015). This change can be long lasting, can promote airway obstructions and can cause recurrent wheezing, especially if the change affects young infants at critical lung development times (Rossi & Colin, 2015).

2.4.3.2 Rhinovirus

Wheezing illnesses induced by RV, whether treated in outpatient or inpatient settings, are stronger risk factors for asthma development than bronchiolitis and early viral wheezing illnesses induced by other viruses (Kusel et al., 2007; Lukkarinen et al., 2017; Midulla et al., 2014; Rubner et al., 2017). During their first post-bronchiolitis year, at least half of children have recurrent wheezing (Midulla et al., 2012), and by school age, up to 60% of these children are diagnosed with asthma (Jackson et al., 2008; Kotaniemi-Syrjänen et al., 2003). Children’s ages during their infections are factors; in a Childhood Origins of Asthma (COAST) birth cohort study of children with high risks of atopy, 47% of children with RV-induced outpatient wheezing illnesses during their first year had asthma at the age of six years. The percentage rose to 88% when wheezing illnesses occurred during a child’s third year of life (Jackson et al., 2008). Further, risks of asthma are increased throughout adolescence (Ruotsalainen, Hyvärinen, Piippo-Savolainen, & Korppi, 2013). Thus, RV is a significant factor of exacerbations among children who have been diagnosed with asthma (Freymuth et al., 1999; Tovey et al., 2015).

Risks of developing of asthma at older childhood ages are especially high among atopic children who have RV-induced wheezing episodes (Kusel et al., 2007). In a Finnish study, 84% of eight-year-old children with atopic asthma had had RV-induced wheezing before the age of 24 months, unlike only 33% of children with nonatopic asthma (Lukkarinen et al., 2017). In the aforementioned COAST study, both aeroallergen sensitisations and RV-induced wheezing illnesses during the first three years of life increased risks of asthma later in childhood. The proportion of children with asthma was higher if the children had been exposed to the risk factors (Rubner et al., 2017). It is notable that certain children with severe RV bronchiolitis might benefit from oral corticosteroids, which is not the case with bronchiolitis in general (Jartti et al., 2015; Koistinen et al., 2017).
However, since atopic characteristics are strongly associated with RV-induced wheezing, it is possible that the infection only reveals children with predispositions to asthmatic symptoms and does not truly affect the development of asthma (Rossi & Colin, 2015).

### 2.4.3.3 Other viruses

Many studies have investigated RSV- or RV-induced bronchiolitis and viral wheezing illnesses, and numbers of children found to have wheezing RTIs caused by other, single viruses have been low. Hence, the effects of these viruses on the development of recurrent wheezing and asthma are difficult to assess. However, there have been studies in which children with RSV- and RV-negative bronchiolitis or viral wheezing have had later wheezing illnesses more often than children with RSV bronchiolitis (Koponen, Helminen, Paasilta, Luukkaala, & Korppi, 2012; Kotaniemi-Syrjänen et al., 2003; Lehtinen et al., 2007; Lukkarinen et al., 2017).

### 2.4.3.4 Viral genomic loads

Data on the effects of viral loads on respiratory symptoms and the development of asthma after the infections are limited: only a minimal number of reports has been published thus far. In one report, a tendency towards earlier subsequent wheezing episodes was found during a one-year follow-up on children hospitalised for bronchiolitis with high RV loads when they were younger than 24 months of age (Jartti et al., 2015). In another report, at a 36-month follow-up, recurrent wheezing was found to be common in infants hospitalised for bronchiolitis with high RSV loads when they were younger than 12 months of age (Nenna et al., 2015). Further, it was found that RV and RSV viral loads that occurred with lower RTIs among children younger than three years old were not associated with subsequent wheezing in a three-year follow-up period (Takeyama et al., 2014). Finally, in a recent Finnish study, it was found that RV loads that occurred during viral wheezing illnesses were not associated with the pulmonary functions of preschool-age children (Leino et al., 2019).

### 2.4.4 Other factors

Although the viral aetiologies of bronchiolitis and early life viral wheezing are important determinants of future risks of asthma, there are other factors that affect the risks of this potentially chronic disease as well. Some of them may be associated with children’s risks of gaining viral infections, while others might be more independent risk factors of the development of asthma itself. Further, the significance of a risk factor can vary among children who present wheezing caused by different viruses (Jackson et al., 2012; Lukkarinen et al., 2017). For example, an age of younger than 12 months at the time of a viral infection, parents who smoke and non-RV, non-RSV infections are associated with nonatopic asthma, while RV infections and atopic characteristics increase risks of atopic asthma (Lukkarinen et al., 2017).
2.4.4.1 Age and sex

A child’s age at the time they present a viral wheezing illness can affect their later development of asthma (Jackson et al., 2008). The onset of wheezing at a young age has been suspected to be associated with a better prognosis (Martinez et al., 1995). However, contradictory results have been presented; an age of younger than 12 months at the time a child presents a viral wheezing illness has been associated with an increased risk of wheezing at an early school age (Lukkarinen et al., 2017). Nonetheless, during the first year of life, the effects of age are likely to vary. For particularly young infants, the reasons for wheezing during respiratory infections are associated with physiologically narrow airways; atopic characteristics are more important later in infancy. Further, in regards to sex, males present recurrent wheezing and asthma during early childhood more often than females (Gissler, Järvelin, Louhiala, & Hemminki, 1999; Jackson et al., 2008; Martinez et al., 1995; Midulla et al., 2012; Selby et al., 2018), although later in life, this risk distribution might reverse (de Marco, Locatelli, Sunyer, & Burney, 2000).

2.4.4.2 Genetic factors

The heritability of asthma has been estimated to be between 60 and 90 percent among children and adolescents (Bunyavanich et al., 2013; Koeppen-Schomerus, Stevens, & Plomin, 2001; Thomsen, Van Der Sluis, Kyvik, Skytte, & Backer, 2010; Ullemar et al., 2016; van Beijsterveldt & Boomsma, 2007). However, a great heterogeneity has been found in both genotypic and phenotypic findings when childhood asthma and wheezing illnesses have been considered. For example, genetic variations at the 17q21 locus increase risks of asthma after RV-induced wheezing illnesses occur in early childhood, but not after RSV-induced wheezing illnesses occur in early childhood (Çalışkan et al., 2013). It should be noted that exposure to animal sheds has been found to be protective towards asthma, especially among children possessing this genotype (Loss et al., 2016).

Other genetic variations also contribute to viral factors associated with asthma. The cell-surface protein Cadherin-related family member 3 (CDHR3) is a transmembrane protein that mediates the binding and replication of RV-C in cells (Bochkov et al., 2015). A certain polymorphism of the gene encoding CDHR3 leads to an increased expression of the receptor and an increase in the binding of RV-C (Basnet et al., 2019). This polymorphism of the CDHR3 gene has been associated with severe asthma exacerbations (Bønnelykke et al., 2014), non-RSV bronchiolitis (Husby et al., 2017) and respiratory illnesses induced by RV-C in early childhood (Bønnelykke et al., 2018).

Further, other genes have been linked to the development of asthma. For example, the polymorphism of genes encoding the TLRs 1 and 10 of the TLR2 subfamily have been associated with post-bronchiolitis asthma in children (Törmänen et al., 2017; Törmänen et al., 2018). Epigenetic mechanisms have been shown to be associated with the development of childhood asthma as well; e.g., small mother against decapentaplegic homolog 3 (SMAD3) methylation in CB cells can increase in the asthmatic children of asthmatic mothers and has been associated with childhood asthma risks (DeVries et al., 2017).
2.4.4.3 Comorbidities

It has been debated whether bronchiolitis leads to the deterioration of lung functions or children with bronchiolitis already have poorer lung functions. Several studies have noted diminished lung functions prior to the contraction of viral wheezing illnesses (Martinez, Morgan, Wright, Holberg, & Taussig, 1988), especially among prematurely born children (Broughton et al., 2006). Some neurological disorders, such as cerebral palsy, can complicate the treatment of asthma but are not associated with the development of the disease (Boel et al., 2019).

2.4.4.4 Atopy

Atopy typically refers to immunoglobulin (Ig) E-mediated sensitisations to allergens and to predispositions for IgE-mediated diseases, such as atopic eczema, allergic rhinitis or conjunctivitis and asthma. Atopic eczema and early sensitisations to foods or aeroallergens have been associated with increased risks of asthma during childhood (Jackson et al., 2008; Koponen, Helminen, Paassilta, Luukkaala, & Korppi, 2002; Lehtinen et al., 2007), and the effects have been seen the most with atopic asthma (Lukkarinen et al., 2017). Allergen sensitisations have been shown to precede RV wheezing illnesses, but RV wheezing illnesses have not been shown to precede allergen sensitisations (Jackson et al., 2012). However, aeroallergen sensitisations do not modify the effects of RV-induced wheezing on the development of asthma, although both increase the risk of it (Jackson et al., 2008).

Eosinophilia presented during a viral wheezing illness has been associated with recurrent wheezing three years after the illness (Midulla et al., 2014) and asthma at the age of six years (Kotaniemi-Syrjänen et al., 2002). Moreover, longitudinal eosinophil levels during childhood have been linearly associated with childhood asthma, and this association has been independent of atopy (Karakoc, Remes, Martinez, & Wright, 2002). The relevance of an early expression of atopy to the development of later asthma tends to decline as patients’ ages at the onset of wheezing increase (Matricardi et al., 2008).

In a Finnish cohort study, bronchiolitis patients whose mothers had histories of asthma had greater risks of developing asthma in childhood (Koponen, Helminen, Paassilta, Luukkaala, & Korppi, 2012). Similarly, in an Italian cohort study, after children presented bronchiolitis, they had increased risks of wheezing during the year following their illnesses if their parents had asthma (Midulla et al., 2012). However, in the following two years, the risk was no longer significant (Midulla et al., 2014). Children of mothers with particularly atopic asthma had higher risks of RV infections than RSV infections (Carroll et al., 2012).

The association of atopy with RV-induced wheezing illnesses is strong (Carroll et al, 2012; Kusel et al., 2007; Lukkarinen et al., 2017). This needs to be considered when interpreting the results of bronchiolitis and early life viral wheezing studies. However, a strong conception is that RV only reveals children with tendencies to present asthmatic symptoms and does not affect the development of asthma.
2.4.4.5 Nutrition

Breastfeeding has been shown to reduce children’s risks of developing asthma and recurrent wheezing, especially atopic children’s risks; this was noted in a systematic review that summarised 35 years of literature (van Odijk et al., 2003). In contrast, in a large European birth cohort study, breastfeeding was found to have no association with prevalences of wheezing in children’s second years of life (Selby et al., 2018). There was, however, a small protective effect seen in an overlap of breastfeeding and the introduction of solid foods (Selby et al., 2018). Thus, it has been suggested that breast milk has beneficial immunomodulatory effects only when other dietary proteins are present (Grimshaw et al., 2013).

Specific nutritional components have also been studied. As evidence for the role of vitamin D in immune regulation has been gathered (Hornsby et al., 2018), it has been speculated that the vitamin affects the development of immune-mediated diseases, such as asthma. Although levels of vitamin D during pregnancy seem to affect the neonatal immune system (Akhtar et al., 2016; Hornsby et al., 2018), the connection between vitamin D and the later development of asthma is still contradictory. In some studies, high maternal levels of vitamin D have been associated with decreased risks of asthma and wheezing among offspring (Wolsk, Harshfield et al., 2017; Wolsk, Chawes et al., 2017), while other studies have not found such connections (Hennessy et al., 2018; Visness et al., 2015). However, the modulation of a foetus’s or infant’s immune system through a maternal diet is a notable possibility regarding the prevention of childhood asthma (Bisgaard et al., 2016).

2.4.4.6 Living environment

As aforementioned, various environmental factors can affect the development of asthma. They might alter immune developments or, more directly, lead to the irritation of airways and provoke symptoms of asthma. Controlling all the factors in living environments that are associated with asthma is difficult. (Lloyd, & Saglani, 2017) However, in general, whether the effects of environments on asthma are similar in rural and urban areas should be noted.

Children who live in farming environments have lower risks of experiencing wheezing and severe respiratory illnesses (Adler, Tager, & Quintero, 2005; Fuchs et al., 2012; Ludka-Gaulke et al., 2018). A similar protective effect has been noticed among urban children living in environments rich in certain bacteria and allergens, e.g., environments with cockroaches, mice and cats (Lynch et al., 2014; O'Connor et al., 2018). Indeed, immature microbial compositions in the guts of one-year-old children of asthmatic mothers were associated with increased risks of asthma in the children (Stokholm et al., 2018). This highlights the importance of microbial diversity in developing the immune system to avoid T helper (Th) 2-type inflammations (Cahenzli, Köller, Wyss, Geuking, & McCoy, 2013; Gollwitzer et al., 2014).

Exposure to tobacco smoke has also been found in many studies to increase risks of recurrent wheezing and asthma (Lukkarinen et al., 2017; Martinez et al., 1995). It has been particularly associated with nonatopic asthma (Lukkarinen et al., 2017) and effects on
children prenatally (O'Connor et al., 2018). Further, air pollutants, such as nitric dioxide, have also been found to increase children’s risks of developing asthma (Gehring et al., 2010).

As aforementioned, siblings and early day care are risk factors for RTIs; they are also risk factors for asthma (von Linstow et al., 2008). In the Tucson children’s respiratory study, these factors were associated with frequent wheezing at the age of two years (Ball et al., 2000). However, by the age of six years, they became protective against the development of the disease (Ball et al., 2000). In contrast, the aforementioned COAST study found that older siblings were risk factors for asthma in six-year-old children who presented wheezing illnesses during the first three years of their lives (Jackson et al., 2008), although this ceased to be a risk factor once the children reached the age of 13 years (Rubner et al., 2017). Dominations of different childhood asthma phenotypes might explain this variation, as children who wheeze while presenting viral infections often ‘outgrow’ asthma by school age (Martinez et al., 1995). Further, the two studies’ birth cohorts were different regarding their basic populations, as the COAST study included only children with high atopy risks (Ball et al., 2000; Jackson et al., 2008; Rubner et al., 2017).

2.4.4.7 Exercise and obesity

Exercise is a known trigger of asthmatic symptoms (Lee & Anderson, 1985), and some individuals have asthmatic symptoms related only to such activity. Further, excess weight and obesity are associated with severities of exercise-induced bronchoconstriction among asthmatic children (van Veen et al., 2017). Obesity is commonly seen as a risk factor for asthma (Akinbami, Rossen, Fakhouri, & Fryar, 2018; Guerra et al., 2004), and has been considered to attribute to increases in the prevalences of asthma in past decades. However, some studies have found that such increases are present among children who do not have excess weight (Akinbami, Rossen, Fakhouri, & Fryar, 2018).

2.5 IMMUNE RESPONSES AT BIRTH AND IN INFANCY

Resistance and defence against foreign pathogens are built on different functions of innate and adaptive immunity. Innate immunity is a first-line mechanism that includes the complement system, natural killer cells and macrophages, among other factors. It involves the rapid recognition of microbes, based on their pathogen-associated molecular patterns, with pattern-recognition receptors, such as TLRs that are not specific to certain pathogens. Innate immunity can stimulate the function of adaptive immunity, which is pathogen specific and requires sensitisation. However, it has become clear that innate immunity reactions are intensified by previous stimulations, although they are not intensified by pathogen-specific stimulations. This response has been referred to as trained immunity (Netea, Quintin, & van der Meer, 2011).

The responses of the immune system can be divided into type 1 and 2, which include both innate and adaptive immunity reactions (Figure 2). Type 1 immune reactions are responsible for defending against various microorganisms, such as bacteria and viruses. The reactions are mediated by Th1 and Th17 cells, cytotoxic cells, certain innate lymphoid
cells, IgM, IgA and IgG. Type 2 reactions defend against larger extracellular parasites, neutralise toxins, maintain metabolic homeostasis and regulate tissue regeneration and wound repair with the functions of Th2 cells, type 2 innate lymphoid cells, basophils, mast cells and eosinophils. Many cytokines that mediate signals between cells are specific to either type 1 immunity or type 2 immunity. Type 2 immunity also functions as a suppressor of type 1 immune reactions. (Wynn, 2015; Iwasaki & Medzhitov, 2015).

Figure 2. The main features of type 1 and 2 immune responses. The figure is an adaptation of figures by Iwasaki and Medzhitov (2015). CTL, Cytotoxic T lymphocyte; AREG, Epithelial growth factor amphiregulin; Tfh, Follicular T-helper cell; ILC, Innate lymphoid cell; IFN, Interferon; Ig, Immunoglobulin; IL, Interleukin; NK, Natural killer; TNF, Tumor necrosis factor; Tr, T-helper cell; TSLP, Thymic stromal lymphopoietin.

During pregnancy, a sterile intrauterine environment surrounds the foetus and there is no immediate need for strong reactions of innate or adaptive immunity. Indeed, such reactions could even be harmful; this was suggested in a case of excessive IFN-γ production that led to a preterm delivery (El-Shazly, Makhseed, Azizieh, & Raghupathy, 2004). However, after birth, the situation rapidly changes, and suddenly, the infant’s environment is rich in foreign antigens. As the child’s adaptive immunity slowly develops, the function of the child’s innate immunity is very important. However, the function of the immune system of newborn babies is not just immature but also different than that of older children and adults (Belderbos et al., 2009). Furthermore, prematurely born babies have distinct functions, unlike babies that are not born prematurely (Collins, Weitkamp, & Wynn, 2018).
2.5.1 Newborn babies’ innate immunity

As aforementioned, the function of the innate immunity of newborn babies is unlike that of older children and adults. Many reports have shown impaired TLR-mediated stimulated cytokine production with decreased IL-12p70, IFN-α and TNF-α and with increased IL-6 and IL-10 levels in CB (Angelone et al., 2006; Belderbos et al., 2009; De Wit et al., 2003; Levy et al., 2004). Low productions of pro-inflammatory cytokines likely predispose newborn babies to infections. The importance of innate immunity in infancy is emphasised by patients with deficiencies in the IL-1 receptor-associated kinase or the myeloid differentiation factor 88, which are components of the TLR signalling pathway. Such patients have severe infections that might lead to death during early childhood, but if they survive, they do well later in life, and this is likely due to a matured adaptive immunity (Picard et al., 2010).

It is well known that chorioamnionitis predisposes newborn babies to early onset sepsis, but it should be noted that it seems to decrease risks of late-onset sepsis (García-Muñoz Rodrigo, Galán Henríquez, Figueras Aloy, & García-Alix Pérez, 2014; Strunk et al., 2012). It has been suggested that this phenomenon is a sign of trained immunity. Despite this, trained immunity is likely to have detrimental effects on newborn babies, especially those born prematurely (Levy & Wynn, 2014), as chorioamnionitis has been associated with the development of bronchopulmonary dysplasia and other complications of prematurity (Lau et al., 2005; Soraisham, Singhal, McMillan, Sauve, & Lee, 2009; Watterberg, Demers, Scott, & Murphy, 1996). Contrasting results have been presented, which may be due to developments in treatments of conditions associated with prematurity (Lahra, Beeby, & Jeffery, 2009; Torchin et al., 2017).

2.5.2 Adaptive immunity maturation

After an infant’s birth, the B- and T-lymphocytes in the immune system lack a preexisting memory of encounters that is needed for efficient reactions against microbes. In addition, the Th cell function of neonates is polarised into Th2 and Th17 directions, and this results in low Th1 activities (Dowling & Levy, 2014; Prescott et al., 1998). Decreased pro-inflammatory Th1 responses in newborn babies might be risks for infections with intracellular pathogens. However, they could be advantageous before foetus’s are born (Makhseed et al., 2001) and during the early colonisation of the skin and the intestinal tract with commensal microbes. Typically, in nonatopic children, Th2 predominance ceases after infancy (Prescott et al., 1999; Tuliic et al., 2011).

2.5.3 Cord blood cytokine production

One way to study the functions of the immune system at the time of birth is to examine the production of cytokines in CB cells. This is typically done by stimulating CB with a known stimulant of the immune system, and later, the production of cytokines is measured (Gern et al., 2006; Pfefferle et al., 2008). As aforementioned, there are differences between CB and adult blood cytokine production. When CB and adult blood have encountered different stimulants, e.g., low IL-12p70 and IFN-α, increased IL-10
production with selectively impaired inductions of TNF-α have been noticed (Levy et al., 2004; De Wit et al., 2003). Further, season of birth, maternal farming activities, the consumption of farm dairy products and pregnancy exposures to ergosterol or endotoxin may affect the production of CB cytokines (Dillie et al., 2008; Keski-Nisula et al., 2010; Pfefferle et al., 2010; Wood et al., 2011). Measuring CB cell cytokine production potential is therefore notable as it provides information on possible prenatal influences on the immune system.

### 2.5.4 Cytokine production disease associations

Differences in the levels of cytokines in CB cells have been associated with various illnesses. Whether a cytokine in question is anti- or pro-inflammatory or is mediating signals in type 1 or type 2 immune reactions, the associated condition may be, e.g., infection or an autoimmune disease. Table 4 summarises the associations between the CB cell production of four cytokines significant to the current study and respiratory tract symptoms and illnesses. The results of some gene polymorphism studies are also included, as cytokine production studies on some of the included cytokines are rare. However, comparing the results of cytokine production and gene polymorphism studies can be difficult as many environmental factors can affect phenotypes, i.e., levels of cytokine production, and, hence, direct comparisons of the results should be avoided. Detailed descriptions of the studies in Table 4 are presented in the following chapters.

Table 4. The associations of cord blood IL-5, IL-10, IFN-γ and TNF-α production with respiratory tract symptoms and illnesses in early childhood, with the results of cord blood cell cytokine production and gene polymorphism studies.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Type of study production</th>
<th>Gene polymorphism</th>
<th>Change in production</th>
<th>Associated disease or symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-5</td>
<td>x</td>
<td></td>
<td>↓</td>
<td>Increases in severe RSV infections&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td>x</td>
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<td>↔</td>
<td>Viral infections&lt;sup&gt;b&lt;/sup&gt;, wheezing in infancy&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>IL-10</td>
<td>x</td>
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<td>↓</td>
<td>Increases in severe RSV infections&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>x</td>
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<td>↔</td>
<td>Viral infections&lt;sup&gt;b&lt;/sup&gt;, wheezing in infancy&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
<td>x</td>
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<td>↑</td>
<td>OM associated with RSV or RV infections&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>IFN-γ</td>
<td>x</td>
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<td>↓</td>
<td>Recurrent wheezing&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>x</td>
<td>↑</td>
<td></td>
<td>Fewer viral RTIs and acute lower respiratory illnesses&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>x</td>
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<td>↔</td>
<td>Wheezing in infancy&lt;sup&gt;c&lt;/sup&gt;</td>
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<td></td>
<td>x</td>
<td>↑</td>
<td></td>
<td>Fewer upper RTIs&lt;sup&gt;c&lt;/sup&gt;, more severe RSV infections&lt;sup&gt;g&lt;/sup&gt;</td>
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<td></td>
<td>x</td>
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<td>↔</td>
<td>OM&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>TNF-α</td>
<td>x</td>
<td>↑</td>
<td></td>
<td>Acute OM&lt;sup&gt;f,h&lt;/sup&gt;</td>
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<td>x</td>
<td>↔</td>
<td></td>
<td>OM&lt;sup&gt;f&lt;/sup&gt;</td>
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</table>

<sup>IFN</sup>, interferon; <sup>IL</sup>, interleukin; <sup>OM</sup>, otitis media; <sup>RSV</sup>, respiratory syncytial virus; <sup>RTI</sup>, respiratory tract infection; <sup>RV</sup>, rhinovirus; <sup>TNF</sup>, tumour necrosis factor.

<sup>a</sup> Juntti, 2009; <sup>b</sup> Copenhaver, 2004; <sup>c</sup> Tadaki, 2009; <sup>d</sup> Alper, 2009; <sup>e</sup> Gern, 2006; <sup>f</sup> Sumino, 2012; <sup>g</sup> Gentile, 2003; <sup>h</sup> Patel, 2006; <sup>i</sup> Joki-Erkkilä, 2002.
2.5.4.1 Early respiratory infections and symptoms

Cytokine production in CB has been associated with courses and numbers of respiratory infections and symptoms in early life (Copenhaver et al., 2004; Ly et al., 2007; Revai et al., 2009; Zhang et al., 2009). For example, low IL-10/high IL-5 T-cell responses after phytohaemagglutinin (PHA) or Staphylococcal enterotoxin B (SEB) stimulations have been associated more with acute RTI susceptibilities than resistant high IL-10/low IL-5 phenotypes in children with high risks of atopy during the first five years of their lives (Zhang et al., 2009). A positive correlation between the granulocyte/macrophage colony stimulating factor: IL-5 responsive colony forming unit and the frequency of acute RTIs with fevers in the first year of life has been reported (Fernandes et al., 2008). In a Finnish study, infants hospitalised for RSV infections had lower IL-5 responses in CB than infants treated for RSV infections as outpatients (Juntti et al., 2009). However, one study did not find that symptomatic viral infections during infancy and PHA induced IL-5 or IL-10 responses in CB correlate (Copenhaver et al., 2004).

Increased CB mononuclear cell IFN-γ responses have been associated with a low number of viral RTIs after PHA stimulations (Copenhaver et al., 2004) and reduced risks of acute lower respiratory illnesses after Blatella germanica 2 allergen stimulations (Ly et al., 2007) in the first year of life. In addition, increased IFNG messenger RNA (mRNA) expressions in CB monocytes in response to RSV have been associated with decreased risks of upper RTIs (Sumino et al., 2012). Cytokine levels, and thus, risks of RTIs, may be affected by genetic variations. For example, children with the IL1β<sup>31</sup> and high production IL6<sup>174</sup> genotypes are susceptible to upper RTIs, whereas children with the IL10<sup>592</sup>, IL5<sup>746</sup>, IL1β<sup>511</sup> and IL8<sup>251</sup> genotypes have decreased RTI risks (Nokso-Koivisto et al., 2014; Revai et al., 2009). Nonetheless, further interpretations of the results can be difficult, as IL8<sup>251</sup> has been associated with increased risks of bronchiolitis (Hull, Thomson, & Kwiatkowski, 2000). There could be risk factors that are different for RTIs in general and for specific infections such as bronchiolitis, which affect results.

2.5.4.2 Middle ear infections

Recurrent acute OM has been associated with the polymorphism of the immune response genes TNFA, IL6 and IL10 (Emonts et al., 2007). Children with acute OM often seem to have high TNF-α or IL-6 production genotypes (Alper, Winther, Hendley, & Doyle, 2009; Patel et al., 2006; Revai et al., 2009), although a Finnish study found no associations between TNFα polymorphisms and risks for OM (Joki-Erkkilä, Puhakka, & Hurme, 2002). Further, OM episodes coincident with RSV and RV infections have been found to be frequent in children with high production IL-10 phenotypes (Alper, Winther, Hendley, & Doyle, 2009). Decreased IFNy mRNA expressions in CB monocytes, in response to RSV, have been associated with increased risks of OM (Sumino et al., 2012). These associations were supported by some gene polymorphism studies (Gentile et al., 2003).
2.5.4.3 Bronchiolitis and the development of asthma and atopy

The development of asthma, especially allergic asthma, has traditionally been associated with the Th2 polarisation of adaptive immunity, e.g., IL-5 is produced by Th 2-type cells and has been linked to the immunological mechanisms of allergic illnesses (Neaville et al., 2003). Th2 polarisation has also been associated with RSV bronchiolitis severities (Caballero et al., 2015). Lower productions of IFN-γ and TNF-α were noted among young children, i.e., children younger than two years of age, who were infected with RSV than among control children (Larrañaga et al., 2009). However, high productions of the IFN-γ genotype have been associated positively with RSV infection severities (Gentile et al., 2003).

There have been reports on associations between the cytokine production in CB cells and wheezing illnesses contracted early in life. In the aforementioned COAST study, wheezing during the first year of life was found to be less likely among children with measurable RSV induced IFN-γ production in CB cells. In addition, children with recurrent wheezing have been found to have lower PHA induced IFN-γ responses and to be less likely to have RV induced IFN-γ responses at birth than children without recurrent wheezing (Gern et al., 2006). Further, high lipopolysaccharide (LPS) stimulated IL-6 and IL-8 and lower IL-1β, IL-2, IL-4, IL-5 and IL-10 responses have been associated with severe RSV infections during infancy (Juntti et al., 2009). However, in one study, no associations were found between wheezing during the first year of life and the production of, e.g., IL-5, IL-10, IFN-γ and TNF-α in CB cells (Tadaki et al., 2009).

Other atopic diseases have also been studied. An inverse relationship has been shown between eczema and IFN-γ production among children with high risks of atopy (Wood et al., 2011). In addition, allergen-specific IgE antibodies have been detectable in CB cells. They have most likely been of foetal origin and have been associated with low productions of IFN-γ (Pfefferle et al., 2008). This might emphasise Th1’s lower activity than Th2’s activity in neonates. It should be noted that the Th2-type pathway of asthma has been widely studied. However, it has become evident that it does not contribute to all childhood asthma, but there are great variations in endotype presentations of the disease (Fahy, 2015; Gelfand, & Schedel, 2018; Lloyd, & Saglani, 2017).

2.6 PET CONTACT IN EARLY LIFE

Approximately every third household in Finland has a pet, and there are around 800,000 dogs and 600,000 cats in the country (Official Statistics of Finland, 2016). These animals are a remarkable part of the country’s living environment and can affect citizens’ health in various ways. These effects range from mood improvements to infections, traumas from bites and scratches and changes to immunological reactions (Bufford et al., 2008; Day, 2016; Shalmon et al., 2006)

2.6.1 Effects on microbiomes

Microbiota, the community of microbes around humans, and microbiomes, collections of microbe genes, have been subjects of great interest in the past few decades. It has become
clear that they have a great effect on health and may affect the development of many diseases by modulating the immune system (Bisgaard et al., 2011). The compositions of microbes in niches of the body, e.g., the skin and airways, have been studied, and the gut microbiome has been found to be important in this matter (Budden, et al., 2017; Bunyavanich et al., 2016; Chen, Fischbach, & Belkaid, 2018; Vatanen et al, 2018). As such, the factors that affect human microbiota have received increased research interest.

Several factors regarding living environments affect human microbiota: cleanliness, the preparation and contents of foods, antibiotics and genetic factors (Fallani et al., 2010; Doan et al., 2017; Lim et al., 2017). Moreover, birth mode affects the gut microbiome and the immunostimulatory potential the biome possesses (Wampach et al., 2018). The skin microbiota of family members appear to resemble each other, more so if the family has a dog (Song et al., 2013). The dog transfers microorganisms between family members, but also enriches the microbiome itself, especially that of children, as studies show that the gut microbiota of small children who have dogs or other pets are more diverse, in terms of microbes, than children without pets (Azad et al., 2013; Tun et al., 2017). Further, human gut microbiota is largely established during the first two to three years of life (Bergström et al., 2014). Hence, the effects of dogs on the microbiomes of humans might be detected most effectively in young children.

2.6.2 Pet contact and immune system responses

Immunological maturation is a lifelong process; the immune system reacts repeatedly when it encounters new microorganisms and potential antigens. These pathways are, however, developed early in childhood or even before birth (Aichbhauumik et al., 2008; Ege et al., 2008). Contact with dogs, but not with cats, in early life and during pregnancy has been associated with decreased TNF-α producing capacities at birth and in the first year of life (Lappalainen et al., 2010). Having a dog in infancy has also been related to increased IL-10 and IL-13 secretions at the age of one year, but after that age, the associations weaken (Bufford et al., 2008; Gern et al., 2004). These findings suggest that early exposure to dogs may modify immune responses in infancy.

2.6.3 Pet contact and the development of allergies and asthma

Previously, it was common for families to avoid or even abandon pets to prevent the development of allergies in their children. However, recently, it has become evident that such developments are not clear, and animal contact in early life may assist immunities in developing along a non-allergic route (Bufford et al., 2008; Ownby, Johnson, & Peterson, 2002). Children born to mothers who have cats, or, especially, dogs during pregnancy have been found to have lower IgE levels at birth than children born to mothers who have not had these pets (Aichbhauumik et al., 2008; Kerkhof et al., 2005). Among one-year-old Dutch children, allergic sensitisation was less likely if a child’s mother lived in a home with cats during their pregnancy (Kerkhof et al., 2005). In addition, according to the aforementioned COAST study, allergen sensitisations and atopic dermatitis are less common during the first year of life if children are exposed to dogs than if children are not exposed to dogs (Gern et al., 2004). This protective effect on
atopic dermatitis is seen at the age of three years, when wheezing is less common if a child has been exposed to dogs at the time of their birth than if the child has not (Bufford et al., 2008). This same protective effect towards atopic skin diseases has been found in other studies involving pets in general (Benn, Melbye, Wohlfahrt, Bjorksten, & Aaby, 2004; Nafstad, Magnus, Gaarder, & Jaakkola, 2001).

In a 10-year nation-wide cohort study in Sweden, with more than 275,000 school-aged children, a child’s chance of developing asthma was 13% lower if the child lived with dogs during their first year, as opposed to children who did not live with dogs during that time (Fall et al., 2015). The inverse relationship between dog exposure and risks of asthma or asthmatic symptoms has been reported elsewhere as well (Remes, Castro-Rodriguez, Holberg, Martinez, & Wright, 2001; Waser et al., 2005). However, contradictory data has been found. In a Finnish study, sensitisation to cats and dogs, together with allergies to the animals, were more common among children exposed to these animals in early childhood than among children who were not exposed to them (Pyrhönen, Näyhä, & Läärä, 2015). Further, in Britain, pets increased risks of rhinitis and wheezing presented without colds among children 12 to 14 years old (Burr et al., 1999). Finally, some studies have not found clear associations between animal contact and allergies and asthma among children (Gold et al., 1999; Lodge et al., 2012). However, timing of animal contact, atopic histories of families and other environmental factors may have affected the results.

2.6.4 Pet contact and respiratory infection and symptom frequencies

Literature on the effects of pet contact on RTIs and respiratory symptoms is less abundant than literature on atopy related illnesses. In the few reports published, no associations have been found between pet exposure and infectious diseases (Benn, Melbye, Wohlfahrt, Bjorksten, & Aaby, 2004), respiratory infections and respiratory symptoms in early life (Biagini et al., 2006; Burr et al., 1999; Rylander & Megevand, 2000; von Linstow et al., 2008). However, these studies have primarily focused on the effects of other potential risk or protective factors.

In a Finnish study, furry pets reduced risks of recurrent acute respiratory tract symptoms in children one to six years old, but no effects were found on recurrent acute OM (Hatakka et al., 2010). Further, having a dog at home has been found to decrease common cold episodes during the first two years of life, but no associations have been found between colds and cat contact (Grüber et al., 2008). In another Finnish study, exposure to cats was considered protective from croup in older children (Pruikkonen, Dunder, Renko, Pokka, & Uhari, 2009). Contradictory results have also been found, as dog exposure has been associated with increased risks of pneumonia and other lower respiratory tract diseases among preschool-aged children (Fall et al., 2015). However, data on this matter are limited.
3 STUDY AIMS

The main purpose of this study was to evaluate the factors associated with frequencies of respiratory infections and post-bronchiolitis asthma in young children. Thus, the research was intended to assist in developing preventive strategies for these common childhood diseases. More precise objectives of the study were to identify the factors that were present at birth or in infancy that affected the frequencies of respiratory infections during the first year of life of children included in two birth cohorts studies. An aim was also to assess the effects of the viral aetiology of bronchiolitis on the use of asthma medication after hospitalisation for bronchiolitis. The specific aims of the study were:

1. Analyse the associations between the stimulated production of cytokines IL-5, IL-10, IFN-γ and TNF-α in CB and the frequencies of respiratory symptoms and infections during the first year of life in a prospective multicentre European birth cohort study.

2. Describe the associations of dog and cat contact with RTI morbidities during the first year of life regarding a prospective Finnish birth cohort study.

3. Evaluate the significance of the viral aetiology of bronchiolitis on the use of asthma control medication during the first year after hospitalisation for bronchiolitis in regard to three-centre Finnish follow-up study.

4. Investigate the relationship between viral findings for children with bronchiolitis who were younger than 24 months, including findings of different RV species, and the use asthma control medication four years after the children’s hospitalisation for bronchiolitis in a three-centre Finnish follow-up study.
4 SUBJECTS AND METHODS

4.1 LITERATURE REVIEW

A literature search was conducted using PubMed (made by the United States National Library of Medicine of the National Institutes of Health, USA). Terms, such as ‘bronchiolitis’, ‘wheezing’, ‘asthma’, ‘respiratory infection’, ‘otitis media’, ‘cord blood cytokine’, ‘risk factor’, ‘dog’, ‘cat’, ‘pet’, ‘rhinovirus’, and ‘RSV’ were used in a search for original papers and review articles. Review papers were read for the purpose of seeking appropriate original articles that were not found in the initial search. To make comparisons to results of this study easy and reliable, articles that considered populations in industrial countries were favoured, when appropriate. Articles that considered bronchiolitis or asthma from a time prior to modern RV diagnostics were generally excluded. Articles in only English were chosen, except for the Finnish Current Care Guidelines.

4.2 PASTURE

The PASTURE project was a prospective multicentre study of rural areas in five European countries: Austria, Finland, France, Germany and Switzerland. The study was conducted to assess the effects of indoor exposure to different microbial products on the developments of asthma and allergies in childhood. It also aimed to investigate the mechanisms of individual responses to these environmental influences (von Mutius & Schmid, 2006).

4.2.1 Subjects

The study’s population consisted of 1,133 children who were and were not from farms and whose mothers were followed beginning with their third trimester of pregnancy. Women who lived on farms with livestock and an equal number of random women who did not live on farms with livestock but did live in nonurban areas were invited to join the study when they were at 20–34 weeks of gestation. The inclusion criteria for the study were an age of at least 18 years, a singleton pregnancy, Finnish as a first language (in Finland), and no plans to move from the study area. The exclusion criteria were a delivery before 36 weeks of gestation, an infant with congenital abnormalities and a failure to obtain CB samples (Karvonen et al., 2009). The included children were born between September 2002 and May 2005. After the exclusions were applied and missing data was addressed, the total number of children in the analysis was between 496 and 550, depending on the cytokine analysed (see Chapter 4.2.2).
4.2.1.1 LUKAS

The LUKAS birth cohort study was a Finnish extension of PASTURE. LUKAS included 208 Finnish PASTURE participants and 216 other mothers and their children (the extension) who were followed with the same protocol as the initial study population and were recruited from May 2004 to May 2005. The children were born in hospitals in Kuopio (all the children in the Finnish extension were born in this city), Jyväskylä, Joensuu and Iisalmi. There were no selections regarding the occupations or living areas of the mothers in the extended Finnish cohort, except for women who lived in apartments. They were excluded to ensure the building environments were comparable between the two parts of the cohort. (Karvonen et al., 2009)

4.2.2 Cord blood cytokine analyses

The children’s cytokine levels were measured using CB collected when the children were born. For the measurements, heparinised CB samples were stimulated for 24 and 48 hours with SEB (a final concentration of 100 ng/ml), LPS (a final concentration of 100 ng/ml) or a combination of phorbol 12-myristate 13-acetate (a concentration of 5 ng/ml) and ionomycin (a concentration of 1 µg/ml), i.e. P/I. Most chemicals were from Sigma Chemicals, a St. Louis, Missouri, USA company. The LPS was from Research Centre Borstel in Borstel, Germany.

The stimulated production of IL-5, IL-10, TNF-α and IFN-γ was determined using ELISA, i.e., a sandwich ELISA conducted with an OptEIA Human ELISA set from BD Biosciences in San Diego, California, USA, in the central laboratory of the study, which was in Marburg, Germany. The detection limits were 10.0 pg/ml for the IFN-γ, 7.7 pg/ml for the TNF-α, 8.0 pg/ml for the IL-5 and 11.4 pg/ml for the IL-10. Cytokine concentrations were standardised for individual white blood cell counts (a pg per 10⁶ white blood cells). Contaminations of the CB with maternal serums were excluded using several means, including the absence of IgA antibodies (Pfefferle et al., 2008).

The percentages of samples above the detection limits ranged from 43.4 to 80.9 for P/I, from 4.2 to 92.5 for LPS and from 7.5 to 76.8 for SEB. Sufficient concentrations of all the measured cytokines were obtained following the P/I stimulation (Pfefferle et al., 2010), and the other stimulations were excluded from the final analyses. Correlations between the cytokines measured at 24- and 48-hour time points were high, but the percentages of detectable cytokine values were in general higher after 24 hours of stimulation. Therefore, the 24-hour time point was selected for further analyses. The final results included the P/I-stimulated IL-5, IL-10, TNF-α and IFN-γ from the 24-hour time point, at which the results were divided into three categories: below the detection limit, below the cohort-specific median (less than or equal to the median) and above the cohort-specific median (greater than the median). If data for a cytokine were missing, the child was excluded from the analysis of that cytokine. In total, 279 children had no cytokine data available and were excluded from all further analyses. In addition, a French study population (for which n was 203) did not contribute to the cytokine data production and was excluded from the analysis.
4.2.3 Diary data on respiratory infections and symptoms

The parents participating in the study completed diary questionnaires (see the appendix A), which included questions on the infectious symptoms and health care visits of each child between the 9th and 52nd postnatal weeks, resulting in a total of 44 diary entries each. In every entry, the parents were asked if their child had been healthy during the previous seven days. If the child had not been healthy, the parents also filled in a questionnaire on different infectious diseases and symptoms, i.e., they answered questions on coughing, wheezing, rhinitis, fevers greater than or equal to 38.5°C, middle ear infections, pneumonia, diarrhoea, urinary tract infections, itchy rashes and other illnesses, that were presented during the past seven days. The use of medications, including antibiotics, was asked about each week.

The outcome definitions of respiratory infections and symptoms that were used in the analyses are presented in Table 5. Middle ear infections, as reported by parents, were included in the analyses as common infections that coexisted with RTIs.

Table 5. The respiratory symptom and infection variables used in studies I (the International cohort) and II (the Finnish cohort).

<table>
<thead>
<tr>
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<th>Study I</th>
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<tr>
<td>Reported number of</td>
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<td>healthy weeks,</td>
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<tr>
<td>i.e., weeks when a child was reported as being healthy,</td>
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<tr>
<td>non-healthy weeks,</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>i.e., weeks when a child was reported as not being healthy,</td>
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<td></td>
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<tr>
<td>weeks with fevers,</td>
<td>x</td>
<td></td>
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<tr>
<td>weeks with rhinitis,</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>weeks with coughing,</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>weeks with wheezing,</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>weeks with pneumonia,</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>weeks with coughing without wheezing,</td>
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<td>x</td>
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<tr>
<td>i.e., coughing in the absence of reported wheezing during the same week,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>weeks with middle ear infections,</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>weeks with respiratory tract infections,</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>i.e., rhinitis or coughing in the absence of reported wheezing during the same week and</td>
<td></td>
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<tr>
<td>weeks with antibiotics,</td>
<td></td>
<td>x</td>
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<tr>
<td>i.e., weeks when the use of systemic antibiotics was reported.</td>
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</table>

Children for whom there were fewer than half the number of possible diary entries (fewer than 23 weeks) were excluded (n was 40 in study I and 27 in study II). If information on health, respiratory symptoms and infections was missing from the diary, the corresponding week was excluded from the analyses.
4.2.4 Pet contact data

In the weekly questionnaires, the parents were asked whether they had a cat or a dog at home and how much time it had spent inside daily during the past seven days: not at all, less than two hours on average, two to six hours on average, six to 16 hours on average, or more than 16 hours on average. For the analyses, cat contact and dog contact were grouped into one, no contact at all; two, a low contact rate (the pet was inside at home up to a maximum of six hours daily); three, a medium contact rate (the pet was inside from six to 16 hours daily) and four, a high contact rate (the pet was inside more than 16 hours daily). The estimated average amounts of daily dog and cat contact during the study period were further evaluated with self-administered one year retrospectively collected questionnaires, which the parents answered when their participating children were 12 months old. The estimated average amounts of daily dog and cat contact were grouped into one, no dog or cat at home or a dog or a cat never inside at home; two, a dog or a cat occasionally inside at home; three, a dog or a cat inside at home often and four, a dog or a cat mostly inside at home. The children with both dog and cat contact were also included in the analyses. Only the Finnish diary forms contained questions about pet contact, and therefore, only the LUKAS cohort was included in these analyses.

4.2.5 Other follow-up data

Data on the children’s sexes, the children’s living environments, the children’s numbers of siblings, the children’s feeding methods, e.g., breastfeeding, the children’s seasons of birth, the children’s deliveries, the parents’ atopy, the mothers’ smoking habits, the children’s day care attendance, the children’s birth weights, the parents’ education levels and the parents’ choices to keep or not keep pets were received from the questionnaires collected during pregnancies and infants’ early childhoods. That is, self-administered questionnaire data were collected from the parents before the children’s births and when the children were two and 12 months of age. Data considering the children’s deliveries were collected separately, and additional data were received from the weekly diaries.

4.3 MARC-30 FINLAND STUDY

The MARC-30 Finland study was a prospective, multicentre cohort study that was part of the MARC-30 program, which was part of the Emergency Medicine Network in Boston, USA. The original study concentrated on factors associated with hospital admissions for and short-term prognoses of bronchiolitis, but there was no follow-up phase. The Finnish part of the study included a follow-up phase.

4.3.1 Subjects

The recruitment total was 408 children from the paediatric wards or intensive care units of the Kuopio, Tampere and Turku University Hospitals in Finland during the 2008–2009 and 2009–2010 winter seasons (from 1 November to 31 March). The children were hospitalised for bronchiolitis and were younger than 24 months when they were
admitted. The exclusion criteria were a previous enrolment in or transfer to a participating hospital more than 48 hours after the original admission time. In addition, a subgroup of 204 infants was identified; these infants were younger than 12 months old and had no histories of wheezing (this was strict bronchiolitis criteria).

4.3.2 Collection of baseline data

During the children’s hospitalisation, their parents were interviewed using a standardised questionnaire that included questions on demographic, environmental and baseline medical data. Hospital medical records were used to collect data on pre-admission evaluations in the emergency department. They were also used to collect data on the children’s inpatient courses, including the children’s respiratory rates, clinical assessments of retractions, the children’s oxygen saturations and medical management (Jartti, et al., 2014).

4.3.3 Microbial studies

Nasopharyngeal wash aspirates were performed, when subjects entered the study, within 18 hours of hospital admission using a standardised protocol (Jartti et al., 2014; Mansbach et al., 2012): 1 ml of normal saline was instilled into each child’s naris, and a suction catheter was used to remove mucus. The procedure was performed on each nostril of each child. Once collected, each sample was added a transport medium, placed on ice and then stored at –80°C before it was analysed at the Baylor College of Medicine in Houston, Texas, USA. PCR assays were conducted as singleplex or duplex two step–real time PCRs and used for the detection of RNA respiratory viruses (RSV types A and B; RV types A, B and C species; parainfluenza virus types 1, 2 and 3; influenza virus types A and B and the 2009 novel H1N1 type; hMPVs; the coronaviruses NL-63, HKU1, OC43 and 229E and enteroviruses) and DNA pathogens (adenovirus, Mycoplasma pneumoniae and Bordetella pertussis).

4.3.4 Follow-up asthma control medication data

4.3.4.1 One-year follow-up

Twelve months after index hospitalisation, study questionnaires (see Appendix B) modified from the International Study of Asthma and Allergies in Childhood questionnaires (Asher et al., 1995), were sent to all the participants. The questionnaires consisted of inquiries on respiratory symptoms and medications consumed during the past 12 months, as well as questions on allergic symptoms in the children and their parents. If the parents did not respond within four weeks, an identical questionnaire was sent again, and finally, if there was no response, the participants were contacted by telephone for a short interview stating only the primary outcome. Questions about the use of systemic corticosteroids or day care attendance were not asked during the telephone interviews. The primary outcome was the use of asthma control medication (an inhaled corticosteroid and/or a leukotriene receptor antagonist) for recurrent wheezing, prolonged coughing or asthma during the 12-month follow-up. The secondary outcome
was the use of systemic, i.e., oral, intramuscular or intravenous, corticosteroid courses during the follow-up period.

### 4.3.4.2 Four-year follow-up

Four to five years after the index hospitalisation, study questionnaires (see Appendix C) modified from the International Study of Asthma and Allergies in Childhood questionnaires (Asher et al., 1995) were sent to all the participants. The questionnaires consisted of inquiries on respiratory symptoms and consumed medications during the 48 month period after the index hospitalisations. If the parents did not respond within six months, they were contacted by telephone for an interview. If any post-bronchiolitis asthma control medication use was reported, the patient’s registers from hospitals were reviewed for exact information concerning the beginning of that control medication. The numbers of children included in each phase of the study are shown in Figure 3. The response rates were 89% and 86% at the one-year and four-year follow-up points, respectively.

![Figure 3. A flow chart of the MARC-30 Finland study.](image)

### 4.4 STATISTICAL ANALYSES

For the PASTURE/LUKAS data, comparisons were made between the frequencies of healthy weeks and durations of respiratory diseases and symptoms among children with different baselines and risk factors. The comparisons were conducted using the Pearson’s Chi-Squared test or the Kruskal–Wallis test. Correlations between the cytokine concentrations at the 24-hour and 48-hour time points were determined using Spearman’s correlation coefficient. For the MARC-30 Finland study, Pearson’s Chi-Squared test was
used for unadjusted analyses of categorised data, and the Mann–Whitney U test was used for unadjusted analyses of continuous data. Binary logistic, Cox and Poisson regression, and GEE models, with first-order autoregressive working correlation matrices, were used for multivariable analyses. Potential confounding variables were selected a priori based on their biological plausibility or were selected using the backward stepwise method with an inclusion criteria $p$ value of less than 0.05. The included variables are presented in Table 6.

Table 6. The potential confounding variables included in the multivariable analyses of the studies I (PASTURE cohort), II (LUKAS cohort), III (MARC-30 Finland one-year follow-up) and IV (MARC-30 Finland four-year follow-up).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>x</td>
</tr>
<tr>
<td>Age on admission</td>
<td></td>
</tr>
<tr>
<td>Living environment</td>
<td></td>
</tr>
<tr>
<td>Comorbid medical disorder</td>
<td></td>
</tr>
<tr>
<td>Siblings</td>
<td></td>
</tr>
<tr>
<td>History of wheezing</td>
<td></td>
</tr>
<tr>
<td>History of atopic eczema</td>
<td></td>
</tr>
<tr>
<td>Maternal smoking</td>
<td></td>
</tr>
<tr>
<td>Exposure to smoking during pregnancy or early childhood</td>
<td></td>
</tr>
<tr>
<td>Parental atopy</td>
<td></td>
</tr>
<tr>
<td>Maternal atopy</td>
<td></td>
</tr>
<tr>
<td>Parental asthma</td>
<td></td>
</tr>
<tr>
<td>Breastfeeding</td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
</tr>
<tr>
<td>Gestational weeks</td>
<td></td>
</tr>
<tr>
<td>Season of birth</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
</tr>
<tr>
<td>Oral intake on index hospital admission</td>
<td></td>
</tr>
<tr>
<td>Use of corticosteroids during index hospital admission</td>
<td></td>
</tr>
<tr>
<td>Length of index hospital stay</td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Age on admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living environment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbid medical disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siblings</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x$^b$</td>
</tr>
<tr>
<td>History of wheezing</td>
<td></td>
<td></td>
<td></td>
<td>x$^c$</td>
</tr>
<tr>
<td>History of atopic eczema</td>
<td></td>
<td></td>
<td>x</td>
<td>x$^b,c$</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure to smoking during pregnancy or early childhood</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Parental atopy</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal atopy</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Parental asthma</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational weeks</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Season of birth</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral intake on index hospital admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of corticosteroids during index hospital admission</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of index hospital stay</td>
<td>x$^c$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>x$^b,c$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ A selection of variables for the final analyses was done using the backward stepwise method.

$^b$ The variables were included in the final binary logistic regression models.

$^c$ The variables were included in the final Cox regression models.

The backward selection was done before entering the viral variables and cohorts into the model, and the final analyses included the children’s ages, siblings, histories of atopic eczema, and cohorts in the binary logistic regression model, and siblings, histories of atopic eczema or wheezing, lengths of hospital stays, uses of corticosteroids during index hospital admissions and cohorts for Cox regression analyses. In Study I, effect modifications were analysed by adding the interaction term ‘cohort × cytokine’ to the multivariable model, and the results were presented separately for each cohort if the interaction term had a $p$ value of less than 0.05. The results were expressed as adjusted odds ratios (aOR), adjusted hazard ratios (aHR) or adjusted relative risks (aRR) and as 95% confidence intervals (CIs). Data analyses were performed by using PASW statistics,
version 18.0, which was made by SPSS Inc. in Chicago, Illinois, USA, and IBM SPSS Statistics, version 21.0, 23.0, 24.0 and 25.0, which were made by IBM Corp. in Armonk, New York, USA. The cut-off level for significance was 0.05.

4.5 ETHICS

The parents of all the children involved in the study gave written informed consent. The research protocols were approved by the local Research Ethics Committees of the participating centres.
5 RESULTS

5.1 RESPIRATORY INFECTIONS AND SYMPTOMS DURING THE FIRST YEAR OF LIFE

5.1.1 Study population characteristics

The mean numbers of weeks spent following the participants were 42.1 and 43.0 per child for the international and Finnish cohorts, respectively, ranging from 23 to 44 weeks. Three (0.6%) children in the international cohort were born before the 37th gestational week, and 64 (11.6%) children were born at the 42nd or 43rd gestational weeks. In the Finnish cohort, 4 (1%) children were born preterm and 43 (10.9%) children were born postterm. Other baseline characteristics of the study populations are presented in Table 7.

Table 7. The baseline characteristics of the international cohort (for which n was 550) and the Finnish cohort (which involved 397 children with 17,124 diary weeks).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>International cohort (I)</th>
<th>Finnish cohort (II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>51.5</td>
<td>49.7</td>
</tr>
<tr>
<td>Birth season</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winter (December–February)</td>
<td>26.0</td>
<td>28.6</td>
</tr>
<tr>
<td>Spring (March–May)</td>
<td>29.8</td>
<td>29.5</td>
</tr>
<tr>
<td>Summer (June–August)</td>
<td>20.5</td>
<td>16.3</td>
</tr>
<tr>
<td>Autumn (September–November)</td>
<td>23.6</td>
<td>25.6</td>
</tr>
<tr>
<td>Maternal/parental atopy(^d)</td>
<td>22.0(^c)</td>
<td>54.8(^d)</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>5.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Farm living environment</td>
<td>48.5</td>
<td>29.2</td>
</tr>
<tr>
<td>Siblings</td>
<td>62.9</td>
<td>64.7</td>
</tr>
<tr>
<td>Cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>17.6</td>
<td>-</td>
</tr>
<tr>
<td>Switzerland</td>
<td>27.5</td>
<td>-</td>
</tr>
<tr>
<td>Germany</td>
<td>23.1</td>
<td>-</td>
</tr>
<tr>
<td>Finland</td>
<td>31.8</td>
<td>50.1</td>
</tr>
<tr>
<td>Extended Finnish</td>
<td>-</td>
<td>49.9</td>
</tr>
</tbody>
</table>

\(^a\)\(^b\) These numbers are presented as percentages from the study population\(^a\) or the study weeks\(^b\).
\(^c\) The Finnish cohort consisted of the Finnish participants, i.e., those from Finland, of the original PASTURE study, i.e., the international cohort, and the extended Finnish cohort, i.e., the study’s Finnish extension not included in the original PASTURE study.
5.1.2 Symptom frequencies

Only one percent of children was reported as being well throughout the entire study period for both cohorts (Table 8). For the international cohort, the median number of weeks with RTIs was five, but the RTIs were not recorded for the Finnish cohort. Rhinitis was reported in 17.0% of the follow-up weeks, coughing was reported in 10.4% of the follow-up weeks, fevers were reported in 4.0% of the follow-up weeks, wheezing was reported in 2.0% of the follow-up weeks and middle ear infections were reported in 2.5% of the follow-up weeks for the Finnish cohort. For the international cohort, during the study period, the median number of weeks with rhinitis was eight, the median number of weeks with coughing (without wheezing) was two, the median number of weeks with fevers was one, and the median number of weeks with middle ear infections was zero. Almost half (47.6%) the children in the Finnish cohort needed systemic antibiotics during the 44-week study.

Table 8. The respiratory symptoms and infections reported in the weekly diaries during the 44-week study period.

<table>
<thead>
<tr>
<th>Symptom or Infection</th>
<th>International cohort (I) (n = 550)</th>
<th>Finnish cohort (II) (n = 397)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-healthy</td>
<td>543 (98.7%)</td>
<td>393 (99.0%)</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>512 (93.1%)</td>
<td>-</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>507 (92.2%)</td>
<td>384 (96.7%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>-</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Coughing</td>
<td>-</td>
<td>335 (84.4%)</td>
</tr>
<tr>
<td>Coughing without wheezing</td>
<td>422 (76.7%)</td>
<td>-</td>
</tr>
<tr>
<td>Wheezing</td>
<td>-</td>
<td>128 (32.2%)</td>
</tr>
<tr>
<td>Fever</td>
<td>390 (70.9%)</td>
<td>285 (71.8%)</td>
</tr>
<tr>
<td>Middle ear infection</td>
<td>119 (21.6%)</td>
<td>157 (9.5%)</td>
</tr>
</tbody>
</table>

5.1.3 Cord blood cytokine production

5.1.3.1 Overall health

A production of TNF-α above the median was associated with a higher number of non-healthy weeks (an aRR of 1.19 with a 95% CI 1.00–1.42) than the production of TNF-α below the detection limit. In contrast, the production of IFN-γ above the median was associated with a lower number of non-healthy weeks (an aRR of 0.85 with a 95% CI 0.73–0.99) than the production of TNF-α below the detection limit. No associations were found between IL-5 or IL-10 production and numbers of non-healthy weeks. The production of these four cytokines were not associated with the RTI frequencies in the international cohort.
5.1.3.2 Rhinitis, coughing and fevers

The measurable production of IL-5 was associated with more frequent coughing than a lack of such a production (Table 9). The production of IFN-γ above the median was associated with less frequent fevers than a lack of IFN-γ production (Table 9). Finally, the production of the four studied cytokines was not associated with occurrences of rhinitis (Table 9).

Table 9. The associations of cord blood cytokine production with frequencies of rhinitis, coughing and fevers during the 44-week study period.

<table>
<thead>
<tr>
<th></th>
<th>Rhinitis</th>
<th>Cough</th>
<th>Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>aRR (95% CI)</td>
<td>aRR (95% CI)</td>
</tr>
<tr>
<td><strong>IL-5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; detection limit</td>
<td>187</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≤ median</td>
<td>184</td>
<td>1.05 (0.89–1.25)</td>
<td>1.31 (1.03–1.65)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>179</td>
<td>1.11 (0.94–1.32)</td>
<td>1.34 (1.05–1.69)</td>
</tr>
<tr>
<td><strong>IL-10</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; detection limit</td>
<td>221</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≤ median</td>
<td>149</td>
<td>1.02 (0.87–1.20)</td>
<td>1.13 (0.92–1.40)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>149</td>
<td>1.07 (0.92–1.26)</td>
<td>0.96 (0.76–1.20)</td>
</tr>
<tr>
<td><strong>IFN-γ</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; detection limit</td>
<td>135</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≤ median</td>
<td>194</td>
<td>0.84 (0.68–1.05)</td>
<td>0.95 (0.74–1.21)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>195</td>
<td>0.98 (0.82–1.17)</td>
<td>0.97 (0.74–1.25)</td>
</tr>
<tr>
<td><strong>TNF-α</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; detection limit</td>
<td>92</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≤ median</td>
<td>204</td>
<td>1.19 (0.90–1.36)</td>
<td>1.00 (0.75–1.30)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>200</td>
<td>1.18 (0.96–1.44)</td>
<td>1.26 (0.96–1.65)</td>
</tr>
</tbody>
</table>

*aRR*, adjusted risk ratios; *CI*, confidence interval; *IL*, interleukin; *IFN*, interferon; *TNF*, tumour necrosis factor.
The cytokine concentrations were measured following 24 h hours of P/I stimulation.
Cohort-specific medians were used for the categorisation of the cytokines.
The aRRs and their 95% CIs were obtained using Poisson regressions and were adjusted for children’s sexes, seasons of birth, living environments (farms), modes of delivery, gestational weeks at birth, siblings, feeding methods (breastfeeding) and day care attendance; maternal smoking habits and histories of asthma or allergic diseases and the cohorts.

5.1.3.3 Middle ear infections

The measurable productions of IL-5 and IFN-γ was associated with a lower number of weeks with middle ear infections (Table 10). Moreover, the production of TNF-α was associated with a higher number of weeks with middle ear infections. However, risks of middle ear infections were statistically significant for only a group below the median production of TNF-α (Table 10).
Table 10. The associations of cord blood cytokine production with frequencies of middle ear infections during the 44-week study period.

<table>
<thead>
<tr>
<th></th>
<th>aRR (95% CI)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; detection limit</td>
<td>0.37 (0.25–0.55)</td>
<td>0.41 (0.22–0.78)</td>
</tr>
<tr>
<td>≤ median</td>
<td>0.41 (0.27–0.61)</td>
<td>0.49 (0.26–0.93)</td>
</tr>
<tr>
<td>&gt; median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; detection limit</td>
<td>0.73 (0.49–1.08)</td>
<td>0.70 (0.40–1.24)</td>
</tr>
<tr>
<td>≤ median</td>
<td>1.21 (0.84–1.73)</td>
<td>0.87 (0.49–1.53)</td>
</tr>
<tr>
<td>&gt; median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN-γ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; detection limit</td>
<td>0.62 (0.40–0.95)</td>
<td>0.46 (0.24–0.88)</td>
</tr>
<tr>
<td>≤ median</td>
<td>0.39 (0.25–0.62)</td>
<td>0.41 (0.21–0.80)</td>
</tr>
<tr>
<td>&gt; median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; detection limit</td>
<td>1.94 (1.04–3.63)</td>
<td>0.82 (0.39–1.71)</td>
</tr>
<tr>
<td>≤ median</td>
<td>1.32 (0.69–2.52)</td>
<td>1.28 (0.62–2.67)</td>
</tr>
</tbody>
</table>

aRR, adjusted risk ratios; CI, confidence interval; aOR, adjusted odds ratios; IL, interleukin; IFN, interferon; TNF, tumour necrosis factor.

The cytokine concentrations were measured following 24 hours of P/I stimulation. Cohort-specific medians were used for the categorisation of the cytokines. The aRRs and their 95% CIs were obtained by Poisson regressions, and aORs and their 95% CIs by logistic regressions and are adjusted for children’s sexes, seasons of birth, living environments (farms), modes of delivery, gestational weeks at birth, siblings, feeding methods (breastfeeding) and day care attendance; maternal smoking habits and histories of asthma or allergic diseases and the cohorts.

In analyses of associations between the frequencies of middle ear infections and CB IFN-γ production, the ‘cohort × cytokine’ interaction term had a p = .002; therefore, the results are presented separately for each cohort, and some variations were seen by country (Table 11).
Table 11. The associations of cord blood IFN-γ production with frequencies of middle ear infections during the 44-week study period, presented separately for each cohort included in the study.

<table>
<thead>
<tr>
<th></th>
<th>aRR (95% CI)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; detection limit</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≤ median</td>
<td>1.28 (0.50–3.27)</td>
<td>0.69 (0.13–3.75)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>0.74 (0.26–2.17)</td>
<td>0.30 (0.05–1.81)</td>
</tr>
<tr>
<td>Switzerland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; detection limit</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≤ median</td>
<td>0.48 (0.17–1.37)</td>
<td>0.21 (0.03–1.53)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>2.58 (1.01–6.59)</td>
<td>1.15 (0.17–7.81)</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; detection limit</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≤ median</td>
<td>2.63 (1.27–5.44)</td>
<td>0.81 (0.14–4.64)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>0.06 (0.01–0.37)</td>
<td>0.04 (0.003–0.64)</td>
</tr>
<tr>
<td>Finland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; detection limit</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≤ median</td>
<td>0.25 (0.12–0.51)</td>
<td>0.27 (0.06–1.17)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>0.18 (0.08–0.39)</td>
<td>0.32 (0.07–1.43)</td>
</tr>
</tbody>
</table>

**aRR**, adjusted risk ratios; CI, confidence interval; **aOR**, adjusted odds ratios. IFN-γ concentrations were measured following 24 h stimulation with P/I. Cohort-specific medians were used for categorization of the cytokines. The aRRs and their 95% CIs are obtained by Poisson regressions, and aORs and their 95% CIs by logistic regressions and were adjusted for children’s sexes, seasons of birth, living environments (farms), modes of delivery, gestational weeks at birth, siblings, feeding methods (breastfeeding) and day care attendance; maternal smoking habits and histories of asthma or allergic diseases.

### 5.1.4 Dog contact

The number of children who experienced contact with a dog at home was 245 (61.7%) of 397 children. Such contact was not always stable; during study weeks 1, 22, and 44, the percentage of children who had no dog contact at home varied from 66.1 to 69.3.

#### 5.1.4.1 Overall health

Children who were reported to have had dog contact at home had more healthy weeks during the study period than children with no dog contact (see Figure 4; \( p \) was less than .001).
Figure 4. The percentages of healthy weeks in relation to the average amount of dog contact children experienced at home. The ps obtained using Chi Squared tests were less than .001 for each individual group compared to the groups with no dogs and dogs that did not live inside.

The multivariable analysis was conducted with both longitudinal (diary) and cross-sectional (one-year questionnaire) data on dog contact. Even after adjustments were made for possible confounders, the beneficial association remained significant (Table 12).

Table 12. The results of the multivariable analyses of associations between dog contact at home and healthy weeks during the 44-week study period.

<table>
<thead>
<tr>
<th>Dog contact at home</th>
<th>Total number of weeks</th>
<th>Number of healthy weeks (%)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>11,569</td>
<td>7500 (64.8)</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>5,346</td>
<td>3926 (73.4)</td>
<td>1.31 (1.13–1.52)</td>
</tr>
<tr>
<td>Amount of dog contact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dog or dog not inside the home</td>
<td>11,569</td>
<td>7500 (64.8)</td>
<td>1</td>
</tr>
<tr>
<td>Dog inside &lt; 6 hrs/day</td>
<td>1,063</td>
<td>805 (75.7)</td>
<td>1.25 (1.04–1.50)</td>
</tr>
<tr>
<td>Dog inside 6–16 hrs/day</td>
<td>1,374</td>
<td>1020 (74.2)</td>
<td>1.21 (0.93–1.57)</td>
</tr>
<tr>
<td>Dog inside &gt; 16 hrs/day</td>
<td>2,909</td>
<td>2101 (72.2)</td>
<td>1.41 (1.14–1.74)</td>
</tr>
<tr>
<td>Dog contact in 1 yr. questionnaire</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dog or dog not inside the home</td>
<td>10,798</td>
<td>6878 (63.7)</td>
<td>1</td>
</tr>
<tr>
<td>Dog temporarily inside the home</td>
<td>1,278</td>
<td>953 (74.6)</td>
<td>1.46 (1.07–2.00)</td>
</tr>
<tr>
<td>Dog often inside the home</td>
<td>1,391</td>
<td>1132 (81.4)</td>
<td>2.08 (1.44–3.00)</td>
</tr>
<tr>
<td>Dog mostly inside the home</td>
<td>3,113</td>
<td>2229 (71.6)</td>
<td>1.34 (1.05–1.70)</td>
</tr>
</tbody>
</table>

aOR, adjusted odds ratios; CI, confidence interval.
The aORs and their 95% CIs were obtained using GEEs and adjusted for the children’s sexes, birth weights, seasons of birth, numbers of siblings, feeding methods (breastfeeding) and living environments; the cohort; maternal smoking habits and parental atopy and the diary months.
5.1.4.2 Rhinitis, coughing, wheezing, fevers and antibiotic usage

In univariate analyses, it was found that children who experienced dog contact at home had many of the symptoms less often compared to children who did not experience dog contact at home, e.g., coughing (during 7.8 to 10.6 percent of the reported weeks, compared to 11.5% of the reported weeks and with a $p$ of .006), rhinitis (during 13.6 to 17.5 percent of reported weeks, compared to 18.4% of the reported weeks and with a $p$ of less than .001) and antibiotic usage (during 1.9 to 3.3 percent of the reported weeks, compared to 4.1% of the reported weeks and with a $p$ of less than .001) were less common. After adjustments for possible confounders, both the average weekly dog contact (according to the diary data) and the average yearly dog contact (according to the one-year questionnaire data) were similarly associated with decreasing respiratory infectious disease morbidities, with significant reductions in antibiotic usage (Table 13). Although fevers were not significantly associated with dog contact in the univariate analyses (during 3.2 to 3.7 percent of reported weeks, compared to 4.4% of reported weeks and with a $p$ of .06), in the multivariable model, children with dog contact presented fevers less often than children without dog contact (the aOR was 0.80 with a 95% CI 0.66–0.98; see Table 13). The highest associations between dog ownership and lower risks of antibiotic usage, rhinitis and fevers were detected among children who had dogs inside their home for less than six hours daily (according to the diary data) or who temporarily or often had a dog inside their home (according to the retrospective data). This association was unlike that of children who did not have any dogs or whose dogs did not live inside their home. No statistically significant associations were found between amount of dog contact and wheezing during the study period.

Table 13. The results of the multivariable analyses of associations between dog contact at home and frequencies of fevers and antibiotic usage during the 44-week study period.

<table>
<thead>
<tr>
<th>Dog contact at home</th>
<th>Fevers</th>
<th>Antibiotic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>aOR (95% CI)</td>
</tr>
<tr>
<td>No</td>
<td>493 (4.4)</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>187 (3.5)</td>
<td>0.80 (0.66–0.98)</td>
</tr>
<tr>
<td>Amount of dog contact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dog or dog not inside the home</td>
<td>493 (4.4)</td>
<td>1</td>
</tr>
<tr>
<td>Dog inside &lt; 6 hrs/day</td>
<td>34 (3.2)</td>
<td>0.63 (0.41–0.97)</td>
</tr>
<tr>
<td>Dog inside 6–16 hrs/day</td>
<td>48 (3.5)</td>
<td>0.85 (0.63–1.15)</td>
</tr>
<tr>
<td>Dog inside &gt; 16 hrs/day</td>
<td>105 (3.7)</td>
<td>0.87 (0.68–1.11)</td>
</tr>
<tr>
<td>Dog contact in 1 yr. questionnaire</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dog or dog not inside the home</td>
<td>447 (4.3)</td>
<td>1</td>
</tr>
<tr>
<td>Dog temporarily inside the home</td>
<td>57 (4.5)</td>
<td>1.04 (0.70–1.53)</td>
</tr>
<tr>
<td>Dog often inside the home</td>
<td>53 (3.8)</td>
<td>0.84 (0.62–1.14)</td>
</tr>
<tr>
<td>Dog mostly inside the home</td>
<td>102 (3.3)</td>
<td>0.86 (0.65–1.12)</td>
</tr>
</tbody>
</table>

aOR, adjusted odds ratio; CI, confidence interval.

$n$ denotes the number and percentage (%) of weeks with fevers or antibiotics use regarding the total population with particular dog exposure.

The aORs and their 95% CIs were obtained using GEEs and were adjusted for the children’s sexes, birth weights, seasons of birth, numbers of siblings, feeding methods (breastfeeding) and living environments; the cohort; maternal smoking habits and parental atopy and the diary months.
5.1.4.3 Middle ear infections

Children who experienced dog contact at home were reported to have had fewer weeks with otitis during the study period than children who did not experience dog contact at home (13.6 to 17.5% percent of reported weeks, compared to 18.4% of reported weeks and with a p of less than .001). In the multivariable analyses, the associations remained significant. The highest protective association between dog ownership and middle ear infections appeared among children who had a dog inside their home for less than six or for six to 16 hours daily (according to the diary data) or who had a dog often or temporarily inside their home (according to the retrospective data) compared with those who did not have any dogs or whose dogs did not live inside their home (Table 14). In sensitivity analyses, the associations were not found to change after the exclusion of children whose families reported the avoidance of pets due to allergies.

Table 14. The results of the multivariable analyses of associations between dog contact at home and frequencies of middle ear infections during the 44-week study period.

<table>
<thead>
<tr>
<th>Dog contact at home</th>
<th>Total number of weeks</th>
<th>Number of weeks with otitis (%)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>11143</td>
<td>33 (3.0)</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>5273</td>
<td>86 (1.6)</td>
<td>0.56 (0.38–0.81)</td>
</tr>
<tr>
<td>Amount of dog contact at home</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dog or dog not inside the home</td>
<td>11143</td>
<td>339 (3.0)</td>
<td>1</td>
</tr>
<tr>
<td>Dog inside &lt; 6 hrs/day</td>
<td>1047</td>
<td>9 (0.9)</td>
<td>0.38 (0.18–0.82)</td>
</tr>
<tr>
<td>Dog inside 6–16 hrs/day</td>
<td>1361</td>
<td>17 (1.2)</td>
<td>0.53 (0.29–0.97)</td>
</tr>
<tr>
<td>Dog inside &gt; 16 hrs/day</td>
<td>2865</td>
<td>60 (2.1)</td>
<td>0.67 (0.41–1.08)</td>
</tr>
<tr>
<td>Dog contact in 1 yr. questionnaire</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dog or dog not inside the home</td>
<td>10361</td>
<td>331 (3.2)</td>
<td>1</td>
</tr>
<tr>
<td>Dog temporarily inside the home</td>
<td>1269</td>
<td>7 (0.6)</td>
<td>0.17 (0.07–0.42)</td>
</tr>
<tr>
<td>Dog often inside the home</td>
<td>1390</td>
<td>12 (0.9)</td>
<td>0.27 (0.12–0.62)</td>
</tr>
<tr>
<td>Dog mostly inside the home</td>
<td>3066</td>
<td>65 (2.1)</td>
<td>0.75 (0.47–1.18)</td>
</tr>
</tbody>
</table>

aOR, adjusted odds ratio; CI, confidence interval. The aORs and their 95% CIs were obtained using GEEs, and were adjusted for the children’s sexes, birth weights, seasons of birth, numbers of siblings, feeding methods (breastfeeding) and living environments; the cohort; maternal smoking habits and parental atopy and the diary months.

5.1.5 Cat contact

Of 397 children, 136 (34.3%) were reported to have had cat contact at home at least once during the study period. In the univariate analyses, children with cat contact at home were significantly healthier during the study period than children with no cat contact at home (during 69.4 to 78.2% percent of reported weeks, compared to 66.1% of reported weeks and with a p of less than .001). Amount of cat contact was also associated with
frequencies of weeks with coughing \((p < 0.001)\), rhinitis \((p < 0.001)\) and middle ear infections \((p = 0.046)\), as well as with the use of antibiotics \((p = 0.004)\). No associations were found between cat contact at home and numbers of weeks with fevers or wheezing. When analyses were conducted using the one-year questionnaire data on cat contact, the results were comparable. After adjustments for potential confounding factors, no significant associations were found between the numbers of different respiratory symptoms or infections and cat contact based on the weekly diary data. However, when cat contact data was derived from the one-year questionnaire, children who had cats temporarily at home during the study period had more healthy weeks \((\text{aOR} = 1.62 \text{ with a 95\% CI of 1.12–2.39})\) and fewer courses of antibiotics \((\text{aOR} = 0.37 \text{ with a 95\% CI of 0.18–0.76})\) than children who did not have cats at home.

### 5.2 POST-BRONCHIOLITIS USES OF ASTHMA CONTROL MEDICATION

#### 5.2.1 Original study population characteristics

At the time of the index hospital admissions, around 15% of subjects were younger than two months old \((29\% \text{ were in a strict bronchiolitis criteria group})\), 50% of subjects were two to 11.9 months old and 35% of subjects were 12 to 23.9 months old. Most of the subjects were boys \((62\%)\), and 13% were born prematurely. Further, at that time, 70% of the children had siblings.

RSV and RV were identified in 72% of the cases: RSV was identified in 40%, RV was identified in 29% and RSV and RV were both identified in 2% of the cases. Half the children had bronchiolitis according to the strict criteria, and among them, RSV caused 62% of the cases, RV caused 11% of the cases and both RSV and RV caused 3% of the cases. In total, at least one virus was detected in 86% of the cases \((\text{and in 88\% of the cases in the strict bronchiolitis criteria group})\).

The children with RSV bronchiolitis were younger and had fewer comorbid medical disorders but needed longer hospitalisations and more frequent treatments in intensive care units \((\text{Table 15})\). Instead, histories of wheezing and atopic eczema and the use of systemic corticosteroids during the initial hospitalisation were more common among children with bronchiolitis not caused by RSV. The patient characteristics of children with RV-A and RV-C infections were similar.
Table 15. The differences in the baseline characteristics of the original study population in relation to viral aetiologies.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RV-A(^a) (n = 24)</th>
<th>RV-C(^b) (n = 74)</th>
<th>RSV(^c) (n = 165)</th>
<th>Non-RSV/RV(^c) (n = 113)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at study entry (in months) and median (IQR)</td>
<td>13.2 (9.4)</td>
<td>13.7 (8.4)</td>
<td>3.7 (5.0)</td>
<td>8.9 (10.0)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Male sex</td>
<td>16 (67)</td>
<td>46 (62)</td>
<td>93 (56)</td>
<td>75 (66)</td>
<td>.36</td>
</tr>
<tr>
<td>Parental history of asthma</td>
<td>3 (13)</td>
<td>14 (19)</td>
<td>43 (27)</td>
<td>30 (27)</td>
<td>.29</td>
</tr>
<tr>
<td>Prematurity</td>
<td>4 (17)</td>
<td>8 (11)</td>
<td>21 (13)</td>
<td>16 (14)</td>
<td>.87</td>
</tr>
<tr>
<td>Comorbid medical disorder</td>
<td>4 (17)</td>
<td>14 (19)</td>
<td>10 (6)</td>
<td>15 (13)</td>
<td>.02</td>
</tr>
<tr>
<td>History of wheezing</td>
<td>16 (42)</td>
<td>27 (37)</td>
<td>36 (22)</td>
<td>35 (31)</td>
<td>.04</td>
</tr>
<tr>
<td>Siblings</td>
<td>16 (67)</td>
<td>36 (49)</td>
<td>132 (80)</td>
<td>82 (73)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Exposure to smoking during pregnancy or early childhood</td>
<td>5 (21)</td>
<td>6 (9)</td>
<td>29 (18)</td>
<td>21 (19)</td>
<td>.22</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>23 (96)</td>
<td>68 (92)</td>
<td>151 (92)</td>
<td>102 (90)</td>
<td>.83</td>
</tr>
<tr>
<td>Hospitalization ≥ three days</td>
<td>6 (25)</td>
<td>14 (19)</td>
<td>71 (43)</td>
<td>29 (26)</td>
<td>.001</td>
</tr>
<tr>
<td>Stay in intensive care unit</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>12 (9)</td>
<td>1 (1)</td>
<td>.01</td>
</tr>
<tr>
<td>Systemic corticosteroid use</td>
<td>8 (33)</td>
<td>27 (37)</td>
<td>11 (7)</td>
<td>27 (24)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

\(^a\) RV, rhinovirus; RSV, respiratory syncytial virus; IQR, interquartile range. The p values are from Pearson Chi-Squared or Kruskal–Wallis tests.

\(^b\) These values include coinfections with viruses other than RSV.

\(^c\) These values include coinfections with viruses other than RV.

At the time of the second follow-up four years after the index hospitalisation, the baseline characteristics were similar in the included and dropout groups, except for the latter regarding fewer males (48%, compared to 64%, respectively) and more children exposed to smoking (25%, compared to 15%, respectively).

### 5.2.2 Viral aetiology outcomes

#### 5.2.2.1 Medication usage during the previous year

For the first year after their hospitalisations for bronchiolitis, 54% of the children had recurrent wheezing (39% experienced it in the strict criteria group) and 35% of the children used asthma control medication (18% used it in the strict criteria group). The proportions of children who used asthma medication during the follow-up year were 61% of the RV bronchiolitis group, 36% of the non-RSV/-RV bronchiolitis group and 15% of the RSV bronchiolitis group. Later, at the time of the second follow-up, around four years after the children’s initial hospitalisations, the parents reported that 27% of the children had used asthma control medication during the previous 12 months. The percentages were 47 for RV positive children, 26 for non-RSV/-RV children and 15 for RSV positive children.

In the multivariable analyses, it was found for both follow-ups that children with RV infections used asthma medication more often than children with RSV infections (at the one-year follow-up, the aOR was 9.05 with a 95% CI of 4.30–19.06 [Table 16] and at the
four-year follow-up, the aOR was 3.67 with a 95% CI of 1.88–7.19 [Table 17]). The children in the non-RSV/-RV group also used asthma control medication during the post-bronchiolitis year more often than the RSV group (the aOR was 2.71 with a 95% CI of 1.32–5.56 [Table 16]). However, by the second follow-up four years after the children’s initial hospitalisations, this difference in the medication use was no longer statistically significant (the aOR was 1.53 with a 95% CI of 0.77–3.05 [Table 17]).

Table 16. The multivariable analysis results of the associations between viral aetiologies of bronchiolitis and asthma control medication usage during the one-year follow-up period after the children’s initial hospitalisations for bronchiolitis.

<table>
<thead>
<tr>
<th>Combined viral groups</th>
<th>All children (n = 329)</th>
<th>Age &lt; 12 months and 1st wheezing (n = 174)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aOR 95% CI p</td>
<td>aOR 95% CI p</td>
</tr>
<tr>
<td>RSVa</td>
<td>1</td>
<td>20.43 4.88–85.55 &lt; .001</td>
</tr>
<tr>
<td>RVb</td>
<td>9.05 4.30–19.06 &lt; .001</td>
<td>3.76 1.10–12.80 .03</td>
</tr>
<tr>
<td>Non-RSV/-RVc</td>
<td>2.71 1.32–5.56 .007</td>
<td></td>
</tr>
<tr>
<td>Viral cause of bronchiolitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only RSV</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>RSV and another virusd</td>
<td>0.89 0.22–3.69 .89</td>
<td>0</td>
</tr>
<tr>
<td>RSV and RVa</td>
<td>7.89 1.73–35.91 .008</td>
<td>19.01 2.30–157.10 .006</td>
</tr>
<tr>
<td>Only RV</td>
<td>8.32 3.55–19.51 &lt; .001</td>
<td>14.21 1.92–105.37 .009</td>
</tr>
<tr>
<td>RV and another virusf</td>
<td>11.35 3.44–37.43 &lt; .001</td>
<td>23.73 3.13–179.80 .002</td>
</tr>
<tr>
<td>Only a non-RSV/-RV virusg</td>
<td>3.25 1.36–7.77 .008</td>
<td>6.89 1.70–27.99 .007</td>
</tr>
<tr>
<td>No virus</td>
<td>1.99 0.85–5.21 .11</td>
<td>1.03 0.15–6.85 .98</td>
</tr>
</tbody>
</table>

aOR, adjusted odds ratio; CI, confidence interval; RSV, respiratory syncytial virus, RV, rhinovirus.
The aORs and their 95% CIs were obtained using logistic regression and were adjusted for the children’s ages, sexes, gestational ages, incidences of atopic eczema, older siblings, oral intakes with admission and use of systemic corticosteroids during their index hospitalisations and for parental asthma.

a These values include cases positive for other viruses, excluding RV.
b These values include cases positive for other viruses, including RSV.
c These values include cases positive and negative for other viruses.
d These values exclude RV.
e The coronavirus HKU 1 presented in one case.
f These values exclude RSV.
g These values exclude RSV and RV.
ultivariable analysis onchiolitis criteria group of children was
During the first post
5.2.2.2 Time to initiation of asthma control medication

Table 17. The multivariable analysis results of the associations between viral aetiologies of bronchiolitis and the use of asthma control medication during the last 12 months leading to the four-year follow-up after the children’s initial hospitalisations for bronchiolitis.

<table>
<thead>
<tr>
<th></th>
<th>All children</th>
<th>Age &lt; 12 months and 1st wheezing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of children in analyses/using medication (%)</td>
<td>aOR (95% CI) (^a)</td>
</tr>
<tr>
<td>RSV</td>
<td>145/21 (15%)</td>
<td>1</td>
</tr>
<tr>
<td>RV (^c)</td>
<td>101/47 (47%)</td>
<td>3.67 (1.88–7.19) &lt; .001</td>
</tr>
<tr>
<td>Non-RSV/-RV</td>
<td>94/24 (26%)</td>
<td>1.53 (0.77–3.05) .22</td>
</tr>
<tr>
<td>RSV</td>
<td>145/21 (15%)</td>
<td>1</td>
</tr>
<tr>
<td>RV-A</td>
<td>24/10 (42%)</td>
<td>3.02 (1.12–8.17) .03</td>
</tr>
<tr>
<td>RV-C</td>
<td>73/35 (48%)</td>
<td>3.72 (1.50–7.66) &lt; .001</td>
</tr>
<tr>
<td>Non-RSV/-RV</td>
<td>94/24 (26%)</td>
<td>1.50 (0.75–1.99) .25</td>
</tr>
</tbody>
</table>

\(a\)OR, adjusted odds ratio; CI, confidence interval; RSV, respiratory syncytial virus, RV, rhinovirus. The aORs and 95% CIs were from logistic regressions.
\(a\) The analyses were adjusted for the children’s ages, histories of eczema and siblings and for the study centres.
\(b\) The analyses were adjusted for the children’s siblings and histories of eczema, the parental histories of asthma and the study centres.
\(c\) These values include cases of RV-A, RV-B and RV-C.

When the presence of coinfections was considered, the percentage of children who used asthma medication during the previous year was 13% for the RSV-only group, 56% for the RSV and RV group, 16% for the RSV and non-RV-virus group, 63% for RV-only group, 68% for the RV and non-RSV group and 36% for both the non-RSV/RV-virus and no virus groups. The associations were similar for the adjusted models when they were compared to the results of the main analyses for the combined virus groups (Table 16). The associations were also similar for the strict bronchiolitis criteria group of children who were younger than 12 months of age during their initial hospitalisations and had no previous histories of wheezing (Tables 16 and 17).

During the first follow-up year, corticosteroid courses were used by 26% of children (13% of the strict criteria group), while repeated corticosteroid courses were used by 12% of children (6% of strict criteria group). Children in the RV group (44%, with an aOR of 6.83 and a 95% CI of 2.66–17.52) and non-RSV/-RV group (34%, with an aOR of 4.28 and a 95% CI of 1.72–10.66) received systemic corticosteroids more often than children with RSV bronchiolitis (8.0%). These figures were higher for the strict bronchiolitis criteria group (the RV and non-RSV/-RV aOR were 8.10 and 9.20 with 95% CIs of 1.16–56.58 and 1.82–46.48, respectively).

5.2.2.2 Time to initiation of asthma control medication

During the first post-bronchiolitis year, children with RSV bronchiolitis were without asthma control medication longer than children with non-RSV/-RV bronchiolitis (the aHR was 2.25 with a 95% CI of 1.22–4.13) and RV bronchiolitis (the aHR was 4.97 with a 95%
Cl of 2.80–8.82; see Figure 5a). Curves decreased less sharply in the children with the strict criteria, but the differences between the groups remained statistically significant (the non-RSV/-RV group had an aHR of 2.92 with a 95% CI of 1.01–8.45 and the RV group had an aHR of 11.50 with a 95% CI of 3.99–33.13, compared to the RSV group [Figure 5b]).

Figure 5. The proportions of children who did not begin asthma control medication during the one-year follow-up period after their initial hospitalisation for bronchiolitis. Graph a shows all the children who had RV (with a p of less than .001) and non-RSV/-RV (with a p of .009), compared to the RSV children. Graph b shows the children with the strict bronchiolitis criteria (index hospitalisations at younger than 12 months and no histories of wheezing). The RV group (with a p of less than .001) and the non-RSV/-RV group (with a p of .049) are compared to the RSV group. The figures and p values are from Cox regressions. RSV, respiratory syncytial virus; RV, rhinovirus.
By the four-year follow-up, 46% of the children had used asthma control medication sometime after their hospitalisations for bronchiolitis. When the times at which they began the asthma medication were analysed, the children in the RV-positive group (with an aHR of 3.19 and a 95% CI of 2.03–5.01, 74% of which used such medication at some point) and the non-RSV/-RV group (with an aHR of 2.02 and a 95% CI of 1.27–3.20, 59% of which used such medication at some point) had started asthma control medication earlier than the children in the RSV-positive group (25% of which used such medication at some point). When only the children who fit the strict bronchiolitis criteria were included in the analyses, the results remained similar (the aHR was 4.29 with a 95% CI of 2.01–9.16, and 63% of the children in RV-positive group had used such medication at some point, while for the non-RSV/-RV bronchiolitis group, the aHR was 3.19 with a 95% CI of 1.58–6.41, and 41% of the children had used such medication at some point. A total of 22% of the RSV group had used asthma medication at some point).

5.2.2.3 Rhinovirus subgroup analyses

The proportions of children who used asthma control medication during the 12 months prior to the four-year follow-up were 42% for the RV-A positive group and 48% fo the RV-C positive group. Both the RV-A and RV-C groups (with aORs of 3.02 and 3.72 and 95% CIs 1.12–8.17 and 1.80–7.66, respectively) were associated with the use of asthma medication (Table 17). Further, the children in both the RV-A positive and RV-C-positive groups (with aHRs of 2.30 and 3.48 and 95% CIs of 1.19–4.44 and 2.17–5.59, respectively), went without asthma control medication for a shorter time than the children in the RSV-positive group (Figure 6a). The results were similar for the children who fit the strict bronchiolitis criteria (Figure 6b).
Figure 6. The proportions of children who did not use asthma control medication during the four-year follow-up period after their initial hospitalisations for bronchiolitis. The graphs show the effect of viral aetiologies. Graph a shows all the children; the RSV group is compared to the RV-A group, which had a $p$ of less than .001; to the RV-C group, which had a $p$ of less than .001 and to the non-RSV/-RV group, which had a $p$ of .001. Graph b shows the children from the strict bronchiolitis criteria group (index hospitalisations at younger than 12 months and no histories of wheezing), excluding the RV-A group ($n$ was 2). The RSV group is compared to the RV-C group, which had a $p$ of less than .001, and the non-RSV/-RV group, which had a $p$ of .001. The figures are from Cox regressions. RSV, respiratory syncytial virus; RV, rhinovirus.
5.2.3 Other risk factors

Being an only child (43% of children who used medication, compared to 31% children without medication, with a $p$ of .03), having a history of atopic eczema (46% of children who used medication, compared to 30% of children without medication, with a $p$ of .005); having an older age (7%, 34% and 49% of children used medication with age groups of less than two, 2–11.9 and 12–23.9 months old, respectively and a $p$ of less than .001) and using systemic corticosteroids during one’s index hospitalisation (55% of children who used asthma medication, compared to 24% of children without asthma medication, with a $p$ of less than .001) were significant risk factors for the use of asthma control medication during the first post-bronchiolitis year. In addition, day care attendance during the follow-up period increased risks of the use of asthma medication in 259 children for whom such data was available. In the patients who met the strict bronchiolitis criteria, being a male was also a significant risk factor (23% of children who used medication, compared to 11% of children without medication, with a $p$ of .04). In the multivariable analyses, however, only age was a significant predictor of future asthma control medication use. Children who were younger than two months old at the time they were hospitalised for bronchiolitis used medication less frequently than children who were 2–11.9 months old at the time they were hospitalised for bronchiolitis (the aOR was 0.26 with a 95% CI of 0.09–0.81).

In unadjusted analyses, it was found that during the follow-up period of four years, an age of more than 12 months at the initial index admission (with an OR of 2.49, a 95% CI of 1.53–4.05 and a $p$ of less than .001), a history of wheezing (with an OR of 2.31, a 95% CI of 1.43–3.75 and a $p$ of .001) and atopic eczema (with an OR of 2.40, a 95% CI of 1.46–3.94 and a $p$ of .001) were associated with more frequent uses of asthma control medication during the 12 months prior to the follow-up. In contrast, the presence of siblings was a protective factor (with an OR 0.45 of 95%, a CI of 0.27–0.73 and a $p$ of .001). However, in final multivariable analyses, only a history of eczema was a significant risk factor for that time period (with an aOR of 2.13, a 95% CI of 1.24–3.69 and a $p$ of .007). When children with RV-C infections were analysed separately, those who had both histories of atopic eczema and fevers greater than 37.5°C when they were first hospitalised were more likely to use asthma medication four years after contracting bronchiolitis (65% of children, with an aOR of 5.0 and a $p$ of .03) than children who had only histories of atopic eczema (50% of children, with an aOR 2.7 and a $p$ of .19), only fevers greater than 37.5°C (54% of children, with an aOR of 2.5 and a $p$ of .16) or neither (33% of children; see Figure 7).
Figure 7. The children’s use of asthma control medication four years after their index hospitalisations for bronchiolitis. The figure shows associations between histories of atopic eczema and fevers greater than 37.5°C and the use of asthma control medication for four years after hospitalisation for RV-C bronchiolitis. Figures are aORs from logistic regressions. aOR, adjusted odds ratio; RV, rhinovirus.

Further, an age of more than 12 months at a child’s time of admission (an HR of 2.41 with a 95% CI of 1.75–3.33 and a p of less than .001), being a male (an HR of 1.70 with a 95% CI of 1.19–2.43 and a p of .004), having a comorbid medical disorder (an HR of 1.75 with a 95% CI of 1.98–2.83 and a p of .02), having a history of wheezing (an HR of 2.96 with a 95% CI of 2.14–4.08 and a p of less than .001), having a history of atopic eczema (an HR of 2.38 with a 95% CI of 1.72–3.30 and a p of less than .001), the presence of siblings (an HR of 0.58 with a 95% CI of 0.42–0.80 and a p of .001) and the use of systemic corticosteroids (an HR of 3.06 with a 95% CI of 2.17–4.32 and a p of less than .001), together with the length of one’s hospital stay (an HR of 0.63 with a 95% CI of 0.43–0.91 and a p of .02, for hospitalisations greater than or equal to three days) were associated with the times until asthma control medication was begun in the four-year follow-up period. After final adjustments were made, however, only associations with a history of wheezing (an aHR of 1.88, a 95% CI of 1.31–2.71 and a p of .001) and a history of atopic eczema (an aHR of 1.74, a 95% CI of 1.22–2.49, and a p of .002) remained significant. Children who received systemic corticosteroids during their index hospitalisations used asthma control medication during the year prior to the first follow-up more often than other children (an aOR of 2.06, a 95% CI of 1.10–3.89 and a p of .03). Finally, in unadjusted analyses, it was found that at the time of the second follow-up, the use of systemic corticosteroids during the initial hospitalisation was associated with initiation time (an HR of 3.06, a 95% CI of 2.17–4.32 and a of less than .001) and asthma medication use (an OR of 2.29, a 95% CI of 1.33–3.94 and a p of .003), but in the multivariable model, the association was significant only for the initiation time (an aHR of 1.61, a 95% CI of 1.06–2.45 and a p of .03).
6 DISCUSSION

6.1 DESIGN AND METHODS

6.1.1 Studies I and II

Depending on the analysis in question, the numbers of children included in the Studies I and II were around 550 and 400, respectively, and these cohorts were large enough to enable analyses of associations between common respiratory symptoms and infections and their risk factors. The data were prospectively collected at different time points from the participants' pregnancies onwards. Study I included children only from rural environment, and although children from suburban areas were included in Study II, the results of both studies might be different from the results of studies conducted in more urban surroundings.

Many paediatric studies in this field have included only children with high risks of allergic diseases (Biagini et al., 2006; Copenhaver et al., 2004; Sumino et al., 2012; Zhang et al., 2009). However, in this study, no exclusions were made based on the atopic backgrounds, which might help in generalisations of the results.

The stimulated production of cytokines in CB cells was measured in a central laboratory. Overall, 279 children did not yield results for any studied cytokine, which indicates the sensitive natures of the analyses. Four different stimulants were used, and the results of cytokine production after P/I stimulation were selected for further analyses. Cytokine production largely depends on the use of a stimulant, and this needs to be considered when comparing the results of different studies. Further, many reports have noted associations between polymorphisms in cytokine encoding genes and different respiratory symptoms and infections (Alper, Winther, Hendley, & Doyle, 2009; Revai et al., 2009). However, environmental factors might affect levels of cytokine production apart from genes. Thus, these methodological differences must be considered when comparing studies on this subject.

Data on respiratory infections and symptoms were prospectively collected using weekly diaries, which is a strength of this study as the occurrence of some of the milder symptoms might be difficult to remember afterwards. However, no objectively collected examination-based data were available and, e.g., the incidences of middle ear infections are based on parental reports. Further, rhinitis, coughing and wheezing can be symptoms of both infections and atopic diseases, and this can complicate the interpretations of studies. Hence, coughing was determined to be coughing without wheezing for Study I, although when patients are young, wheezing episodes are often associated with viral infections (Turunen et al., 2014).

Information on pet contact was collected in two different ways: prospectively and retrospectively. This made the results more reliable. In particular, data on amount of pet contact was collected, and this was important to the interpretations of the results,
as environments where animals spend their time can affect human health. This study’s evaluation of the impacts of short time variations on amounts of animal contact was possible due to the weekly information gathered and the statistical methods that were used. Further, the results were presented separately for cats and dogs, which has not been done in every animal contact study (Burr et al., 1999; Hatakka et al., 2010; Rylander & Megevand, 2000; von Linstow et al., 2008).

It is possible that atopic parents choose not to adopt pets, and this influences the effects animal contact has on frequencies of respiratory tract symptoms and infections (Bornegag, Sundell, Hagerhed, & Janson, 2003; Hatakka et al., 2010). Hence, parental atopy was included in the multivariable analyses as a confounder, and with it, associations did not diminish. Similarly, associations did not change when analyses were repeated while excluding subjects with reported family histories of pet avoidance. There has been some evidence that atopic families do not necessarily avoid keeping pets (Bertelsen et al., 2010), but the influence of possible atopic predispositions on this study’s participants and results could not be completely eliminated.

### 6.1.2 Studies III and IV

The data for Studies III and IV were obtained from a prospective three-centre study on children two years old or younger who were hospitalised for bronchiolitis. The diagnosis of bronchiolitis is clinical, and in the MARC-30 study protocol, it was defined according to guidelines by the American Academy of Paediatrics. Children with bronchiolitis typically have acute respiratory illnesses with some combinations of rhinitis, coughing, tachypnea, wheezing, crackles and/or retractions (Subcommittee on Diagnosis and Management of Bronchiolitis, 2006). A history of previous wheezing was not an exclusion criterion for this study.

Across literature, the definition of bronchiolitis varies, e.g., concerning upper age limits and the inclusion of children with wheezing histories (Midulla, et al., 2010; Hasegawa, Tsugawa, Brown, Mansbach, & Camargo, 2013), and this needs to be taken into account when comparing the results of different reports. To overcome these challenges, analyses were conducted separately, including only children younger than 12 months old who did not have wheezing histories. The results did not substantially change, although the groups were smaller. In addition, differences in the definitions of bronchiolitis and viral wheezing illnesses that were used in different studies may have biased the literature search, leading to a misinterpretation of the results.

Standardised methods were used in the collection, preparation and storage of nasopharyngeal wash aspirates. Among the main strengths of this study was an extensive panel used for viral testing, including PCR tests for nearly all known respiratory viruses. This enabled the observation of the effects of coinfections, which are known to be common (Jartti, Lehtinen, Vuorinen, & Ruuskanen, 2009; Mansbach et al, 2012; Skjerven et al., 2016). Further, large number of RSV- and RV-positive patients allowed for comparisons between these groups.
The strengths of this study also included prospective data collection during hospitalisations and the follow-ups one and four years later with 89% and 86% participation rates, respectively. The follow-up data were collected through only questionnaires and telephone interviews, without clinical examinations or immunological tests; this was a limitation of the study. However, some data included in the analyses, such as the use of asthma control medication, could be collected reliably using the questionnaires (Koster et al., 2010).

Furthermore, the diagnosis of asthma is rarely based on objective diagnostic examinations of young children, and a wide range of lung symptoms can be predictive of asthma. After the second follow-up, patients’ records were checked to supplement information about initiations of asthma medication. The data might have been biased by the possibility that children whose parents felt the study was important and decided to reply to the questionnaire used asthma medication more often than children who were lost during the follow-up periods. The follow-ups of the children in this study were also relatively short and did not enable effective comparisons of different childhood asthma phenotypes in that regard. Finally, because all the participants were hospitalised, the results were not easy to generalise regarding children who had bronchiolitis that was not severe enough for hospitalisation and were treated at home.

6.2 IMMUNE RESPONSES AT BIRTH AND RESPIRATORY INFECTIONS IN INFANCY

In this study, both Th1-type and Th2-type cytokine responses at birth were found to predict a lower number of middle ear infections during the first year of life. Some, although less significant, associations were also found with other health and respiratory infection markers. This suggests that early regulations of adaptive immune responses may provide some protection from later infections.

IL-5 is a Th-2 type pro-inflammatory cytokine that impacts the development of allergic diseases and asthmatic inflammation. In this study, a higher CB IL-5 production level after the P/I stimulation was associated with an increased risk of presenting coughing without wheezing and a decreased risk of presenting a middle ear infection. The few extant studies published on this topic reported variable results, as high IL-5 production levels in CB cells have been linked to susceptibilities of acute respiratory infections (Zhang et al., 2009), and low IL-5 production levels in CB cells have been linked to more severe RSV infection (Juntti et al., 2009). Two studies have found, however, that there are no associations between IL-5 production and viral infections or wheezing (Copenhaver et al., 2004; Tadaki et al., 2009).

IFN-γ is a Th1-type pro-inflammatory cytokine that has numerous impacts on defences against different infections. In this study, its production was associated with more healthy weeks and fewer weeks with fevers and middle ear infections than a lack of such production. This is understandable, because IFN-γ has antiviral, immunostimulatory and immunomodulatory effects. The results agree with the
results of previous reports that have shown that low risks of RTIs and middle ear infections are associated with high IFN-γ production (Copenhaver et al., 2004; Ly et al., 2007; Sumino et al., 2012). Therefore, IFN-γ likely has a role in early immune maturations and in the maintenance of a healthy immune defence. This ability of leukocytes to produce IFN-γ during early life seems to be genetically determined.

The production of the Th2-type anti-inflammatory cytokine IL-10 in CB cells was not associated with the studied respiratory health outcomes. However, previously, genotypes associated with low IL-10 production levels were linked to increased risks of pneumonia during RSV infections (Gentile et al., 2003). Finally, high production levels of the acute phase proinflammatory cytokine TNF-α were associated with more non-healthy weeks and weeks with middle ear infections. These results support the findings of studies of different TNF-α phenotypes (Alper et al., 2009; Patel et al., 2006), though cytokine production studies are scarce. Altogether, the variations in results suggest that many factors affect the occurrence of RTIs and cytokine levels.

As aforementioned, environments can affect the production of cytokines and RTI morbidities in various ways (Pfefferle et al., 2010; Jackson, Gern, & Lemanske, 2017). For this study, some analyses were conducted separately for each of the four cohorts, and some differences between the study’s countries were detected. Disparities in living environments can partly explain these differences, because the surroundings of farms and homes may differ by country. Further, the use of health care facilities might also differ (van Esso et al., 2010), and this may have affected the reported frequencies of some symptoms and infections, such as middle ear infections. Finally, the frequencies of certain respiratory tract symptoms and infections for each cohort may indeed vary. When occurrences are low, the impacts of a few infected children can be significant in subgroup analyses.

These results suggest that at birth, adaptive immunity functions differ between children who will or will not develop respiratory infections during their first year. However, further studies are needed to clarify the impacts and potential significance of this finding in regard to the prevention of infections. One question that may guide future research is whether cytokine responses are causally related to the frequencies of respiratory infections or are proxies of other factors.

6.3 THE EFFECTS OF PET CONTACT ON HEALTH

This study showed that experiencing dog contact during infancy is associated with increased healthy weeks and that dog contact protects from respiratory tract symptoms and infections. Further, cat contact is associated with a weaker protective role than dog contact. These results support previous studies, which showed that acute respiratory tract symptoms and common cold episodes are less common among young children with furry pets, such as dogs, in their homes (Grüber et al., 2008; Hatakka et al., 2010). The protective effects of dog contact are particularly effective regarding middle ear infections, as was found in this study, and this can likely to be explained by the specific nature of the illness’s diagnosis compared to the
diagnosis of, e.g., rhinitis. However, the present study found no significant relationship between dog contact and occurrences of coughing and wheezing, and this supports some earlier results (Gold et al., 1999).

Cat contact also decreases risks of respiratory tract symptoms and infections, although not as strongly as dog contact. This association was weakened in adjusted analyses. Similarly, previous studies often found no connection between cat contact and respiratory infections or symptoms (Biagini et al., 2006; Gold et al., 1999). However, contrasting results have been presented, as croup was found to be less common among children with more cat contact in a Finnish study (Pruikkonen, Dunder, Renko, Pokka, & Uhari, 2009).

Although pet contact seems to be associated with fewer respiratory tract infectious disease morbidities, the effects of pets on health might change if different atopic diseases are considered. A meta-analysis showed that risks of atopic dermatitis reduced with dog exposure, but not with cat exposure (Pelucchi, Galeone, Bach, La Vecchia, & Chatenoud, 2013). In a pooled analysis of over 22,000 children, no associations were found between having dogs or cats at an age of younger than two years and allergic asthma or rhinitis at school age (Lødrup Carlsen et al., 2012). However, children with early dog contact were found to be less likely to have aeroallergen sensitisations later in their childhoods (Lødrup Carlsen et al., 2012). Previously, sensitisations to indoor allergens were shown to be associated with wheezing and asthma in childhood, but exposure to these allergens without sensitisation did not increase wheezing or asthma (Lau et al., 2000). Further, reductions in children’s risks of allergic sensitisations to dogs at six to seven years of age were found to be larger if the children were exposed to more than one dog during their first year (Ownby, Johnson, & Peterson, 2002). Finally, in some studies, the protective effects of dog contact on the symptoms of allergic diseases were seen only in children from families with no allergy histories (Pohlabeln, Jacobs, & Böhmann, 2007); other subgroup differences, e.g., race, sex and delivery mode, may exist (Wegienka et al., 2017).

Having a dog at home during early childhood or pregnancy has been associated with the production of many cytokines in infancy (Gern et al., 2004; Lappalainen et al., 2010). In addition, it has been shown that mothers with cats or dogs at home during their pregnancies deliver children with lower IgE levels in CB than mothers without cats and dogs (Aichbbaumik et al., 2008), and these lower levels can be seen during early childhood (Havstad et al., 2011) and may be associated with lower risks of allergic sensitisations (Kerkhof et al., 2005; Tariq, Arshad, Matthews, & Hakim, 1999). These findings indicate that pet contact influences the functions of the immune system even in early life.

The reasons for the protective effects of dog contact on respiratory disease morbidities, whether infectious or atopic, are obscure. One possible reason is that amounts of dirt are higher inside homes in which dogs live. This might stimulate infant immune systems to react efficiently to microbes, and this partially follows the hygiene hypothesis posited by Strachan (Strachan, 1989). In agreement with this
theory, and its evolved version, the ‘old friends hypothesis’ (Rook, 2010), is the finding that children who live in houses where dogs spend only part of their day inside have the lowest risks of respiratory tract symptoms and infections in this study. In many studies, dogs have been found to substantially affect microbial communities in regard to household dust (Levin et al., 2016; Maier et al., 2010; Sitark et al., 2018). It is possible that the amount of dirt and the diversity of microbes brought inside by dogs is higher if they spend more time outside.

The present results are in accordance with a study that compared 7–16 year olds in neighbouring towns on either side of the Finnish-Russian border in Karelia. There were large differences in the socio-economic conditions of the areas despite a short geographical distance. The study showed that dog contact during childhood was protective against asthma among Finnish children, but not among Russian children, for whom the cat contact increased risks of asthma (Hugg, Jaakkola, Ruotsalainen, Pushkarev, & Jaakkola, 2008).

In farm environments, high endotoxin levels have been found to be protective against atopic diseases (Braun-Fahrländer et al., 2002; Stein et al., 2016). Although no reductions have been seen in aeroallergen sensitisations or wheezing in relation to dog or endotoxin exposures, reduced wheezing has been present if endotoxin levels are high and a child has been exposed to more than one dog (Campo et al., 2006). Another study found that high levels of endotoxins were associated with increased risks of wheezing, although the risks decreased over time (Litonjua et al., 2002). Differences in atopic characteristics might be a factor explaining the variabilities of associations. However, exposures to endotoxins, ergosterol and muramic acid have not explained changes in immune development or reductions in wheezing and atopy associated with dog contact (Bufford et al., 2008).

In a Finnish study, children perinatally exposed to pets had wheezing bronchitis less frequently than non-exposed children during their first two years of life (Nermes et al., 2013). There also seemed to be differences in faecal samples obtained in early infancy; non-wheezing children exposed to pets had more Bifidobacterium longum in their faeces, and Bifidobacterium breve was more abundant among wheezing non-exposed children (Nermes et al., 2013). This emphasises the role of certain Bifidobacteria on the development of atopic diseases (Kalliomäki et al., 2001).

Despite this, the effects pet exposure has on children’s health remains unclear. There is no need to avoid pets to prevent infections or allergic diseases. On the contrary, pet exposure in infancy protects children from atopic diseases, likely due to changes to the compositions and diversities of microbiomes in homes and in children’s guts (Nermes, Endo, Aarnio, Salminen, & Isolauri, 2015). These findings have been confirmed in animal models (Fujimura et al., 2014). However, there are great variations in the effects of animal contact on health because species of animal, environments and amounts and timings of animal exposure, together with the atopic backgrounds of children, all affect the outcomes. The children included in the present study were primarily from the countryside, while some lived in suburban areas. The
effects of dog contact might have been different for urban areas, in which dogs spend more time inside, and the outside areas comprise streets and maintained parks.

6.4 THE VIRAL AETIOLOGIES OF BRONCHIOLITIS AND EARLY CHILDHOOD ASTHMA

This study showed that children hospitalised for RV bronchiolitis have high risks of later contracting asthma; almost three out of four children used asthma control medication during early childhood after RV bronchiolitis. This result supports a recent meta-analysis of associations between RV illnesses and the development of asthma (Liu et al., 2017). The use of asthma medication was most common among RV-infected children. The medications were also started quite early after the children were hospitalised for bronchiolitis, with fewer new medications started as the time elapsed.

In this study, 27% of children used asthma medication four years after their hospitalisation for bronchiolitis. This figure is similar to those presented in previous Finnish post-bronchiolitis studies (Kotaniemi-Syrjänen, Reijonen, Korhonen, & Korppi, 2002; Lukkarinen et al., 2017). This study’s children with RV-induced bronchiolitis used asthma control medication most often during the four-year follow-up period. While the proportion, 47%, was lower than the percentage of children with asthma in a previous Kuopio cohort (64%), it was higher than the percentage of children with asthma in a Turku cohort (34%) (Kotaniemi-Syrjänen, Reijonen, Korhonen, & Korppi, 2002; Lukkarinen et al., 2017). There are some differences in the studies that could explain these variations in proportions of asthma. The Turku cohort included children up to 36 months of age, and follow-up visits were close to school age in the Kuopio and Turku cohorts. In the present study, the youngest children were only four years old at the time of the follow-up. Finally, the present study compared the use of asthma medication among cohorts, but the other studies used asthma diagnoses as endpoints. Despite these differences, the proportions of children who used asthma medication (15%) and who were diagnosed with asthma (10–15%) after RSV infections were close (Kotaniemi-Syrjänen, Reijonen, Korhonen, & Korppi, 2002; Lukkarinen et al., 2017).

When infants who had bronchiolitis at an age of younger than six months were studied in Tampere, 14% of children with RV bronchiolitis and 8% of children with RSV bronchiolitis had asthma at 5–7 years old (Koponen et al., 2012). In the present study’s strict bronchiolitis criteria group, 16% of children used asthma medication after RSV infections, and 47% of children used asthma medication after RV infections. The figures after RV bronchiolitis were high, and this was likely due to the test panel including RV-C, which had not been used for all such studies previously.

The reasons behind increased risks of asthma after bronchiolitis are still unclear (Jartti & Gern, 2017). Viral wheezing illnesses might alter immunological responses, damage airways leading to later developments of asthmatic symptoms or merely unveil children prone to asthma. The children in this study were hospitalised, and
therefore, the results were not necessarily comparable to studies of children treated as outpatients. Hospitalised children most likely have more serious infections, which might affect their later prognoses (Carroll et al., 2009). However, these children may have some genetic or environmental factors that predispose them to both more severe infections and the development of asthma.

In this study, children hospitalised for bronchiolitis at younger than two months of age were less likely to use asthma control medication later on than children hospitalised for bronchiolitis at older ages. The higher proportion of RSV-positive children with fewer risk factors for asthma in this age group might explain this result. In addition, children at such a young age have anatomically small airways (Thurlbeck, 1982), and during all respiratory infections, these airways are easily blocked with mucus and other debris that cause obstructions. This can lead to hospitalisations because of difficulties in breathing and eating, regardless of type of virus and other risk factors, such as atopic histories.

Compared to non-RSV bronchiolitis cases, classic RSV bronchiolitis cases were associated with less frequent needs for later uses of asthma control medication. RSV bronchiolitis cases are known to be associated with profound changes in airway epithelia, and with various immunological effects, lead to recurrent wheezing and asthma (Henderson et al., 2005; Ruotsalainen, Hyvärinen, Piippo-Savolainen, & Korppi, 2013). However, whether this association between RSV infections and future respiratory symptoms has a direct causality has been debated. The effects of palivizumab, a monoclonal antibody that works against RSV, treatments of preterm infants on the later developments of asthmatic symptoms are unclear. A recent study showed that although palivizumab treatments decrease recurrent wheezing, the treatments have no effect on the development of atopic asthma by the age of six years among former preterm infants born from 33 to 35 weeks of gestation (Mochizuki et al., 2017). In otherwise healthy preterm children, the prevention of RSV infection with palivizumab had no major impacts on lung function or asthma at that same age (Scheltema et al., 2018).

RV causes less direct cytotoxicity than, e.g., RSV, but it is more extensive in terms of inflammatory responses to airway epithelia (Rossi & Colin, 2015). Evidence suggests that atopic children, especially if they have been sensitised to many environmental factors, are inclined to develop respiratory infections caused by RV (Jackson et al., 2012; Turunen, Jartti, Bochkov, Gern, & Vuorinen, 2016). Impaired antiviral responses are also associated with RV infections, both as risk factors and as consequences, e.g., in forms of low IFN production (Durrani et al., 2012; Gern et al., 2006). RV infections may cause changes to DNA methylation or RNA expressions of genes involved in asthma pathogeneses and immune responses against viral infections (Pech et al., 2018). Hence, RV infections may lead to more profound damages to the airways of atopic children, which may already be inflamed.

In the current study, RV-C was the most common RV species detected, and it was associated with the greatest risk for future uses of asthma control medication. Further, although RV-A was less common, it increased risks of later asthma
medication use as well. Previous studies have shown that RV-A and RV-C are associated with more severe diseases than the relatively rare species B (Cox & Bizzintino, 2013; Lee et al., 2012). A variant of CDHR3, a receptor for RV-C, has been associated with the development of asthma and RV-C respiratory illnesses and may partly explain the association between RV-C and asthma (Bønnelykke et al., 2018). Although the risk allele rs6967330-A has been found to be over-represented among wheezing children, they have had reduced CDHR3 mRNA levels (Stenberg Hammar et al., 2018). Nevertheless, gathering of knowledge of RV receptors is notable because the receptors might offer opportunities to treat these infections.

It should be noted that children with atopic eczema were found to be at risk for future uses of asthma medication after the children contracted RV-C bronchiolitis, especially if they had fever during the bronchiolitis. The association between RV-induced wheezing and the development of asthma among atopic children is well known (Kusel et al., 2007; Rubner et al., 2017). Some reports have shown febrile viral infections to be a risk factor for later wheezing and asthma in childhood (Kusel, Kebadze, Johnston, Holt, & Sly, 2012; von Mutius et al., 1999). A fever might indicate a stronger inflammatory process that caused more damage to tissues in airways. It seems that the airways of atopic children have a predisposition to chronic obstructions, which RV infections increase. However, as the children in this study with RV-induced bronchiolitis were older than children infected with other viruses and had more histories of wheezing and atopic eczema prior to their hospitalisations than the other children, it is possible that these children were predisposed to asthma and that no direct causality exists between RV bronchiolitis and the development of childhood asthma. However, the identification of this group of children with high risks of asthma is still notable when opportunities for preventing childhood asthma are considered.

As interest in microbiomes has increased in recent years, knowledge of variations of the compositions of airway microbiota has increased as well. The colonisation of airways during the neonatal period or during the first year of life with, e.g., Moraxella, Haemophilus or different Streptococcus species has been associated with respiratory infection severity (Hasegawa et al., 2016; Teo et al., 2015) and even later developments of asthma (Bisgaard et al., 2007; Teo et al., 2015). Different bacteria cause different immune stimulations of the airway mucosa, e.g., Moraxella and Haemophilus have mixed Th1-, Th2- and Th17-type responses, which may lead to chronic inflammation (Følsgaard et al., 2013). It has been suggested that RV infections cause shifts in the microbial compositions of airways that differ depending on symptom severity and, possibly, viral quantity (Kloepfer et al., 2017). Notably, nasopharyngeal microbiota were found to be distinct between children infected with RSV and RV (Mansbach et al., 2016), and even RV types might make a difference (Toivonen et al., 2019). In addition, RV and RSV were shown to be associated with divergent metabolic pathways, which may affect the development of asthma (Stewart et al., 2018).
Children hospitalised for RV bronchiolitis have high risks of future asthma control medication use. Such medication is given to young children if they have recurrent wheezing episodes, but research should investigate whether it should be started even earlier for children who are hospitalised with RV-induced wheezing. Although RV infections may not cause asthma, diminishing its inflammatory processes with asthma medication and removing symptoms of obstruction help children and their families. Further, the challenge of preventing the development of asthma should be addressed. Current data suggest that bronchiolitis consists of subgroups that have different risk factors, genetics, pathogeneses and aetiologies that lead to different responses to treatment and distinct prognoses (Jartti et al., 2019). The results suggest that preventive strategies targeting RV-C in particular, or the inflammatory response it induces, could help avert some asthma phenotypes in childhood.

6.5 FUTURE CONSIDERATIONS

The immunological system is complex, and there are numerous genetically regulated and environmental factors that affect the early life development of children’s immunity. Controlling these various modifiers and confounders is difficult when studying health and diseases in this field. Nevertheless, progress has occurred, but often, such progress has raised new questions.

The prevention of infections and the emergence of atopy, which primarily explain risks for later occurrences of wheezing, could be the ultimate goal. Instead of treating infections and allergic symptoms only when they are presented, the deleterious mechanisms of immunology that lead to these diseases should be blocked from turning on initially. CB cytokine studies help in evaluating the immune system before and shortly after birth. Perhaps expectant mothers may eat, breathe or touch something that guides immune reactions away from allergies and atopy to beneficial resistances against infectious microbes. For example, higher maternal vitamin D levels have decreased risks of asthma and wheezing among offspring (Wolsk, Harshfield et al., 2017; Wolsk, Chawes et al., 2017).

In the present study of rural and suburban surroundings, dog contact was found to reduce respiratory tract symptoms and infections in infancy. Globally, alterations occur often in microbiomes regarding the biodiversity of living environments, due to urbanisation, pollution and climate change. The beneficial effects of the farm environment on allergic diseases are well known, but it is not known if something concrete in the countryside can be transferred to urban living environment.

The development of medicines targeting respiratory viruses is challenging. Many microbes induce similar symptoms, and clinically, the diseases are often mild and self-limiting. Evidently, the amount of viral material in a host during an infection, as well as the duration of an infection, influence its later prognosis and, likely, the emergence of chronic diseases, such as asthma. These connections need further confirmation. Indeed, there might be a need for different treatment strategies for
bronchiolitis or other viral wheezing illnesses caused by different viruses in different individuals. As children with RV wheezing illnesses are at the greatest risk of use of asthma medication later on, particular attention should be given to this population.

Currently, recommendations for diagnoses and treatments of bronchiolitis do not include virological testing. If it is conducted, it is primarily used for determining cohorts of children in hospital wards. However, it has been suggested that treating children who have severe RV-induced wheezing illnesses with oral prednisolone may prevent the development of asthma (Jartti et al., 2015; Koistinen et al., 2017; Lehtinen et al., 2007; Lukkarinen et al., 2013). If this is confirmed in various populations, there might be a reason to perform quick virological tests for bronchiolitis on patients in clinical practices. Since the introduction of multiple bedside tests, viral testing is easier and cheaper than in the past. The present study showed that RV types affect prognoses. RV-C was found to be more common than RV-A, but the number of children, especially in the RV-A group, was too small to form any final conclusions. Future studies should evaluate whether patients with RV-A or RV-C associated wheezing differ in terms of clinical characteristics and other risk factors of later developments of asthma.

Some biomarkers can be used in the phenotyping of asthma, including eosinophils, other markers of eosinophil activity, total and specific IgE, and fractional exhaled nitric oxide, which primarily reflect Th2-type immune reactions. Omalizumab is a monoclonal antibody that binds to human IgE and is currently used to treat severe, chronic asthma and urticaria. It has improved asthma control and reduced the seasonal peaks of exacerbations often associated with RV infections (Lanier, et al., 2009; Busse et al., 2011; Jartti et al., 2018). Notably, omalizumab also improves IFN-α responses to RV, and thus, this biological drug may have antiviral properties (Teach et al., 2015). In general, more personalised and specific treatments and, hopefully, prevention strategies that consider the precise processes behind inflammation may be available for asthma in the future.
7 CONCLUSIONS

The aim of this study was to determine what factors affect the frequencies of respiratory infections and post-bronchiolitis asthma in young children. The following four conclusions can be made:

1. The responses of the Th1-associated cytokine IFN-γ and the Th2-associated cytokine IL-5 at birth, assessed using CD cytokine production, provide protection from later developments of middle ear infections. This and other minor findings suggest that the functional status of the adaptive immunity may be different at birth for children who will or will not develop respiratory infections during the first years of their lives.

2. Dog contact seems to have a protective effect on RTIs during the first year of life. This beneficial association is strongest in regards to middle ear infections. Similar but weaker associations exist for cat contact.

3. Children hospitalised for RV-positive bronchiolitis use asthma control medication more often, and start such use earlier, than children hospitalised for RV-negative bronchiolitis during the first and fourth years after the infection.

4. The most commonly detected RV species is type C, and this type has the strongest association with the later uses of asthma control medication, especially if a child has a history of atopic eczema and a fever during hospitalisation.

There are differences in immunological responses from early life on, and these differences are affected by environments. Because of this, the ways we react to and are impacted by microbes vary. Thus, there are many phases that can be researched to determine opportunities for preventive measures and to enhance children’s respiratory health.

7.1 RESEARCH IMPLICATIONS

CB cells may be used to study the earliest phase of immunity in a subject. This study examined four cytokines in CB, including the pro-inflammatory Th1 and Th2 and anti-inflammatory Th2 types of cytokines. The results showed that both Th1 IFN-γ and Th2 IL-5 cytokines protect from middle ear infections. These findings can be used as a basis to study other cytokines and mechanisms beyond cytokine production.
Dog contact in early life is protective from middle ear infections, and RTIs in general. Further research with follow-up studies, which in this paper were limited to 12 months, needs to be conducted. For example, follow-up periods that continue until participants reach school age would allow for evaluations of the associations of early-life dog contact and CB cytokines with childhood asthma and allergies.

Children hospitalised for RV wheezing at a young age were found to be at risk of contracting asthma, but whether the infection affects only children with atopy and asthma, which are often subclinical at that age, or truly affects the emergence of asthma, needs to be clarified. In both cases, the recognition of the RV aetiologies assists in identifying young children with high asthma risks. Future studies can hopefully determine whether RV-A and RV-C contribute differently to childhood wheezing and subsequent asthma. Another notable topic for future studies is the link between dog contact at home during pregnancies, CB cytokine levels at birth, RV-induced wheezing in infancy and asthma and allergies at school age. However, a new study should be conducted, because CB cytokines and RV determinations were not obtained from the same subjects used for this research.

### 7.2 PRACTICE IMPLICATIONS

The results of this thesis confirmed the beneficial effects of early life dog contact on decreasing middle ear infections in infancy and on decreasing antibiotic courses. However, any conclusions, such as recommendations of dog keeping in families with expectant mothers and young children, cannot be made at this time. The results may be interpreted at a general population level in that time spent in different natural environments with diverse microbiota, including, e.g., contact with dogs, may be recommendable.

The results of this study also confirmed that asthma control medication is often needed after RV-induced wheezing, especially after wheezing induced by RV-C. However, preventing the development of asthma is challenging. Indeed, bronchiolitis and viral wheezing presented in young children form heterogeneous groups that consists of different disease entities. The most important factors separating these entities are age, disease severity, clinical atopy, atopic diathesis, and, as confirmed in this study, viral aetiologies of wheezing. Consequently, bedside tests for respiratory viruses, including RVs, and, perhaps specifically, RV-C, should be conducted for at least young children hospitalised for wheezing. Infants who present with bronchiolitis and young children who present with viral wheezing form the greatest group that requires hospital care among children with no underlying diseases. While high-technology solutions are being researched, much can be done with traditional clinical methods: the use of careful examinations to correctly diagnose illnesses and the use of careful anamnesis to correctly identify wheezing subgroups.
REFERENCES

Acute otitis media. Current Care Guidelines. Working group set by the Finnish Medical Society Duodecim, the Finnish association of otorhinolaryngology and head and neck surgery, the Finnish Paediatric Society, the Finnish Otolaryngological Society and the Finnish Association for General Practice, 2017 (referred November 6, 2019). Available online at: www.kaypahoito.fi


asthma on the cause and severity of infant acute respiratory tract infections. 
Journal of Allergy & Clinical Immunology, 129(5), 1236-1242.


SMAD3 methylation at birth to asthma in children of asthmatic mothers. *Journal of Allergy & Clinical Immunology, 140*(2), 534-542.


function, and exhaled nitric oxide. *Journal of Allergy & Clinical Immunology, 130*(2), 382-388.e6.


respiratory syncytial virus infection. *Journal of Allergy & Clinical Immunology, 124*(1), 52-58.e2.

Kalliomäki, M., Kirjavainen, P., Eerola, E., Kero, P., Salminen, S., & Isolauri, E. (2001). Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *Journal of Allergy & Immunology, 107*(1), 129-134.


Koster, E. S., Wijga, A. H., Raaijmakers, J. A. M., Koppelman, G. H., Postma, D. S.,
Kerkhof, M., Hoekstra, M. O., de Jongste, J. C., Smit, H. A., Brunekreef, B., &
Maitland-van der Zee, A. H. (2010). High agreement between parental reported
inhaled corticosteroid use and pharmacy prescription data. *Pharmacoepidemiology
& Drug Safety, 19*(11), 1199-1203.

Wheezing requiring hospitalization in early childhood: Predictive factors for
asthma in a six-year follow-up. *Pediatric Allergy & Immunology, 13*(6), 418-425.

Kotaniemi-Syrjänen, A., Vainionpää, R., Reijonen, T. M., Waris, M., Korhonen, K., &
Korppi, M. (2003). Rhinovirus-induced wheezing in infancy—the first sign of
childhood asthma? *Journal of Allergy & Clinical Immunology, 111*(1), 66-71.

(2001). Persistent wheezing in very young children is associated with lower
respiratory inflammation. *American Journal of Respiratory & Critical Care Medicine,
163*(6), 1338-1343.


(2006). Role of respiratory viruses in acute upper and lower respiratory tract
illness in the first year of life: A birth cohort study. *The Pediatric Infectious Disease

respiratory illnesses in infancy and atopy are risk factors for persistent asthma

Kusel, M. M. H., de Klerk, N. H., Kebadze, T., Vohma, V., Holt, P. G., Johnston, S. L.,
& Sly, P. D. (2007). Early-life respiratory viral infections, atopic sensitization, and
risk of subsequent development of persistent asthma. *Journal of Allergy & Clinical Immunology, 119*(5), 1105-1110.


sepsis, and chronic lung disease: A 13-year hospital cohort study. *Pediatrics,
123*(5), 1314-1319.

Three Study Group. (2009). Global variation in the prevalence and severity of
asthma symptoms: Phase three of the international study of asthma and allergies
in childhood (ISAAC). *Thorax, 64*(6), 476-483.

Omalizumab for the treatment of exacerbations in children with inadequately
controlled allergic (IgE-mediated) asthma. *Journal of Allergy & Clinical Immunology, 124*(6), 1210-1216.


after bronchiolitis is associated with rhinovirus infections and blood eosinophilia. *Acta Paediatrica,* 103(10), 1094-1099.


N., & Knight, R. (2013). Cohabiting family members share microbiota with one another and with their dogs. *eLife, 2*, e00458. doi:10.7554/eLife.00458


treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *Journal of Allergy & Clinical Immunology, 136*(6), 1476-1485.


APPENDICES

APPENDIX A: LUKAS/PASTURE STUDY WEEKLY DIARY FORM

APPENDIX B: MARC-30 FINLAND ONE-YEAR FOLLOW-UP QUESTIONS

APPENDIX C: MARC-30 FINLAND FOUR-YEAR FOLLOW-UP QUESTIONS
Lapsuuden kasvuympäristö ja allergiat 2

TERVEYSPÄIVÄKIRJA

VIIKOT 1 - 4

KANSANTERVEYSLAITOS
YMPÄRISTÖTERVEYS
KUOPIO
1. Viikko

Täyttöpäivä: _____ / _____  20 _____
Aikaväli:  _____ / _____  -  _____ / _____

1. Lapseni on ollut terve ja pirteä viimeisten 7 päivän ajan.
   1) Ei
   2) Kyllä  ⇒ siirtyää suoraan kysymykseen 6

2. Lapseni on ollut sairas viimeisten 7 päivän aikana, hänellä oli ...
   1) yskää _____ päivän ajan
   2) hengityksen vinkunaa tai pihinää _____ päivän ajan
   3) nuhaa _____ päivän ajan
   4) kuumetta (yl 38,5°C) _____ päivän ajan
   5) välikorvantulehdus _____ päivän ajan
   6) keuhkokuume _____ päivän ajan
   7) ripulia vähintään 2 päivän ajan _____ päivän ajan
   8) virtsatieinfektio _____ päivän ajan
   9) kuitavaa ihottomaa käsivarsissa, sääriä tai kasvoissa _____ päivän ajan
   10) muita sairauksia, mitä? _____ päivän ajan

________________________________________________________________________
________________________________________________________________________

3. Käytimme lasta lääkärissä viimeisten 7 päivän aikana, koska hänellä oli:

Diagnoosi: ____________________________________________________________

4. Lapseni oli sairaalahoidossa viimeisten 7 päivän aikana, koska hänellä oli:

________________________________________________________________________
Sairaalahoito kesti _____ päivää
5. **Lapseni on saanut viimeisten 7 päivän aikana seuraavia lääkkeitä (myös rohdistuotteet, vaatteet):**

<table>
<thead>
<tr>
<th>Laakkeen nimi</th>
<th>Laakehoidon kesto</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>___ paivaa</td>
</tr>
<tr>
<td></td>
<td>___ paivaa</td>
</tr>
<tr>
<td></td>
<td>___ paivaa</td>
</tr>
</tbody>
</table>

6. **Lapseni on ollut navetassa, sikalassa tai hevostallissa viimeisten 7 päivän aikana**

| 1 | Ei |
| 2 | Kyllä Yhteensä tämän viikon aikana noin ___ tunnin ajan |

7. **Lapseni on ollut kanalassa viimeisten 7 päivän aikana**

| 1 | Ei |
| 2 | Kyllä Yhteensä tämän viikon aikana noin ___ tunnin ajan |

8. **Lapseni on ollut heinäladossa viimeisten 7 päivän aikana**

| 1 | Ei |
| 2 | Kyllä Yhteensä tämän viikon aikana noin ___ tunnin ajan |

**KOIRAT JA KISSAT**

9. **Kotonamme sisätiloissa on ollut koira ( tai koiria) viimeisten 7 päivän aikana**

| 1 | Ei lainkaan |
| 2 | Kyllä, koira oli vähän sisällä (keskimäärin alle 2 tuntia päivässä) |
| 3 | Kyllä, koira oli sisällä keskimäärin 2-6 tuntia päivässä |
| 4 | Kyllä, koira oli sisällä keskimäärin 6-16 tuntia päivässä |
| 5 | Kyllä, koira oli pääosin sisällä (keskimäärin yli 16 tuntia päivässä) |

10. **Kotonamme sisätiloissa on ollut kissa ( tai kissoja) viimeisten 7 päivän aikana**

| 1 | Ei lainkaan |
| 2 | Kyllä, kissa oli vähän sisällä (keskimäärin alle 2 tuntia päivässä) |
| 3 | Kyllä, kissa oli sisällä keskimäärin 2-6 tuntia päivässä |
| 4 | Kyllä, kissa oli sisällä keskimäärin 6-16 tuntia päivässä |
| 5 | Kyllä, kissa oli pääosin sisällä (keskimäärin yli 16 tuntia päivässä) |

11. **Viimeisten 7 päivän aikana lapseni on viettänyt aikaa kodin ulkopuolella sisätiloissa (esimerkiksi hoitajan tai isovanhempien luona), jossa on samanaikaisesti ollut koira tai koiria**

| 1 | Ei lainkaan |
| 2 | Kyllä, keskimäärin alle 2 tuntia päivässä |
| 3 | Kyllä, keskimäärin 2-6 tuntia päivässä |
| 4 | Kyllä, keskimäärin 6-16 tuntia päivässä |
| 5 | Kyllä, keskimäärin yli 16 tuntia päivässä |
12. Viimeisten 7 päivän aikana lapseni on vietänyt aikaa kodin ulkopuolella sisätiloissa (esimerkiksi hoitajan tai isovanhempien luona). Jossa on samanaikaisesti ollut kissa tai kissoja
1 Ei lainkaan
2 Kyllä, keskimäärin alle 2 tuntia päivässä
3 Kyllä, keskimäärin 2-6 tuntia päivässä
4 Kyllä, keskimäärin 6-16 tuntia päivässä
5 Kyllä, keskimäärin yli 16 tuntia päivässä

13. Oletteko imettänyt lastanne viimeisten 7 päivän aikana?
1 Kyllä, lapseni on saanut vain rintamaitoa. Olen imettänyt lastani keskimäärin _____ kertaa päivässä ⇒ siirtykää suoraan kysymykseen 15
2 Kyllä, mutta lapseni on saanut muutakin ruokaa kuin rintamaitoa. Olen imettänyt lastani keskimäärin _____ kertaa päivässä
3 En

14. Lapseni sai seuraavaa äidinmaidonkorviketta:

________________________

15. Lapseni on saanut lehmänmaitoa suoraan omalta tai toiselta tilalta viimeisten 7 päivän aikana
1 Ei
2 Kyllä _________ tuttipullolista (noin 200 ml) päivässä

16. Lapseni oli viimeisten 7 päivän aikana yhdessä muiden kuin sisarustensa kanssa esimerkiksi lapsenvahdin hoitamana, päivähoidossa tai äiti-lapsi – piireissä?
1 Ei
2 Kyllä yhdessä noin _____ lapsen kanssa

Jos vastasitte Kyllä:
Lapseni oli viimeisten 7 päivän aikana suunnilleen _________ tuntia muiden lasten kuin sisarustensa kanssa.

KIITOS!
MARC-30
TUTKIMUS

1. VUODEN KYSELYLOMAKE
ASTMAN KEHITTYMISEN RISKITEKIJÄT

1) Onko lapsen vanhemilla koskaan ollut astmaa?
   1) kyllä
   2) ei

2) Onko lääkäri koskaan todennut lapsellanne atooppista ihottumaa?
   1) kyllä
   2) ei

3) Onko lapsellanne koskaan ollut uloshengityksen vinkunaa muulloin kuin flunssan yhteydessä?
   1) kyllä
   2) ei

4) Onko lapsellanne koskaan ollut allergiaa lemmikkieläimille?
   1) kyllä
   2) ei

   4b) Jos kyllä: Missä diagnoosi on tehty?
       ______________________________

5) Onko lapsellanne koskaan ollut siitepölyallergiaa?
   1) kyllä
   2) ei

   5b) Jos kyllä: Missä diagnoosi on tehty?
       ______________________________

6) Onko lapsellanne koskaan ollut pölypunkkiallergiaa?
   1) kyllä
   2) ei

   6b) Jos kyllä: Missä diagnoosi on tehty?
       ______________________________

7) Onko lääkäri koskaan sanonut, että lapsellanne on ruoka-aineallergia?
   1) kyllä
   2) ei

   Jos kyllä:
   7b) Mitä allergioita?
       ______________________________

   7c) Missä diagnoosi on tehty?
       ______________________________

8) Onko lapsellanne koskaan otettu verikokeita allergiatestejä varten?
   1) kyllä
   2) ei

   8b) Jos kyllä: Missä näytteet on otettu?
       ______________________________
LAPSEN TERVEYDENTILA KULUNEEN 12 KUUKAUDEN AIKANA
(Lukuun ottamatta sairaalahoitojaksoa, jolloin teitä pyydettiin mukaan tutkimukseen!)

9) Onko lapsellanne ollut uloshengityksen vinkunajaksoja tai astman
pahenemisvaiheita?
   1) kyllä
   2) ei

   9b) Jos kyllä: Kuinka monta jaksoa? _________

10) Onko lapsellanne ollut tiukkaa yskää (lukuun ottamatta kohdan 9
vinkunajaksoja)?
   1) kyllä
   2) ei

   10b) Jos kyllä: Kuinka monta jaksoa? _________

11) Onko lapsen hyötynyt keuhkoputkia avaavasta astmalääkkeestä (ns.
bronkodilataattorista esim. Airomir, Bricanyl, Serevent tai Ventoline)
uloshengityksen vinkunajaksojen tai astman pahenemisvaiheiden aikana?
   1) kyllä
   2) ei

   11b) Jos kyllä: Kuinka monen jakson aikana? _________

   11c) Alleviivaa käytössä oleva valmiste: Airomir Bricanyl Serevent Ventoline

12) Onko lapsen hyötynyt hyötynyt keuhkoputkia avaavasta astmalääkkeestä
(ns. bronkodilataattorista esim. Airomir, Bricanyl, Serevent tai Ventoline)
tiukkojen yskäjaksojen aikana (lukuun ottamatta kohdan 11 vinkunajaksoja)?
   1) kyllä
   2) ei

   12b) Jos kyllä: Kuinka monen jakson aikana? _________

   12c) Alleviivaa käytössä oleva valmiste: Airomir Bricanyl Serevent Ventoline

13) Onko lapsellanne ollut uloshengityksen vinkunajaksoja tai astman
pahenemisvaiheita, jotka kestivät kauemmin kuin vuorokauden ja vaikuttivat
lapsen uneen?
   1) kyllä
   2) ei

   13b) Jos kyllä: Kuinka monta jaksoa? _________

14) Onko lapsellanne ollut tiukan yskän jaksoja, jotka kestivät kauemmin kuin
vuorokauden ja vaikuttivat lapsen uneen (lukuun ottamatta kohdan 13
vinkunajaksoja)?
   1) kyllä
   2) ei

   14b) Jos kyllä: Kuinka monta jaksoa? _________
15) Onko lapsenne tarvinnut avaavaa lääkettä jatkuvan hengityksen vinkunan, tiukan yskän tai astman pahenemisen vuoksi toistuvasti yli kuukauden ajan (toistuvalla tarkoittamme useammin kuin kaksi kertaa viikossa)?
   1) kyllä
   2) ei

16) Onko lapsellanne ollut akuuttia uloshengityksen vinkunaa, tiukkaa yskää tai astman pahenemisvaiheita, jolloin hän on tarvinnut systeemistä (suun kautta, lihakseen tai verisuoneen annettuna) kortikosteroidia (Prednison, Prednisolon, Dexametason tai Oradexon)?
   1) kyllä
   2) ei

16b) Jos kyllä: Kuinka monen jakson aikana? _________

17) Onko lapsellanne ollut akuutti uloshengityksen vinkunaa, tiukkaa yskää tai astman pahenemisvaiheen jaksoa, jolloin hän tarvitsi systeemistä kortikosteroidia?
   1) kyllä
   2) ei

18) Onko lapsellanne ollut päivystyskäyntejä lääkärissä akuutin uloshengityksen vinkunaa, tiukan yskän tai astman pahenemisen vuoksi (lukeen ottamatta kertoja jolloin hänet otettiin sairaalaan osastolle)?
   1) kyllä
   2) ei

   Jos kyllä:

   18b) Kuinka monta kertaa? _________

   18c) Missä terveyskeskuksessa tai sairaalassa olette käyneet?

19) Onko lapsellanne ollut akuttiin hengityksen vinkunaa, tiukkaa yskää tai astman pahenemisvaiheita, jolloin hänet otettiin hoitoon sairaalaan osastolle?
   1) kyllä
   2) ei

   Jos kyllä:

   19b) Kuinka monta kertaa?________

   19c) Missä sairaalassa lapsenne oli hoidossa?

20) Onko lapsellenne määrätty viimeisen 12 kuukauden aikana säännöllistä hoitavaa lääkitystä toistuvan hengityksen vinkunaa, pitkittyneen yskän tai astman vuoksi?
   1) kyllä
   2) ei

   Jos kyllä:

   20b) Milloin lääkitys aloitettiin (kk/v)? ____/____

   20c) Missä lääkitys aloitettiin?

   20d) Kuinka monta kuukautta lääkettä on käytetty? _____kk

   20e) Onko hoitavaa lääke ollut käytössä viimeisen kuukauden aikana?
      1) kyllä
      2) ei
21) Onko lääkäri kutsunut viimeisen vuoden aikana lapsen hengitysvaikeutta "astmaksi"?
   1) kyllä
   2) ei

   Jos kyllä:
   21b) Milloin ensimmäisen kerran (kk/v)? ____/____
   21c) Missä? ____________________________

22) Onko lapsellanne ollut kutiavaa ihottumaa (atooppista ihottumaa) viimeisten 12 kk aikana?
   1) kyllä
   2) ei

   22b) Jos vastasitte kyllä: Onko ihottumaa ollut jossakin seuraavista paikoista: kyynärtaipeet, polvitaipeet, nilkkojen etupuoli, pakarataipeet, niska, kaula tai korvien ja silmien ympärillä?
       1) kyllä
       2) ei

23) Onko lapsellanne esiintynyt allergista nuhaa tai allergisia silmäoireita (eli nuha tai silmäoireita ilman kautta välittyvistä allergeneista kuten siitepölystä, huonepölystä tai eläimistä)?
   1) kyllä
   2) ei

   Jos kyllä:
   23b) Milloin alkoi (kk/vuosi): ____/____
   23c) Mikä on todennäköisesti aiheuttaja?
       ____________________________________________________________

24) Onko lapsellanne käytössä jokin muu kuin tässä kaavakkeessa aiemmin kysytty säännöllinen (>1 kk jatkunut) lääkitys?
   1) kyllä
   2) ei

   24b) Jos kyllä:
       Mikä Milloin alkoi Kesto yht. (kk) Mistä määrätty
       ____________________________________________________________
       ____________________________________________________________
       ____________________________________________________________

   AIKAISEMPI TERVEYDENTILA

   Onko lapsellanne edeltävää vuotta aiemmin ollut

25) Akuutti uuloshengitysvaikeus tai bronkioliitti?
   1) kyllä
   2) ei

   25b) Jos kyllä. Milloin 1. kerran (kk/vuosi): ____/____
26) Lääkärin toteama atooppinen ihottuma?
   1) kyllä
   2) ei

   26b) Jos kyllä. Milloin alkoi (kk/vuosi): ___ / _____

27) Allerginen nuha?
   1) kyllä
   2) ei

   27b) Jos kyllä: Milloin alkoi (kk/vuosi): ___ / _____

28) Jokin muu pitkäaikaissairaus, mikä?

-----------------------------------------------

KYSYMYKSIÄ LAPSEN TAUSTASTA

29) Millainen on asuinpaikkanne?
   1) kaupunki
   2) maaseudun taajama
   3) maaseudun haja

30) Onko lapsenne viikoittain tekemisissä eläinten kanssa?
   1) kyllä
   2) ei

   30b) Jos kyllä: Minkä? _______________________________________

31) Onko teillä nykyisin lemmikkieläimiä?
   1) kyllä
   2) ei

   31b) Jos kyllä: Mitä eläimiä? __________________________________

32) Käykö lapsenne tiloissa, joissa pidetään eläimiä?
   1) kyllä
   2) ei

   Jos kyllä:
   32b) Missä?
   1) navetassa
   2) sikalassa
   3) hevostallissa
   4) muu, mikä?

   32c) Kuinka usein lapsenne käy edellä mainituissa tiloissa?
   1) päivittäin tai useimpina päivinä
   2) 1-2 kertaa viikossassa
   3) 1-2 kertaa kuukaudessa
   4) harvemmin
33) Tupakoidaan kotonanne (kukaan/missään)?
   1) kyllä (isä, äiti vai lastenhoitaja, ympyröi)
   2) ei

   33b) Jos vastasitte kyllä: Tupakoidaan siellä,
   1) yleensä sisätiloissa
   2) yleensä ulkotiloissa
   3) aina ulkotiloissa

34) Mikä on lapsenne päivähoitomuoto?
   1) koti
   2) perhepäiväkoti
   3) päiväkoti
   4) muu hoitopaikka,

35) Kokonaishoitoaika viimeisten 12 kuukauden aikana:
   27a) koti ___ kk
   27b) perhepäivähoito ___ kk
   27c) päiväkoti ___ kk

36) Perheen lasten lukumäärä tällä hetkellä (samassa taloudessa asuvat alle 18-vuotiaat)? _____ lasta

37) Kuinka monta vuotta lapsen äiti on opiskellut peruskoulun jälkeen?
   _____ vuotta

D-VITAMIINIKYSYMYKSET

37) Imetyksen kokonaiskesto: _____ kk

38) Onko D-vitamiini annettu neuvolanohjeiden mukaan?
   1) kyllä
   2) ei

39) Mitä valmistetta pääsääntöisesti käytitte (kauppanimi):

   __________________________

   Jos ette muista nimeä, käytettäinkö valmistetta
   1) 3-5 tippaa /vrk
   2) 12-20 tippaa /vrk

40) Unohtuiko D-vitamiinia antaa?
   1) hyvin vähän
   2) kohtalaisesti
   3) melko usein
   4) usein

41) Käyttääkö lapsenne tavallisia maitotuotteita?
   1) kyllä
   2) ei

42) Mahdolliset ruoka-aineroja/kohtelutukset:

   ____________________________________________________________
   ____________________________________________________________
ALLERGIA- JA ASTMAKYSYMÄKSET ÄIDILLÄ

Lapsen nimi: ________________________  Äidin nimi: ________________________

43) Onko lapsen äidillä koskaan ollut allergista nuhaa (eli hengitystieoireita ilman kautta välittyvistä allergeeneista kuten siitepölystä, huonepölystä tai eläimistä)?
   1) kyllä
   2) ei

Jos kyllä:
43b) Mitkä aiheuttivat?

43c) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
   1) kyllä
   2) ei

43d) Onko edelleen oireita, mutta lääkäri ei ole niitä varmistanut?
   1) kyllä
   2) ei

43e) Onko edelleen oireita ja tarvetta lääkärin seurantaan?
   1) kyllä
   2) ei

44) Onko lapsen äidillä koskaan ollut lääkärin toteamaa astmaa?
   1) kyllä
   2) ei

Jos kyllä:
44b) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
   1) kyllä
   2) ei

44c) Onko edelleen astmaoireita, mutta lääkäri ei ole niitä varmistanut?
   1) kyllä
   2) ei

44d) Onko edelleen astmaoireita ja tarvetta reseptiaistmalääkkeisiin?
   1) kyllä
   2) ei

44e) Oireiden aiheuttajat (esim. allergeenit, rasitus, kylmä ilma, flunssat, työperäiset tekijät, lääkkeet tms.)?

44f) Missä diagnostoiutu?
45) Onko lapsen äidillä koskaan ollut lääkärin toteamaa ruoka-allergiaa?

1) kyllä
2) ei

Jos kyllä:
45b) Mitkä varmistettu ihopistokeilla tai verikokeella?

___________________________________________________________
___________________________________________________________

45c) Mitkä varmistettu lääkärin valvomalla altistuksella?

___________________________________________________________

45d) Muut ruoja-allergiat

45e) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?

1) kyllä
2) ei

45f) Mistä ruoka-aineista tulee edelleen oireita?

___________________________________________________________

45g) Missä diagnosoitu ja testit tehty (kaikki)?

___________________________________________________________

46) Onko äidillä koskaan ollut lääkärin toteamaa atooppista ihottumaa?

1) kyllä
2) ei

Jos kyllä:
46b) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?

1) kyllä
2) ei

46c) Onko edelleen oireita, mutta tarvetta ajoittain tai säännöllisesti vain perusvoiteisiin tai korkeintaan mietoihin kortisonivoiteisiin?

1) kyllä
2) ei

46d) Onko edelleen oireita ja tarvetta keskivahvoihin- tai vahvoihin kortisonivoiteisiin, takro- tai pimekrolimuusivoiteisiin tai valohoitoihin?

1) kyllä
2) ei

46e) Missä diagnosoitu?
ALLERGIA- JA ASTMAKYSYMYSISÄLLE

Lapsen nimi: ________________________  Isän nimi: ________________________

47) Onko lapsen isällä koskaan ollut allergista nuhaa (eli hengitystieoireita ilman kautta välittyvistä allergeeneista kuten siitepölystä, huonepölystä tai eläimistä)?
   1) kyllä
   2) ei

Jos kyllä:
47b) Mitkä aiheuttivat?
___________________________________________________________

47c) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
   3) kyllä
   4) ei

47d) Onko edelleen oireita, mutta lääkäri ei ole niitä varmistanut?
   3) kyllä
   4) ei

47e) Onko edelleen oireita ja tarvetta lääkärin seurantaan?
   3) kyllä
   4) ei

48) Onko lapsen isällä koskaan ollut lääkärin toteamaa astmaa?
   1) kyllä
   2) ei

Jos kyllä:
48b) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
   3) kyllä
   4) ei

48c) Onko edelleen astmaoireita, mutta lääkäri ei ole niitä varmistanut?
   3) kyllä
   4) ei

48d) Onko edelleen astmaoireita ja tarvetta reseptiastmalääkkeisiin?
   3) kyllä
   4) ei

48e) Oireiden aiheuttajat (esim. allergeenit, rasitus, kylmä ilma, flunssat, työperäiset tekijät, lääkkeet tms.)?
___________________________________________________________

48f) Missä diagnosoitu?
49) Onko lapsen isällä koskaan ollut lääkärin toteamaa ruoka-allergiaa?

1) kyllä
2) ei

Jos kyllä:
49b) Mitkä varmistettu ihopistokokeilla tai verikokeella?

___________________________________________________________

49c) Mitkä varmistettu lääkärin valvomalla altistuksella?

49d) Muut ruoja-allergiat

49e) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
3) kyllä
4) ei

49f) Mistä ruoka-aineista tulee edelleen oireita?

49g) Missä diagnosoitu ja testit tehty (kaikki)?

50) Onko isällä koskaan ollut lääkärin toteamaa atooppista ihottumaa?

1) kyllä
2) ei

Jos kyllä:
50b) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
3) kyllä
4) ei

50c) Onko edelleen oireita, mutta tarvetta ajoittain tai säännöllisesti vain perusvoiteisiin tai korkeintaan mietoihin kortisonivoiteisiin?
3) kyllä
4) ei

50d) Onko edelleen oireita ja tarvetta keskivahvoihin- tai vahvoihin kortisonivoiteisiin, takro- tai pimekrolimuusivoiteisiin tai valohoitoihin?
3) kyllä
4) ei

50e) Missä diagnosoitu?

KUITOS!
MARC-30
-TUTKIMUS

4-5. VUODEN KYSELYLOMAKE

PÄIVÄMÄÄRÄ: / /

LAPSEN NIMI:
SYNTYMÄAIKKA:
LOMAKKEEN TÄYTTI:
OSOITE:
SÄHKÖPOSTI:
PUHELIN:
ASTMAN KEHITTYMISEN RISKITEKIJÄT

1) Onko lapsen vanhemilla koskaan ollut astmaa?
   1) kyllä    2) ei

2) Onko lääkäri koskaan todennut lapsellanne atooppista ihottumaa?
   1) kyllä    2) ei

3) Onko lapsellanne koskaan ollut uloshengityksen vinkunaa muulloin kuin flunssan yhteydessä?
   1) kyllä    2) ei

4) Onko lapsellanne koskaan ollut allergiaa lemmikkieläimille?
   1) kyllä    2) ei
   4b) Jos kyllä: Missä ja milloin diagnoosi on tehty?

5) Onko lapsellanne koskaan ollut sittepölyallergiaa?
   1) kyllä    2) ei
   5b) Jos kyllä: Missä ja milloin diagnoosi on tehty?

6) Onko lapsellanne koskaan ollut pölypunkkialler giaa?
   1) kyllä    2) ei
   6b) Jos kyllä: Missä ja milloin diagnoosi on tehty?

7) Onko lääkäri koskaan sanonut, että lapsellanne on ruoka-aineallergia?
   1) kyllä    2) ei
   Jos kyllä: 7b) Mitä allergioita?
   7c) Missä ja milloin diagnoosi on tehty?

8) Onko lapsellanne koskaan otettu verikokeita allergiatestejä varten?
   1) kyllä    2) ei
   8b) Jos kyllä: Missä näytteet on otettu?
LAPSEN TERVEYDENTILA VIIMEISEN KUUKAUDEN AIKANA

9) Kuinka usein lapsen nährä hengitysvaikeudesta kuten uloshengitysvaikeudesta, yskästä tai hengenahdistuksesta?
   1) ei lainkaan 2) 1-3 kertaa 3) kerran viikossa
   4) 2-3 kerta viikossa 5) 4 tai useampana kertoja viikossa 6) ei tietoa

10) Kuinka usein lapsen nährä heräsi keskellä yöä hengitysvaikeuden (uloshengitysvaikeuden, yskän tai hengenahdistuksen) vuoksi?
    1) ei lainkaan 2) 1-3 kertaa 3) kerran viikossa
    4) 2-3 kerta viikossa 5) 4 tai useampana kertoja viikossa 6) ei tietoa

11) Kuinka paljon hengitysvaikeudet kuten uloshengitysvaikeus, yskä tai hengenahdistus rajoittivat lapsen nährä leikkimistä, päivähoitoon menoaa tai muuta normaalia aktiviteettia?
    1) ei lainkaan 2) hieman 3) jonkin verran 4) melko paljon
    5) erittäin paljon

12) Kuinka monena päivänä viikossa keskimäärin lapsen nährätarvitsi hengitettävää keuhkoputkia avaaavaa lääkettä (esim. Airomir, Bricanyl, Buventol, Foradil, Formoterol, Oxis, Salbutamol, Serevent, Symbicort (kohtauslaakseen käytettynä), Ventilasin, Ventoline) hengitysvaikeuksien takia?
    1) ei lainkaan 2) harvemmin kuin kerran viikossa
    3) kerran viikossa 4) kahdesti viikossa
    5) kolme kerta viikossa 6) 4-5 kerta viikossa
    7) päivittäin 8) useita kertoja päivässä

LAPSEN TERVEYDENTILA VIIMEISEN 12 KUUKAUDEN AIKANA

13) Onko lapsellanne ollut uloshengitysvaikeutta tai astman pahennemisvalheita?
    1) kyllä 2) ei

13b) Jos kyllä: Kuinka monta jaksoa?
13c) Liittyikö tähän uloshengityksen vinkunaa tai pihinää?
    1) kyllä 2) ei

14) Onko lapsellanne ollut tiukkaa yskää (luukuun ottamatta kohdan 13 uloshengitysvaikeusjaksoja)?
    1) kyllä 2) ei

14b) Jos kyllä: Kuinka monta jaksoa?
15) Onko lapsenne hyötynyt nopeavaikutteisesta keuhkoputkia aavaavasta astmalääkkeestä eli ns. bronkodilataattorista esim. Airomir, Bricanyl, Buventol, Fomeka, Foradil, Formoterol, Oxis, Salbutamol, Serevent, Symbicort (kohtauslääkkeenä käytettyä), Ventilastin, Ventoline **ulooshengitysvaikeusjaksojen tai astman pahenemisvaiheiden aikana**?
   1) kyllä 
   2) ei

   15b) Jos kyllä: Kuinka monen jakson aikana?

   15c) Mitä valmistettu?:

16) Onko lapsenne hyötynyt nopeavaikutteisesta keuhkoputkia aavaavasta astmalääkkeestä eli ns. bronkodilataattorista esim. Airomir, Bricanyl, Buventol, Fomeka, Foradil, Formoterol, Oxis, Salbutamol, Serevent, Symbicort (kohtauslääkkeenä käytettyä), Ventilastin, Ventoline **tiukkojen yskäjaksojen aikana** (lukuun ottamatta kohdan 15 uloshengitysvaikeusjaksoja)?
   1) kyllä 
   2) ei

   16b) Jos kyllä: Kuinka monen jakson aikana?

   16c) Mitä valmistettu?:

17) Onko lapsellenne ollut **ulooshengitysvaikeusjaksoja tai astman pahenemisvaiheita**, jotka kestivät kauemmin kuin vuorokauden ja vaikuttivat lapsen ueneen?
   1) kyllä 
   2) ei

   17b) Jos kyllä: Kuinka monta jaksoa?

18) Onko lapsellenne ollut **tiukan yskän jaksoja**, jotka kestivät kauemmin kuin vuorokauden ja vaikuttivat lapsen ueneen (lukuun ottamatta kohdan 17 uloshengitysvaikeusjaksoja)?
   1) kyllä 
   2) ei

   18b) Jos kyllä: Kuinka monta jaksoa?

19) Onko lapsenelle tarvinnut toistuvasti avaavaa lääkettä jatkuvan uloshengityksen vaikeuden, tiukan yskän tai astman pahenemisen vuoksi toistuvasti yli kuukauden ajan (toistuvalla tarkoittamme useammin kuin kaksi kertaa viikossa)?
   1) kyllä 
   2) ei

20) Onko lapsellenne ollut **akuuttiuloshengityksen vaikeutta**, **tiukkaa yskää tai astman pahenemisvaiheita**, jolloin hän on tarvinnut systeemistä (suun kautta, lihakseen tai verisuoneen annettuna) kortikosteroidia (Prednison, Prednisolon, Dexametason tai Oradexon)?
   1) kyllä 
   2) ei

   20b) Jos kyllä: Kuinka monen jakson aikana?
21) Onko lapsellanne ollut kuuden kuukauden aikana vilmeisen 12 kuukauden sisällä vähintään kaksi akuutin uloshengityksen vaikeuden, tiukan yskän tai astman pahenemisvaiheen jaksoa, jolloin hän tarvitsi systeemistä kortikosteroidia eli kortikosteroidia (Prednison, Prednisolon, Dexametason tai Oradexon) tabletteina tai lihakseen tai suoneen annettuna?
   1) kyllä
   2) ei

22) Onko lapsellanne ollut päivystyskäytejä lääkärissä akuutin uloshengityksen vaikeuden, tiukan yskän tai astman pahenemisen vuoksi (lukuun ottamatta kertoja jolloin hänet otettiin sairaalan osastolle)?
   1) kyllä
   2) ei

   Jos kyllä:
   22b) Kuinka monta kertaa?
   22c) Missä terveyskeskuksessa tai sairaalassa olette käyneet?

23) Onko lapsellanne ollut akuuttie uloshengityksen vaikeutta, tiukkaa yskää tai astman pahenemisvaiheita, jolloin hänet otettiin hoitoon sairaalan osastolle?
   1) kyllä
   2) ei

   Jos kyllä:
   23b) Kuinka monta kertaa
   23c) Missä sairaalassa lapsenne oli hoidossa?

24) Onko lapsellenne määrätty viimeisen 12 kuukauden aikana säännöllistä hoitavaa lääkitystä (hengitettävää tai suun kautta otettavaa lääkettä esim. Aerobec, Astecen, Beclomet, Budesonid, Dexas, Depo-Medrol, Dexametason, Filoxotin, Lomudal freoniton, Medrol, Montelukast, Novopulmon, Prednison, Prednison, Pulmicort, Seretide, Singulair, Solomet, Solu-medrol, Symbicort, Tiade freoniton, Xolair) toistuvan uloshengityksen vaikeuden, pitkätyneen yskän tai astman vuoksi?
   1) kyllä
   2) ei

   Jos kyllä:
   24b) Mita lääkettä/lääkkeitä?
   24c) Milloin lääkitys aloitettiin (kk/vä)? /
   24d) Missä lääkitys aloitettiin?
   24e) Kuinka monta kuukautta lääkettä on käytetty?  kk
   24f) Onko hoitava lääke ollut käytössä viimeisen kuukauden aikana?
      1) kyllä
      2) ei

25) Onko lääkäri kutsunut lapsenne hengitysvaikutetta ”astmaksi”?
   1) kyllä
   2) ei

   Jos kyllä:
   25b) Milloin ensimmäisen kerran (kk/vä)? /
   25c) Missä?
26) Onko lapsellanne ollut *kutiava ihottumaa* (atooppista ihottumaa) viimeisten 12 kk aikana?
   1) kyllä  2) ei

26b) Jos vastasitte kyllä:
   Onko ihottumaa ollut jossakin seuraavista paikoista: kynärtalpeet, polvitalpeet, nikkojen etupuoli, pakaratalpeet, niska, kaula tai korvien ja silmien ympärillä?
   1) kyllä  2) ei

27) Onko lapsellanne esiintynyt *allergista nuhaa tai allergisia silmäoireita* (eli nuha tai silmäoireita ilman kautta välittyvistä allergineista kuten siitepölystä, huonepölystä tai elämistä johtuen)?
   1) kyllä  2) ei

   Jos kyllä:
   27b) Milloin alkoi (kk/vuosi): /
   27c) Mikä on todennäköisesti aiheuttaja?

28) Onko lapsellanne käytössä jokin muu kuin tässä kaavakkeessa aiemmin kysytty säännöllinen (≥1 kk jatkunut) lääkitys?
   1) kyllä  2) ei

28b) Jos kyllä:
   Mikä
   Milloin alkoi Kesto yht. (kk) Mistä määrätty

AIKAISEMPI TERVEYDENTILA
Onko lapsellanne edeltäneitä 12 kuukautta aiemmin ollut

29) Akuutti uloshengitysvalkeus tai bronkioliitti?
   1) kyllä  2) ei

29b) Jos kyllä. Milloin 1. kerran (kk/vuosi): /

30) Lääkärin toteama atooppinen ihottuma?
   1) kyllä  2) ei

30b) Jos kyllä. Milloin alkoi (kk/vuosi): /

31) Allerginen nuha?
   1) kyllä  2) ei

31b) Jos kyllä: Milloin alkoi (kk/vuosi): /
32) Jokin muu pitkäaikaisairausta, mikä?

KYSYMYSIÄ LAPSEN TAUSTASTA

33) Onko lapsellanne koskaan todettu astmaa?
   1) kyllä  
   2) ei

33b) Jos kyllä, milloin diagnoosi tehtiin

34) Onko lapsen syntyynyt alatlesynnytyksellä vai kelsarinleikkausella?
   1) alatle  
   2) kelsarinleikkaus

35) Millainen on asuinpaikkanne?
   1) kaupunki  
   2) maaseudun taajama-alue
   3) maaseudun haja-asutusalue

36) Onko lapsenne viikoittain tekemisissä eläinten kanssa?
   1) kyllä  
   2) ei

36b) Jos kyllä: Minkä?

37) Onko teillä nykyisin lemmikkieläimiä?
   1) kyllä  
   2) ei

37b) Jos kyllä: Mitä eläimiä?

38) Käykö lapsenne tiloissa, joissa pidetään eläimiä?
   1) kyllä  
   2) ei

Jos kyllä:
38b) Missä?
   1) navetassa  
   2)sikalassa  
   3)hevostalliissa
   4) muu, mikä?

38c) Kuinka usein lapsenne käy edellä mainituissa tiloissa?
   1) päivittäin tai useimpina päivinä  
   2) 1-2 kertaa viikossa
   3) 1-2 kertaa kuukaudessa
   4) harvemmin

39) Tupakoidaanko kotonanne (kukaan/missään)?
   1) kyllä (isä , äiti vai lastenhoitaja , valitse kaikki sopivat)
   2) ei

39b) Jos kyllä: Tupakoidaanko kotona,
   1) yleensä sisätiloissa  
   2) yleensä ulkotiloissa
   3) aina ulkotiloissa
40) Mikä on lapsenne päivähoitomuoto?
   1) koti  2) perhepäiväkoti  3) päiväkoti
   4) muu hoitopaikka, mikä?

41) Kokonaishoitoaika viimeisten 12 kuukauden aikana:
   41a) koti  kk
   41b) perhepäivähoito  kk
   41c) päiväkoti  kk

42) Perheen lasten lukumäärä tällä hetkellä (samassa taloudessa asuvat alle 18-vuotiaat)?  lasta

43) Kuinka monta vuotta lapsen äiti on opiskellut peruskoulun jälkeen?  vuotta

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D-VITAMIINIKSYMYKSET

44) Imetyksen kokonaiskesto:  kk

45) Onko D-vitamiini annettu neuvolanohjelmen mukaan?
   1) kyllä  2) ei

46) Mitä valmistetta pääsääntöisesti käyttö (kauppanimi):
   Jos ette muista nimeä, käytettiinkö valmistetta
   1) 3-5 tippaa /vrk  2) 12-20 tippaa /vrk

47) Unohtuiko D-vitamiinia antaa?
   1) hyvin harvoin  2) harvoin  3) melko usein
   4) usein

48) Käyttääkö lapsenne maitotuotteita?
   1) kyllä  2) ei

49) Mahdolliset ruoka-ainerajoitukset:

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KYSYMYS

50) Kun lapsen olis ulkona viime kesänä, kuinka usein hän:
a) käytti aurinkovoidetta jonka suojakerroin on vähintään 15?
   1) ei koskaan 2) harvoin 3) ajoittain
   4) usein 5) aina 6) ei tietoa

b) välitti suoraa aurinkopäistettä kello 10 ja 16 välisenä aikana? (Käytti suojaavia
   vaatteita tai pysyl sisätiloissa)
   1) ei koskaan 2) harvoin 3) ajoittain
   4) usein 5) aina 6) ei tietoa

51) Miten lapsenne iho reagoi 15-30 minuutin oleskeluun keskipäivän auringossa
   alkukesästä?
   1) palaa aina, el rusketu
   2) yleensä palaa, ruskettuu keskimääräistä vähemmän (ei helposti)
   3) joskus palaa hieman, ruskettuu keskimääräisesti
   4) palaa tuskin koskaan, ruskettuu keskimääräistä enemmän (helposti)
   6) ei tietoa

52 a) Viettikö lapsenne päivittäin aikaa ulkona auringossa?
   1) kyllä 2) ei

52 b) Jos kyllä: Motako tuntia keskimäärin:
   a) arkipäivinä  tuntia
   b) viikonloppuisin  tuntia

53) Vastasiko viimekesäinen auringolle altistumisen määrä lapsenne tavanomaista
   altistumisen määrää kesäaikaan?
   1) kyllä
   2) ei, vähemmän altistumista kuin normaalisti
   3) ei, enemmän altistumista kuin normaalisti
   4) ei tietoa

VAUVAUNITIKYSYMYS

54) Kävittekö lapsenne kanssa vauvaunissa?
   1) kyllä 2) ei

55) Minkä ikäisenä lapsenne aloitti vauvauninnit?  kk

56) Kuinka monta kertaa kävitte yhteensä vauvaunissa?  kertaa

57) Oliko vesi klooripitoista ulmahallivetä?
   1) kyllä 2) ei

Tässä olivat lastanne koskevat kysymykset. Kiitos vastaamisesta!
ALLERGIA- JA ASTMAKSYMYKSET ÄIDILLE

Lapsen nimi: Äidin nimi:

58) Onko lapsen äidillä koskaan ollut allergista nuhaa (eli hengitystieoireita ilman kautta välittyvistä ala- ja aita-asteissa kuten siltelöystä, huonepölyystä tai elämistä johtuen)?
   1) kyllä
   2) ei

Jos kyllä:
58b) Mitkä aiheuttivat?
58c) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
   1) kyllä
   2) ei
58d) Onko edelleen oireita, mutta lääkäri ei ole niitä varmistanut?
   1) kyllä
   2) ei
58e) Onko edelleen oireita ja tarvetta lääkärin seurantaan?
   1) kyllä
   2) ei

59) Onko lapsen äidillä koskaan ollut lääkärin toteamaa astmaa?
   1) kyllä
   2) ei

Jos kyllä:
59b) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
   1) kyllä
   2) ei
59c) Onko edelleen astmaoireita, mutta lääkäri ei ole niitä varmistanut?
   1) kyllä
   2) ei
59d) Onko edelleen astmaoireita ja tarvetta reseptiastmalääkkeisiin?
   1) kyllä
   2) ei
59e) Oireiden aiheuttajat (esim. ala- ja aita-asteissa, siltelöystä, huonepölyystä, työpäiväiset, jättäytyminen, tms.)?
59f) Missä diagnoositu?

60) Onko lapsen äidillä koskaan ollut lääkärin toteamaa ruoka-allergiaa?
   1) kyllä
   2) ei

Jos kyllä:
60b) Mitkä varmistetti ihopistokeilla tai verikokeella?
60c) Mitkä varmistetti lääkärin valvomalla altistuksella?
60d) Muut ruoka-allergiat
60e) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
   1) kyllä
   2) ei
60f) Mistä ruoka-alheltta tulee edelleen oireita?
60g) Missä diagnoositu ja testit tehty (kaikki)?
61) Onko äidillä koskaan ollut lääkärin toteamaa atooppista ihottomaa?
   1) kyllä    2) ei

Jos kyllä:
61b) Olko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
   1) kyllä    2) ei

61c) Onko edelleen oireita, mutta tarvetta ajoittain tai säännöllisesti vain
    perusvoiteisiin tai korkeintaan mietoihin kortisonivoiteisiin?
   1) kyllä    2) ei

61d) Onko edelleen oireita ja tarvetta keskivahvoihin- tai vahvoihin
    kortisonivoiteisiin, takro- tai pimekrolimuusivoiteisiin tai valoihoitoihin?
   1) kyllä    2) ei

61e) Missä diagnosolult?
ALLERGIA- JA ASTMUKSYMYKSET ISÄLLE

Lapsen nimi: Isän nimi:

62) Onko lapsen isällä koskaan ollut allergista nuhhaa (eli hengitystieoireita ilman kautta välittyvistä allergeneista kuten siitepölystä, huonepölyystä tai eläimistä johtuen)?
   1) kyllä 2) ei
   
   Jos kyllä:
   62b) Mitkä aiheuttivat?
   62c) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
      1) kyllä 2) ei
   62d) Onko edelleen oireita, mutta lääkäri ei ole niitä varmistanut?
      1) kyllä 2) ei
   62e) Onko edelleen oireita ja tarvetta lääkärin seurantaan?
      1) kyllä 2) ei

63) Onko lapsen isällä koskaan ollut lääkärin toteamaa astmaa?
   1) kyllä 2) ei
   
   Jos kyllä:
   63b) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
      1) kyllä 2) ei
   63c) Onko edelleen astmaoireita, mutta lääkäri ei ole niitä varmistanut?
      1) kyllä 2) ei
   63d) Onko edelleen astmaoireita ja tarvetta reseptiastmalääkkeisiin?
      1) kyllä 2) ei
   63e) Oireiden aiheuttajat (esim. allergeenit, rasitus, kylmä ilma, fnussat, työperäiset tekijät, lääkkeet tms.)?
   63f) Missä diagnosoitu?

64) Onko lapsen isällä koskaan ollut lääkärin toteamaa ruoka-allergiaa?
   1) kyllä 2) ei
   
   Jos kyllä:
   64b) Mitkä varmistettu ihopistokokeilla tai verikokeilla?
   64c) Mitkä varmistettu lääkärin valvomalla alkistusalla?
   64d) Muut ruoka-allergiat
   64e) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
      1) kyllä 2) ei
   64f) Mistä ruoka-aleneista tulee edelleen oireita?
   64g) Missä diagnosoitu ja testit tehty (kaikki)?
65) Onko isällä koskaan ollut lääkärin toteamaa atooppista ihottumaa?
   1) kyllä  2) ei

Jos kyllä:
65b) Oliko lapsena, mutta ei merkittäviä oireita enää ≥16-vuotiaana?
    1) kyllä  2) ei

65c) Onko edelleen oireita, mutta tarvetta ajottain tai säännöllisesti vain
     perusvoiteisiin tai korkeintaan mietoihin kortisonivoiteisiin?
     1) kyllä  2) ei

65d) Onko edelleen oireita ja tarvetta keskivahvoluin- tai vahvoluin
     kortisonivoiteisiin, takro- tai pimekrolimuusivoiteisiin tai valohoitoihin?
     1) kyllä  2) ei

65e) Missä diagnosoitut?

KIITOS!
Young children often contract respiratory infections. Bronchiolitis, a viral respiratory infection associated with the development of asthma, is one of the most common hospitalisation reasons in young children. However, there is a lack of information on how to prevent these diseases. This thesis addresses factors associated with frequent respiratory infections and the development of asthma during early childhood to assist in developing preventive strategies for these common childhood diseases.