OULU 2008
D 962

ACTA UNIVERSITATIS OULUENSIS

Teija Dunder

ENVIRONMENT AND ATOPY AND ASTHMA IN CHILDHOOD

THE EFFECT OF DIETARY FATS, COMMON INFECTIONS AND ASTHMA TREATMENT PRACTISES ON MORBIDITY RATES

FACULTY OF MEDICINE,
INSTITUTE OF CLINICAL MEDICINE,
DEPARTMENT OF PAEDIATRICS,
UNIVERSITY OF OULU;
INSTITUTE OF CLINICAL MEDICINE,
DEPARTMENT OF PEDIATRICS,
UNIVERSITY OF KUOPIO

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ENVIRONMENT AND ATOPY AND ASTHMA IN CHILDHOOD

The effect of dietary fats, common infections and asthma treatment practises on morbidity rates

Academic dissertation to be presented, with the assent of the Faculty of Medicine of the University of Oulu, for public defence in Auditorium 12 of the Department of Paediatrics, on April 11th, 2008, at 12 noon

OULUN YLIOPISTO, OULU 2008

Acta Univ. Oul. D 962, 2008

Supervised by
Professor Matti Uhari

Reviewed by
Docent Minna Kaila
Docent Merja Kajosaari

ISBN 978-951-42-8750-3 (Paperback)
ISBN 978-951-42-8751-0 (PDF)
http://herkules.oulu.fi/isbn9789514287510/
ISSN 0355-3221 (Printed)
ISSN 1796-2234 (Online)
http://herkules.oulu.fi/issn03553221/

Cover design
Raimo Ahonen

OULU UNIVERSITY PRESS
OULU 2008

Dunder, Teija, Environment and atopy and asthma in childhood. The effect of dietary fats, common infections and asthma treatment practises on morbidity rates

Faculty of Medicine, Institute of Clinical Medicine, Department of Paediatrics, University of Oulu, P.O.Box 5000, FI-90014 University of Oulu, Finland; Institute of Clinical Medicine, Department of Pediatrics, University of Kuopio, P.O. Box 1627, FI-70211 Kuopio

Acta Univ. Oul. D 962, 2008
Oulu, Finland

Abstract

Despite the common recommendations of the criteria for the diagnosis of asthma there is still a wide variation within different regions in diagnoses, use of medications and hospitalisation rates especially among young children. This thesis elucidates the role of spesified environmental risk factors associated with the development of atopic diseases in childhood.

In two prospective follow-up surveys we found that allergies and asthma associate with the consumption of margarines, butter and fish and that the common infection of childhood, RS-virus infection, does not increase asthma morbidity in adolescence. In a randomised set-up we were able to verify that the common childhood infections do not protect from allergies and asthma. In a retrospective survey we found that hospitalisation rates can reflect medication practices in different regions.

Our results indicate that consumption of fat in the diet can be one triggering factor for allergies but common childhood infections are merely markers of susceptibility to allergies and asthma rather than the cause of it.

Keywords: allergy, asthma, child, diet, fatty acids, hospitalisation rate, hygiene hypothesis, respiratory syncytial infection

To Rosa-Maria and Ville

Acknowledgements

The work for this thesis was carried out at the Department of Paediatrics, University of Oulu, during the years 1997-2007. I am grateful to Professor Mikko Hallman, MD, Head of the Department, for creating an inspiring atmosphere for scientific work during these years.

I wish to express my deepest gratitude to my supervisor, Professor Matti Uhari, MD. I respect his profound knowledge of statistics and professional attitude to scientific work and teaching. I admire his creative and intelligent ideas in solving scientific dilemmas. My sincere thanks are due to Docent Päivi Tapanainen, MD, Chief Physician of the Department of Paediatrics, for her support and for creating good atmosphere for scientific and clinical work in our clinic. I warmly thank Olavi Linna, MD and Docent Mika Mäkelä, MD (Skin and Allergy Hospital), for supervising me in the interesting and challenging field of Paediatric Allergology.

I thank my official referees Docent Minna Kaila, MD and Docent Merja Kajosaari, MD, for their valuable and constructive criticisms during the preparation of the manuscript.

My warmest thanks are due to Professor Matti Korppi, MD for his constructive comments and encouragement and I warmly thank my co-authors Kaj Korhonen, MD, Liisa Kuikka, MD, Professor Leena Räsänen, Terhi Tapiainen MD, Hanna Juntti, MD, Docent Matti Waris, Tiina Reijonen MD, Kyllikki Remes MD and Docent Timo Klaukka. I am very grateful to Tytti Pokka BSc and Juha Turtinen BSc for their friendly and skilful assistance with statistics and computers. My thanks are due to Mrs Marjatta Paloheimo and Mrs Maija Veikkola for their friendly assistance.

I warmly thank all my colleagues and friends at the Department of Paediatrics for encouraging and inspiring conversations during these years. My dear thanks are due to Docent Marjo Renko for her true friendship and valuable advice during these years. I thank warmly Outi Peltoniemi, MD, for warm friendship and supportive conversations during these years and Outi Aikio, MD for interesting, inspiring discussions and support in scientific studies of exhaled nitric oxide. I thank Markku Leskinen, MD, Matti Nuutinen, MD, Sami Turunen MD and Timo Saarela MD for our humorous debriefing sessions with a cup of coffee in Monday mornings.

I thank my dearest friends Mrs Riitta Palviainen-Lehtoranta, Outi Vuorimäki, MD, Anne Kunelius, MD, Riitta Kaarteenaho-Wiik, MD, Mrs Virpi Matala and Mrs Anuirmeli Sallamo-Lavi for their joyful friendship and support in my life.

I thank my parents, Tuula and Kalevi, for helping me in all possible ways during these years and my brother Jukka and his wife Marjukka for help and support. I also thank my dear grandmother Siviä for her brave, firm and humorous attendance in my life.

Finally, my dearest thanks are due to my partner Raimo Kivari. His loving support, enthusiastic attitude and companionship in everyday life and during holidays have been helping me many times. My beloved children Ville and Rosa-Maria have brought action and happiness in my life and I thank them for their bravery and patience during these years. Ville and Rosa, you are absolutely the best. Finally, I thank my sweet stepdaughter Elina for her kind and joyful attitude in everyday life.

This research was supported financially by Foundation of Pediatric Research in Finland, Oulu, Finland, the Alma and K.A. Snellman Foundation, Oulu Finland and the Finnish Medical Society Duodecim.

Oulu, December 2007 Teija Dunder

Abbreviations

AA	arachidonic acid
ADAM33	a disintegrin and metalloproteinase
CD 14	high-affinity receptor for bacterial lipopolysaccharide
CDCC	child day care centre
CI	confidence interval
DHA	docosahexaenoic fatty acid
HLA	human leucocyte antigen
EPA	eicosapentaenoic fatty acid
FcεRI-β	β-chain of the high-affinity receptor for IgE
GATA 3	GATA-binding protein
GPRA	G protein-coupled receptor 154
IFN	interferon
IgE	immunoglobulin E
IL	interleukin
ICSs	inhaled steroids
LTs	leukotrienes
LXs	lipoxins
NOD1	nucleotide-binding oligomerization domain
OR	odds ratio
RR	relative risks
PUFAs	polyunsaturated fatty acids
PGs	prostaglandins
P/S	ratio of polyunsaturated to saturated fatty acids
RSV	respiratory syncytial virus
SND test	standard normal deviate test
Txs	thromboxanes
uPA	urokinase-type plasminogen activator
VDR	vitamin D receptor

List of original papers

This thesis is based on following papers which are referred in the text by their Roman numerals:

I Dunder T, Kuikka L, Turtinen J, Räsänen L & Uhari M (2001) Diet, serum fatty acids and atopic diseases in childhood. Allergy 56: 425-8.

II Dunder T, Tapiainen T, Pokka T & Uhari M (2007) Infections in child day-care centres and later development of asthma, allergic rhinitis and atopic dermatitis Prospective Follow-Up Survey 12 Years After Controlled Randomized Hygiene Intervention. Archives of Pediatrics & Adolescent Medicine 161: 972-977.

III Dunder T, Juntti H, Renko M, Kokkonen J, Waris M & Uhari M (2007) Consumption of asthma medication after RS-virus epidemic – A population based survey. Pediatric Allergy and Immunology 18: 105-109.

IV Korhonen K, Dunder T, Klaukka T, Reijonen TM, Issakoff K, Kiviharju M, Linna O, Remes K & Korppi M (2004) Do inhaled steroids differ from cromones in terms of hospital admission rates for asthma in children? Acta Paediatrica 93: 1612-1618.

Contents

1 Introduction

Atopic diseases including asthma, allergic rhinitis and allergic eczema/dermatitis syndrome have been in special focus during the past decade in western societies. These conditions are common and thus constitute a major health burden and furthermore their incidence rates have been claimed to increase (Strachan *et al.* 1997, Austin *et al.* 1999, Devenny *et al.* 2004). This has lead to a significant increase in the scientific work in this field in order to reliably evaluate differences in epidemiology of atopic diseases in different societies and to search for environmental risk factors that might predispose to these diseases (Seaton *et al.* 1994, Lau *et al.* 2000, Woodcock *et al.* 2004) (Figure 1).

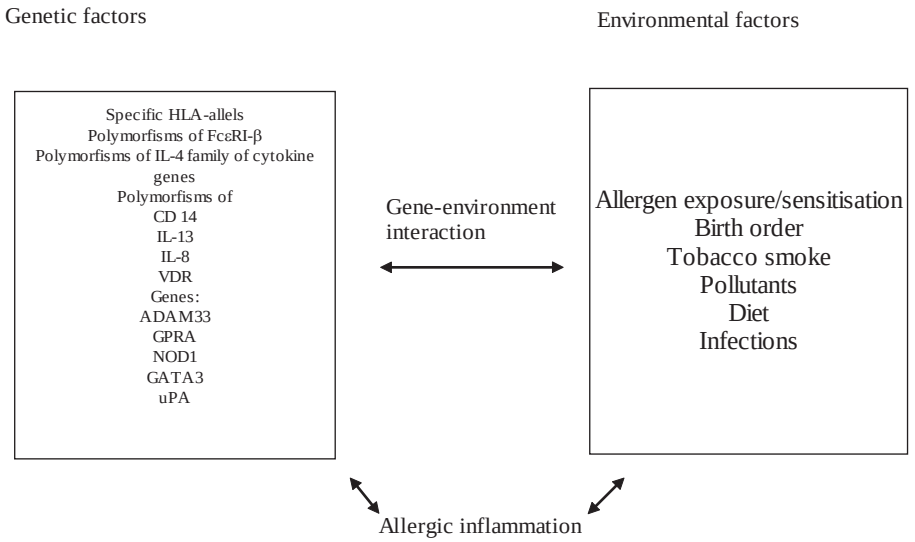

Fig. 1. Genetic and environmental factors related to the development of atopic disease (Kay 2001, McKeever *et al.* 2001, Lau *et al.* 2002, Laitinen *et al.* 2004, Raby *et al.* 2004, Kormann *et al.* 2005, Hysi *et al.* 2005, Depner *et al.* 2007, Kabesch *et al.* 2007, Begin *et al.* 2007).

The changes in diet in the western world that have taken place during the past three decades have been proposed to be possible predisposing factor to allergies in childhood (Black & Sharpe 1997). Current nutritional knowledge that has lead to a successful decrease in cardiovascular diseases has, at the same time, increased the amount of polyunsaturated fatty acids and decreased the amount of

saturated fatty acids in our diet (Viikari *et al.* 1991). This shift in fatty acid content in the diet has been proposed to favour allergies (von Mutius *et al.* 1998). Another major change, the decrease in infectious disease morbidity in childhood achieved by better hygiene practices and vaccinations, has been proposed to favour development towards allergic constitution in children (Alfven *et al.* 2006). Understanding of the immunological mechanisms behind allergies has widened and changed our views rapidly (Prescott *et al.* 1999, Netea *et al.* 2005). Epidemiological studies offer the means to find the major environmental risk factors that can then be targeted in preventive strategies. However, in epidemiological surveys the differences in definitions of symptoms, treatment and management practices of asthma and allergies in different populations can lead to differences in morbidity rates, study outcomes and thus biased conclusions.

This thesis elucidates the role of specified environmental risk factors associated with the development of atopic diseases in childhood. Atopic disease is defined as atopic dermatitis, allergic rhinitis and/or asthma diagnosed by a physician. Three epidemiological surveys were conducted, one to discover the role of diet and two studies on common respiratory infections and their relation to the development of atopic diseases. In a cross-sectional patient record assessment measuring asthma hospitalisation rates we wanted to demonstrate the effect of different treatment policies on the burden of asthma in children.

2 Review of the literature

2.1 Dietary fats and atopic diseases

In 1997, Black and Sharpe suggested that changes in dietary fat intake may have contributed to the reported increase of asthma rates in industrialized countries (Black & Sharpe 1997). In cross-sectional studies changes in the consumption of dietary fats, trans-fatty acids and serum lipid profile findings have been associated with allergic diseases in children (Weiland *et al.* 1999, Sausenthaler *et al.* 2006, Pesonen *et al.* 2008).

Increased intake of margarines and vegetable oils in diet and low consumption of fish have been suggested to play a role in the development of asthma, atopic dermatitis and allergic rhinitis (Roberts 1991, Chang *et al.* 1993, Hodge *et al.* 1994, Hodge *et al.* 1996). Already in the 1930's it was found that rats fed with deficient unsaturated fats developed a scaly dermatitis which resembled atopic dermatitis (Burr & Burr 1929). After that observation numerous studies of polyunsaturated fatty acids (PUFAs) in serum, erythrocytes and adipose tissue in relation to atopic diseases, especially atopic dermatitis have been published in children and adults (Lindskov & Holmer 1992, Leichsenring *et al.* 1995). These studies indicate that reduced activity of Δ6-desaturase enzyme that converts linoleic acid to γ-linoleic acid and α-linoleic acid to stearidonic acid is in a causal association with the development of asthma (Manku *et al.* 1984, Strannegard *et al.* 1987, Biagi *et al.* 1993). The major omega-6 fatty acid in the human diet is linoleic acid which is converted to arachidonic acid (AA) (Figure 2).

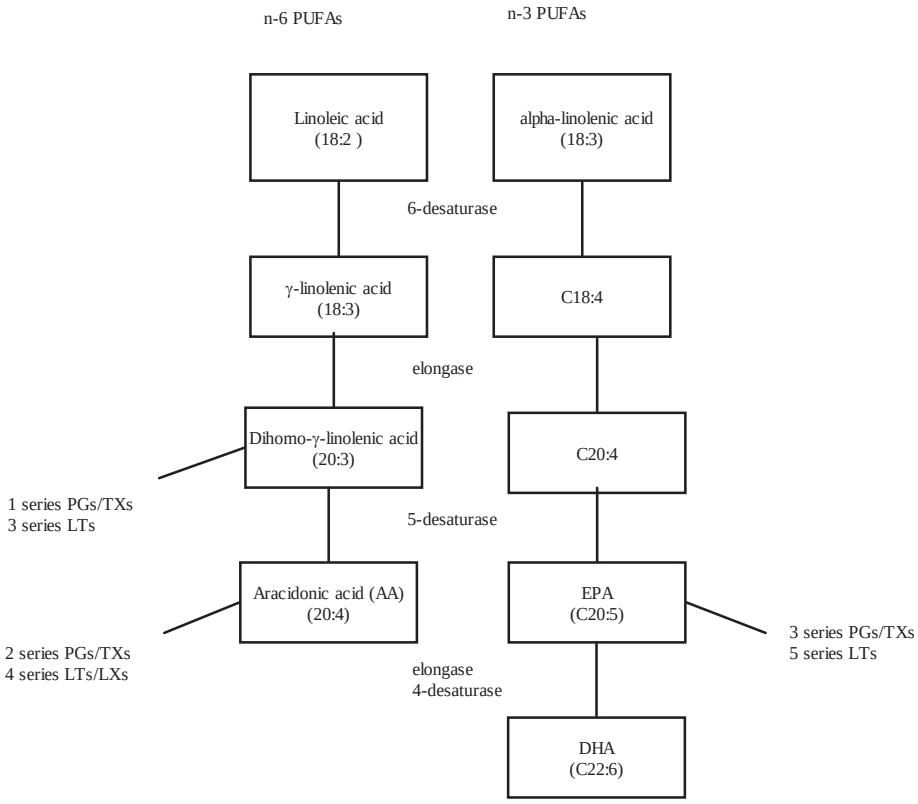

Fig. 2. Flow chart of n-6 and n-3 polyunsaturated fatty acid (PUFA) metabolism. PGs prostaglandins, EPA eicosapentaenoic acid, DHA docosahexaenoic acid, LTs leukotrienes, LXs lipoxins, Txs thromboxanes.

Margarine is rich in n-6 linoleic content. Inflammatory and immune cells contain high proportions of arachidonic acid (Calder & Grimble 2002). Arachidonic acid is a substrate for the two-series prostaglandins (e.g. PGE2) and four-series leukotrienes. PGE2 has been reported to increase the production of Th2-lymphocytes stimulating cytokines IL-4, IL-5 and IL-10 and to decrease the production of Th1-lymphocytes stimulating cytokines IFN-y and IL-2 (Snijdewint *et al.* 1993, Naito *et al.* 1996, Benbernou *et al.* 1997, Calder *et al.* 2002, Miles *et al.* 2003).

High intake of PUFAs has been reported to increase the risk of having asthma in 3-5 year old children (Haby *et al.* 2001). Von Mutius has found an inverse association between changes in the consumption of butter and hay fever and

atopic sensitization in eastern Germany (von Mutius *et al.* 1998). Similarly an association between margarine consumption, allergic sensitization and rhinitis symptoms in 5-14 year old children was found, even though there was no association with hay fever and asthma (Bolte *et al.* 2001, Bolte *et al.* 2004). Diet is suggested to be one explanation for the protective effects against allergies and asthma in a farm environment (Riedler *et al.* 2001) and in those families following the so called anthroposophic lifestyle (Alm *et al.* 1999).

A low consumption of oily fish which is rich in n-3 PUFA associates with an increased risk of asthma in children (Hodge *et al.* 1996). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found in high proportions of the tissues of oily fish. In the absence of consumptions of oily fish α-linolenic acid is the major dietary source for omega-3 fatty acid. Omega-6 and omega-3 fatty acids compete for the enzymes that metabolise them and thus the relative reduction in omega-3 fatty acid intake may exacerbate the effect of the increase in omega-6 fatty acid intake. Both relative and absolute increases in omega-3 fatty acid intake reduce the amount of arachidonic acid produced (Irvine 1982). However the addition of fish oil to the diet and the supplementation of eicosapentaenoic acid have failed to improve already developed asthma (Arm *et al.* 1988, Kirsch *et al.* 1988, Hodge *et al.* 1998, Woods *et al.* 2002).

There are three methods used in assessing the impact of dietary intake in studies. Questionnaires inquiring types of foods eaten, 48 h recall of dietary intake and semi-quantitative food frequency questionnaire (Wijga *et al.* 2003, Calvani *et al.* 2006, Murray *et al.* 2006a). Calculation of actual nutrient intake can be performed with nutrient analysis programs. All dietary questionnaires rely on recall and furthermore food composition tables are not available for all nutrients. This causes biases in dietary surveys. An objective measure of dietary fat consumption in a nutrition survey is to analyse serum fatty acids but so far these measurements have been used in a limited number of trials (Yu & Bjorksten 1998a, Yu & Bjorksten 1998b). Dietary fatty acid exposures can be measured by the gas chromatography method from serum cholesterol esters, red cell phospholipids and plasma phospholipids (Moilanen *et al.* 1992, Yu & Bjorksten 1998b, Newson *et al.* 2004). A limitation in cross-sectional studies is that changes in fatty acid status may be a consequence of established atopic disease.

2.2 Infections and development of atopic diseases

The mean annual number of acute respiratory illnesses in children aged 0-4 years is 4.9 (Monto & Sullivan 1993). The care of a child in a day care centre (CDCC) is a marked risk factor for common infections (Celedon *et al.* 1999, Koopman *et al.* 2001, Revai *et al.* 2007). Child day care increases the risk of common colds as compared with children cared for at home by approximately 70 percent in the 1-year age group and by 10 percent in the 3-year age group (Louhiala *et al.* 1995). The risk of acute otitis media in day care is 2.5 relative to home care (Uhari *et al.* 1996). Attendance at day care has been shown both to decrease and increase the occurrence of asthma (Ball *et al.* 2000, McKeever *et al.* 2002, Svanes *et al.* 2002, Hagerhed-Engman *et al.* 2006). Numerous respiratory tract infections in early childhood have been related to the increased risk of asthma (Bodner *et al.* 1998, Nafstad *et al.* 2000, Klinnert *et al.* 2001, Hagerhed-Engman *et al.* 2006).

The original “hygiene hypothesis” postulates that the inverse association between the number of siblings in the family and hay fever at the age of 11 and 23 years noted in a British cohort was due to the protective effect of specific environmental factors such as infections in infancy (Strachan 1989). Since then numerous observational surveys of the linkage between bacterial, viral and helminth infections and atopy in different populations have been published (Nyan *et al.* 2001, Karadag *et al.* 2006, Flohr *et al.* 2006, Obihara *et al.* 2006, Bisgaard *et al.* 2007). Rare systemic infections in infancy like measles, hepatitis A and mycobacteria have inversely been associated to allergic diseases in distinct populations (Lewis & Britton 1998, von Hertzen *et al.* 1999, Matricardi *et al.* 2000). The concept of original ”hygiene hypothesis” has expanded further to cover the gut microflora of domestic animals in the environment. Domestic animals produce higher endotoxin levels in the home environment (Campo *et al.* 2006). High endotoxin level has been associated with protection from allergies and asthma in Estonia and German but in Cyprus it increased the risk of allergies (Braun-Fahrlander *et al.* 2002, Bottcher *et al.* 2003, Nicolaou *et al.* 2006). The differences are suggested to result from variation in gene-environment interactions in different populations (Eder *et al.* 2004, Simpson *et al.* 2006). Recent data suggests that the development of infant gut microbiota after birth may have an effect on later immunological functions and thus also on allergies (Huurre *et al.* 2007).

The original “hygiene hypothesis” postulated that infections in infancy could be protective against allergies (Strachan 1989). The association between asthma

and common respiratory infections is difficult to analyse since asthma itself may cause symptoms such as cough and rattle in the chest that resemble viral respiratory infections (Monto & Sullivan 1993). On the other hand, the symptomatology of rhinoviral infections, which is the most common cause of respiratory infection, is often markedly different among individuals with normal airway reactivity and those with hyper-reactive airways (Johnston *et al.* 1996, Skoner *et al.* 1996, Seear & Wensley 1997, Kotaniemi-Syrjanen *et al.* 2003, Xepapadaki *et al.* 2005). Therefore the respiratory viral disease of an asthmatic is more likely to be prolonged or to be classified as a lower respiratory infection than an upper respiratory infection which can lead to misclassification biases in observational surveys. In a recent survey the number of upper respiratory tract infections in infancy associated with a decreased risk of asthma at the age of 7 while the number of lower respiratory tract infections associated with an increased risk of asthma (Illi *et al.* 2001). When infections of the upper and lower respiratory tract are added together the association with asthma disappears. Thus this finding is most probably due to diagnostic practices and not due to development of asthma. A child with asthmatic predisposition will easily be diagnosed to have lower respiratory tract infection even during upper viral infection.

In cross-sectional and cohort studies, validity problems are possible as the exposure is not determined by chance and thus could be influenced by behaviour. For instance, asthmatic parents might be afraid to put their child in day care because their child would be exposed to more infections (van Schayck & Knottnerus 2004). Observational surveys serve as a source of hypotheses, which then should be tested in controlled, randomised intervention trials in order to properly control for confounding factors. However, this has not been done, for example, for the hygiene hypothesis. It is not feasible to induce infections in a randomised manner to evaluate the development of allergic disorders. It is possible, however, to evaluate the effect of prevention of infections in a randomised controlled trial (Uhari & Mottonen 1999).

2.3 Early RS-virus infection in infancy and development of asthma

Respiratory synsytial –virus is the single most important cause of lower respiratory tract infection during infancy (Domachowske & Rosenberg 1999, Hyvarinen *et al.* 2007). Several follow-up studies have confirmed that there is an association between RSV bronchiolitis in infancy and recurrent wheezing in early

life (Pullan & Hey 1982, Sigurs *et al.* 1995, Noble *et al.* 1997, Schauer *et al.* 2002). In a systematic review of prospective case-control studies with the follow-up of at least 10 years, rates of asthma were increased in two studies out of four (Table 1). Mild lung function abnormalities, such as decreased forced expiratory volume in one second and mid-expiratory flow, have been reported in 18-20 year old adults with a history of RSV hospitalisation in infancy even though the rates of asthma have been comparable to control subjects (Korppi *et al.* 2004). There is a debate whether RSV bronchiolitis is also a risk factor for allergic sensitization and early onset of immunoglobulin (Ig) E associated asthma (Korppi *et al.* 2004, Sigurs *et al.* 2005). In our own recent survey those who had RSV bronchiolitis in infancy had less allergic sensitization at 8 years of age than their controls (Juntti *et al.* 2003).

In a prospective cohort study from Tucson mild RSV bronchiolitis not requiring hospital admisson increased the risk of wheezing at the age of 6 years but this risk disappeared by the age of 13 years (Stein *et al.* 1999). In a prospective cohort with children hospitalised for RSV bronchiolitis nearly half of the patients had recurrent wheezing during the first year of follow-up. This proportion decreased over time with a seasonal pattern (Bont *et al.* 2004). The burden of wheezing was at greatest during winter season suggesting that viral upper respiratory tract infections were the predominant triggers.

The epidemiology of RSV in Finland, with its 2-year pattern, is well established since we have had a systematic monthly follow-up of viral infections since 1979 (Waris *et al.* 1988, Waris 1991). This allows the evaluation of the association of RSV and asthma by epidemiological means between exposed and unexposed infants. During an RSV-epidemic more than two thirds of infants under 12 months of age will catch the infection and virtually all children will be infected at least once by 24 months of age (Glezen *et al.* 1986). Thus, if an RSV infection in infancy were to lead to asthma, this should be seen in the use of asthma medication at the population level in the age group of 3 to 16 years, because the infection is so common. A possible mechanism for the increased risk of asthma might be the permanent immunomodulatory effect induced by the RS-virus during the first 6 months of life, which is considered a critical period for the development of the immune response (Prescott *et al.* 1999, Prescott *et al.* 2003, Thornton *et al.* 2004). Another possibility is that RSV bronchiolitis in infancy serves as a marker for the presence of immunological abnormalities that would lead to development of asthma in the future (Bont *et al.* 2000, Bont *et al.* 2001, Pala *et al.* 2002, Juntti *et al.* 2005, Perez-Yarza *et al.* 2007).

Table 1. RSV bronchiolitis requiring hospital admission in infancy and asthma rates in prospective case-control studies with the follow-up at least 10 years.

Reference	No of cases	No of controls	Age on admission (months)	Age at the follow-up (years)	Occurrence of asthma %	Definition of asthma
Pullan-82	130	111	3.5	10	*6.2 vs 4.5	Symptoms and medication
Noble -97	61	47	3.8	10	**39 vs 13	Symptoms and medication
Sigurs-05	47	93	3.8	13	#43 vs 8	Symptoms, last 12 mo
Korppi-04	36	45	<24	18-20	*17 vs 11	Diagnosed by doctor

*No statistically significant difference between the groups

** OR 4.43 (95% CI 1.63 to 12.0), P-value 0.004

RR 5.7 (95% CI 2.6-12.5), P-value < 0.001

2.4. Asthma treatment policies and hospitalisation rates

The prevalence of asthma in different countries has shown conflicting trends after the 1990´s. In some populations the prevalence has been rising, while in others it has been stable or decreasing. The variability among countries may be due to differences in definitions and diagnosis of asthma and asthma symptoms (Asher *et al.* 2006). Despite differences in the prevalence of asthma in different countries hospital admissions have been decreasing during the last decade (Wennergren *et al.* 1996, Morrison & McLoone 2001, Wennergren & Strannegard 2002, Engelsvold & Oymar 2003, Castro *et al.* 2003, Priftis *et al.* 2005, Priftis *et al.* 2007). The decreasing trend in hospitalisations has been proposed to be the result of an increased use of inhaled steroids at the population level for anti-inflammatory maintenance medication for asthma (Wennergren *et al.* 1996, Haahtela & Laitinen 1996, Morrison & McLoone 2001, Haahtela *et al.* 2006, Saynajakangas *et al.* 2007). Steroids have been shown to be more effective than cromones in the treatment of asthma (Price & Weller 1995, van der Wouden *et al.* 2003, Zielen *et al.* 2006). Improved control of asthma has decreased, especially the risk of repeated hospital admissions (Bisgaard & Moller 1999, Minkovitz *et al.* 1999, Malmstrom *et al.* 2000, Wever-Hess *et al.* 2001). In particular, in young children the diagnoses of asthma differ regionally and hospitalisations have varied more than twofold in different regions in Finland (Csonka *et al.* 2000, Valovirta *et al.* 2002). The most confounding diagnosis causing biases in asthma studies in

young children is obstructive bronchitis and this should be taken into account when hospital discharge registers are used for asthma hospitalisation surveys.

Since most of the data derived to support the increase of asthma and allergic diseases is based on the consumption of health care services rather than the occurrence of the disease, we should study the differences and explanations behind them in various populations and in hospital catchment areas. Different asthma treatment policies may be one confounding factor (Donahue *et al.* 2000).

3 Aims of the study

To evaluate the effect of specified environmental risk factors on the development of atopic diseases in childhood

1. by evaluating the association between dietary fatty acids and the occurrence of atopic diseases (I).
2. by comparing the development of atopic dermatitis, allergic rhinitis and asthma between intervention and control groups in a follow-up survey 12 years after randomised hygiene intervention trial (II).
3. by evaluating the impact of RSV exposure in infants under 6 months of age to the use of asthma medication and prevalence of diagnosed asthma later in childhood (III).
4. by studying hospital admissions for asthma in two areas with different practices used for maintenance medications of steady-state asthma in children 2 to 15 years of age (IV).

4 Subjects and methods

This thesis was done during 1997-2007 at the Department of Paediatrics and Adolescence in the Oulu University Hospital in Finland. The approval of the local ethics committee for studies I, II, IV and written informed consent from subjects or their parents were obtained before the study for studies I and II. The study III is register-based study without patient-specific medical record collection and therefore ethics committee approvals were redundant. The principles of the Declaration of Helsinki were followed. The subjects, design and primary outcomes in the studies I-IV are shown summarised in Table 2.

Table 2. Summary of the subjects and methods involved in the studies.

Study	Methodology	Setting	N	Ages of the participants	Primary outcomes
I	a) Case control	Cohort	4320	3, 6, 9, 12, 15, 18 y	a) Fat intake and serum fatty acids in cases with *atopic diseases vs. controls
	b) Prospective follow-up				b) fat intake and serum fatty acids in 1980 in those developing *atopic diseases during next 9 years vs. healthy subjects
II	Prospective follow-up of a randomised controlled trial	Day care centers	1354	15 y (mean)	Number of respondents with *atopic disease Number of those who reported symptoms
III	Ecological database study	Exposed vs. unexposed cohorts	637 922	0-6 m	Purchase of asthma medication Prevalence of *asthma in exposed and unexposed cohorts
IV	Cross-sectional	Hospitalised children	711	2-15 y	Hospital admissions and readmissions for *asthma

y= years, m= months

N= number of subjects at the beginning of the study.

*atopic diseases =atopic dermatitis, allergic rhinitis and/or asthma diagnosed by a physician.

4.1 Association between dietary fatty acids and the occurrence of atopic diseases (I).

We compared the dietary data, serum fatty acid composition and the occurrence of atopic diseases in 231 sex and age matched pairs in 1980 and 154 pairs in 1986. The pairs were selected separately in 1980 and 1986. In order to minimise the effect of possible regional differences in the diagnosis of atopic diseases or in diet, the pairs were also matched by the place where they lived. The pairs we selected from a longitudinal population-based database (LASERI) (Akerblom *et al.* 1985) and they were chosen in case complete information on dietary data, serum fatty acid composition and occurrence of atopic diseases existed (Figure 3).

The dietary surveys were carried out by nutritionists using a 48 h recall method. The intakes of dietary constituents were calculated from the food composition files of the Department of Nutrition, University of Helsinki. The serum fatty acid results were expressed as percentages of the total area of fatty acids from 14:0 to 22:6 as peaks in gas chromatography.

In this survey we used two set-ups; the case-control and prospective monitoring of those who developed an atopic disease during 1980-1989 compared with those who remained healthy. The dietary data and fatty acid composition was compared between those who developed atopic disease and those who remained healthy.

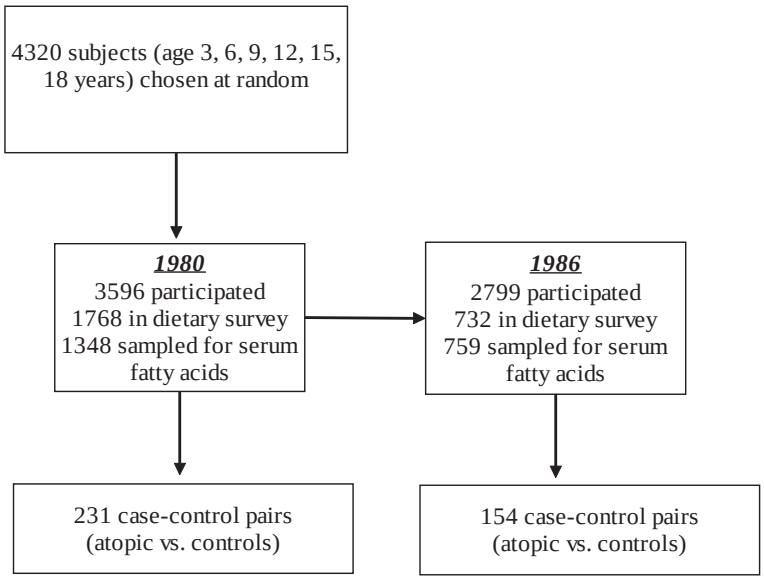

Fig. 3. Selection of case-control pairs.

4.2 Prevention of common viral or bacterial respiratory and enteric infections and development of atopic diseases (II).

We evaluated by prospective follow-up survey the effect of successful prevention of common infections in child day care centres (CDCC`s) on the later development of atopic diseases. Atopic disease is defined as atopic dermatitis, allergic rhinitis and/or asthma diagnosed by a physician. The hygiene intervention was conducted in 10 child day care centres (CDCC`s), while other 10 randomly allocated centres matched with them for size and geographical location served as controls. The intervention included several steps of intensified hand-washing, use of disposable towels, washing of toys and directions for diaper-changing practices but the most important was the improvement of hand hygiene by the use of an alcohol-based hand rub. A questionnaire was send 12 years after controlled randomised hygiene intervention to 1354 (98%) prior participants in the intervention trial conducted in 1991-1992 in Oulu (Uhari & Mottonen 1999)(Figure 4). The main outcome measures were the number of respondents who had a diagnosis of asthma, allergic rhinitis and/or atopic dermatitis made by a physician and the number of those with self-reported symptoms.

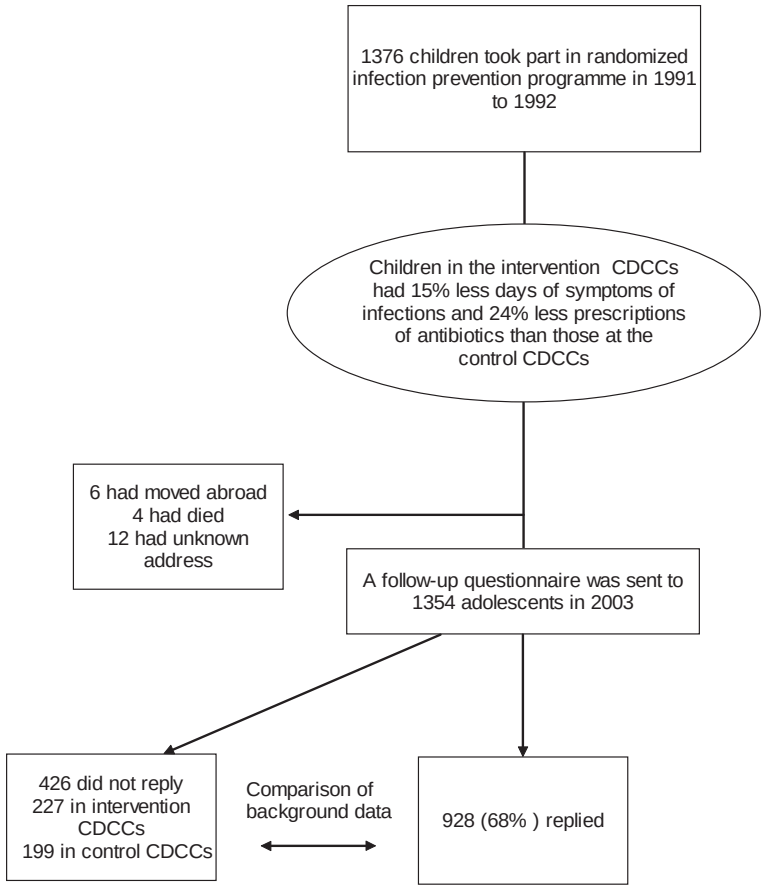

Fig. 4. Study profile.

4.3 RSV exposure in infants under 6 months of age and the use of asthma medication and prevalence of diagnosed asthma later in childhood (III)

The RSV epidemics have a special two-year pattern in Finland and this allows the evaluation of the association of RSV and asthma by epidemiological means between the exposed and unexposed infants (Waris 1991). Monthly data on RS-virus epidemics was obtained from the Department of Virology, University of Turku, which supplies these laboratory services throughout the country. The data of children born during 1986-1995, their asthma medication purchases and

reimbursement data were received from the Social Insurance Institution. The consumption of asthma medication at the age of 3 to 16 years and the number of those entitled to special reimbursement for asthma medication were identified for a total of 637 922 children. These subjects were grouped in cohorts according to whether they had been aged 0-6 months (exposed) or not (unexposed) during an RSV epidemic (Figure 5 and 6). The means of the proportions purchasing asthma medication and of those receiving reimbursement were calculated for each cohort. These outcome measures were compared between the exposed and unexposed cohorts.

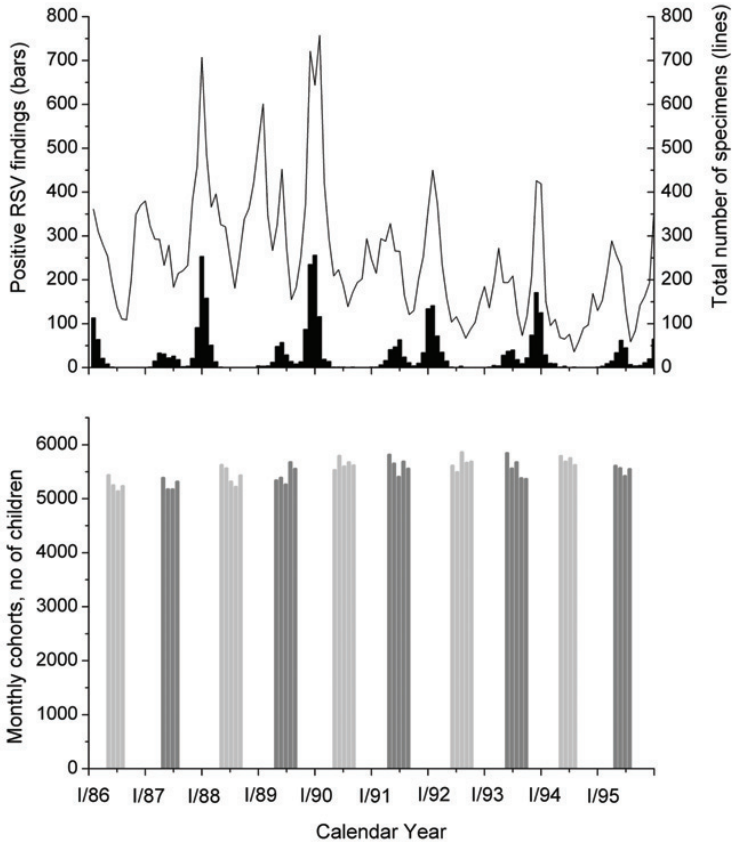

Fig. 5. Respiratory syncytial virus epidemics in Finland, total number of specimens during the years 1986 to 1995 and division of the child cohorts into those exposed or unexposed to RSV at an age younger than 6 months of age. Exposed cases are represented by dark grey bars and unexposed ones by light grey bars.

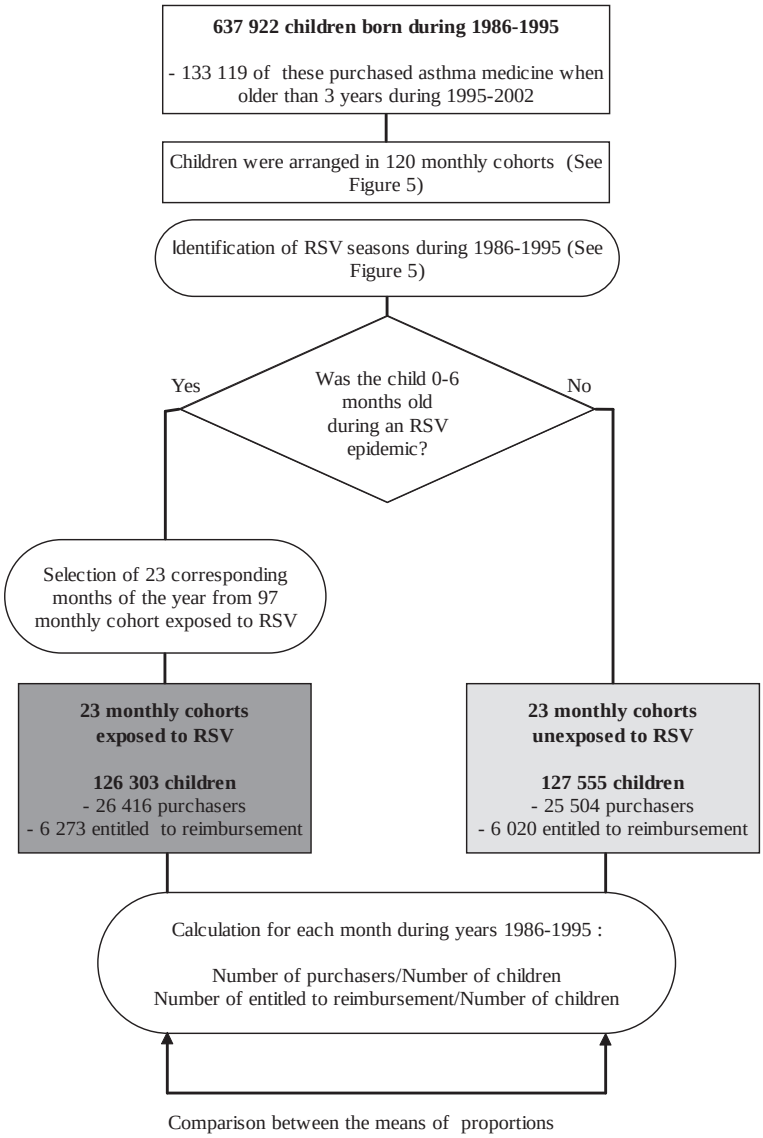

Fig. 6. Study profile.

4.4 Hospital admissions and readmissions for asthma in two areas with different practices used for maintenance medications of steady-state asthma in children 2 to 15 (IV)

We evaluated the impact of different treatment policies of maintenance medication for steady state asthma on hospitalisations in children. Inhaled steroids were used as the primary maintenance therapy in Oulu in children over 2 years of age whereas a stepwise policy with inhaled cromones as first choice and inhaled steroids as second choice was used in Kuopio in 1995-1999 (table 3). The data on the use of inhaled steroids and cromones were obtained from the purchase-based prescription drug dispensing register of the Social Insurance Institution of Finland. Patients were identified from hospital discharge registers (International Classification of Diseases codes 9 and 10 493**, J45*, J46*for asthma and 466**, J21.9 for wheezy bronchitis). In order to confirm consistent diagnoses, all cases were reviewed from patient-specific medical records using identical protocols. Asthma was confirmed despite discharge diagnosis 466** or J21.9 in case two or more expiratory obstructions leading to emergency treatment in secondary care were recorded before the first admission.

Annual community-based population data were obtained from Finnish Official Statistics (www.stat.fi). The annual numbers of total, first and readmissions were expressed as rates per 1000 children and calculated by using exact population data at the end of each year. The data was analyzed into two subgroups: children 2-5 and 6-15 years of age.

Table 3. Characteristics of patients with asthma in the two study areas.

Variable	Kuopio area n (%)	Oulu area n (%)	P-value
Population (2-15 y)	42311	68963	
Number of children on maintenance medication	8552 (20.2)	16038 (23.2)	
ICSs	4337 (51)	14920 (93)	<0.001
Cromones	1953 (23)	783 (5)	
Cromones with intermittent ICS	2262 (26)	335 (2)	

n = total number of children aged 2 to 15 years in the population receiving reimbursement for asthma medication during years 1995 to 2000.

4.5 Statistical methods

Study I

The differences in the dietary composition and serum fatty acids between the case-control pairs with and without atopic diseases were tested with the paired sample t-test. Consumption of nutrient intake is presented as means with standard deviation (SD) with 95% confidence intervals for the difference of means. The effect of fat intake on the occurrence of an atopic disease was analysed by logistic regression analysis for matched case control data (Hosmer DW & Lemeshow S 1989). The fat intake was adjusted with the mother's education.

The dietary data in 1980 for the children who developed an atopic disease during the next six or nine years were compared with the data for those who did not have an atopic disease on any occasion using the independent sample t-test.

Study II

The data was analysed in randomised set-up and in observational set-up (Figure 7). The randomised set-up is presented in the published article (Dunder *et al.* 2007). The observational set-up was designed to evaluate the association of atopic diseases and infections prior to the atopy diagnosis.

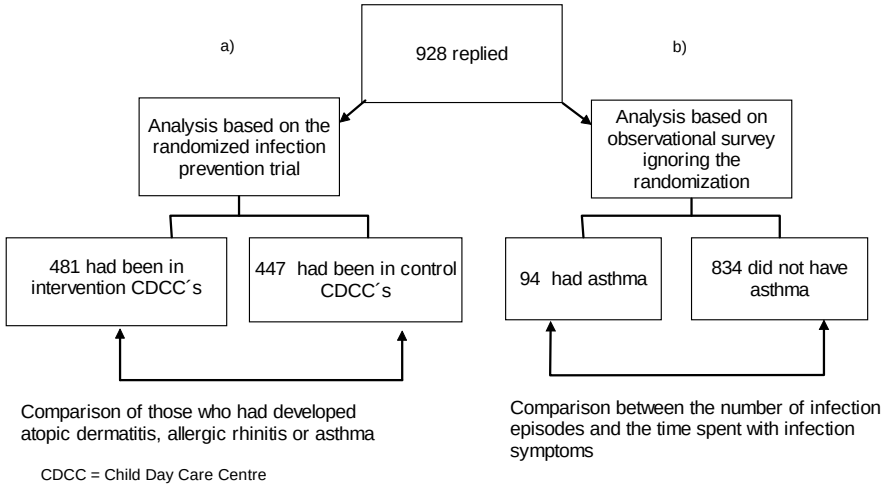

Fig. 7. Study profiles both when taking into account a) the randomised set-up and b) when ignoring it.

The differences between the proportions were tested with the binomial (SND) test and differences in parametric variables between the intervention CDCC and control CDCC participants with the *t* test (Armitage *et al.* 2002). The possible increases in the risks of developing atopic dermatitis, allergic rhinitis and asthma were evaluated according to diagnoses made by a physician or corresponding self-reported symptoms after the hygiene intervention by calculating relative risks (RR) with 95% confidence intervals (CI) between the hygiene intervention and control groups. Ages at the time of diagnosis of asthma, allergic rhinitis or atopic dermatitis were compared between the intervention and control participants with cumulative hazard curves and log rank test.

The effect of time with infection symptoms on the later diagnosis of allergic disease at the age of 15 years was analysed in the whole population using logistic regression analysis adjusted for the total duration of attendance at a CDCC. The number of episodes of respiratory tract infection and the effect of time (months) on antimicrobials on later allergic morbidity were analysed in a similar manner. The logistic regression results are presented as odds ratios (OR) and 95% confidence intervals (CI). The data were analysed using SPSS for Windows, version 12.0.

Study III

We compared the means of the proportions receiving reimbursement or consuming asthma medications in the child cohorts by analysis of covariance adjusted for time because of the trend for an annual increase in the use of asthma medication. Likewise, the adjusted mean number of purchased packages of inhaled corticosteroids and β_2-agonists per child was compared between the exposed and unexposed cohorts. The results are presented as differences in the adjusted means of proportions and in the adjusted mean number of packages and 95% confidence intervals (CI) for the differences. The data were analysed using SPSS for Windows, version 12.0.1.

Study IV

The admission rates and the maintenance medication rates at the population level in Oulu and Kuopio areas were assessed by calculating the standardized incidence ratios (SIR) and related 95% confidence intervals (Gardner MJ & Altman DG 1989). Mean rate of the admissions and maintenance medication was used for the statistical comparisons between the areas.The non-parametric Mann-Whitney U-test was used to test the difference for age and for length of hospital stay and the Fischer's exact probability test for the frequencies of readmissions between the Kuopio and Oulu areas.

5 Results

5.1 Association between dietary fatty acids and the occurrence of atopic diseases (I).

The diet of the children with atopic dermatitis and allergic rhinitis in 1980 differed from that of the non-atopic children regarding the consumption of saturated and unsaturated fat standardised to energy intake. The mean amount of margarine consumed by children with atopic dermatitis was 8.2 and that of butter 9.3 g/1000 kcal, as compared with 6.3 (p=0.04) and 11.5 g/1000 kcal (p=0.03) by the control group. The corresponding mean values among the children with allergic rhinitis and their controls were 9.9 vs 11.7g/1000 kcal (p=0.04) for butter, whereas for margarine the difference was not statistically significant. The children with any atopic disease in 1980 consumed significantly more margarine (p=0.04) than the non-atopic children, and less butter (table 4, p=0.002).

Table 4. Consumption of butter, margarine and fish (as g/1000 kcal of energy intake) and P/S ratio and serum fatty acids in 1980 in children with any atopic disease (atopic dermatitis, allergic rhinitis or asthma; cases) as compared with controls matched for age, sex and place of residence.

Variable	Cases		Controls		Difference		
	Mean	(SD)	Mean	(SD)	p-value	95%	CI
N=229							
P/S ratio	0.25	(0.13)	0.22	(0.11)	0.04	0.01,	0.05
Margarine	8.6	(6.9)	7.3	(7.0)	0.04	0.8,	2.6
Butter	9.4	(7.2)	11.6	(8.0)	0.002	-3.4,	-0.8
Fish	6.3	(13.8)	6.4	(12.6)	0.90	-2.6,	2.3
N=231							
c18:2 (linoleic acid)	51.00	(4.88)	50.83	(4.81)	0.68	-0.7,	1.01
c14:0 (myristic acid)	0.97	(0.28)	0.99	(0.25)	0.39	-0.1,	0.03
c20:5 (eicosapentaenoic acid)	1.18	(0.32)	1.22	(0.36)	0.22	-0.1,	0.02
c22:6 (docosahexaenoic acid)	0.65	(0.18)	0.68	(0.19)	0.09	-0.06,	0.005

P/S = ratio of polyunsaturated to saturated fatty acids

Serum fatty acids and atopy The percentage of myristic acid (c14:0) in the serum fatty acids was significantly lower in the children with atopic dermatitis in 1980 (table 5). The fatty acids EPA (c20:5) and DHA (c22:6), which are found in fish,

were lower in the children with atopic dermatitis both in 1980 (table 5) and also in 1986. Their mean values for EPA were 0.91 in the children with atopic dermatitis vs 1.02 in the control group in 1986 (p=0.02), and those for DHA 0.55 vs 0.61 (p=0.01) in 1986.

Table 5. Serum fatty acid composition in children with atopic dermatitis, allergic rhinitis or asthma (cases) as compared with age and sex matched controls living in the same area in 1980.

Variable 1980	Cases		Controls		Difference		
	Mean	(SD)	Mean	(SD)	p-value	95%	CI
Atopic dermatitis (N = 126)							
c18:2 (linoleic acid)	51.53	(5.00)	51.30	(4.80)	0.68	-0.9	1.4
c14:0 (myristic acid)	0.93	(0.26)	1.01	(0.27)	0.02	-0.15	-0.02
c20:5 (EPA)	1.11	(0.27)	1.22	(0.38)	0.01	-0.2	-0.03
c22:6 (DHA)	0.64	(0.16)	0.69	(0.17)	0.01	-0.09	-0.01
Allergic rhinitis (N = 145)							
c18:2 (linoleic acid)	50.99	(4.87)	51.41	(4.74)	0.47	-1.5	0.7
c14:0 (myristic acid)	0.97	(0.27)	0.99	(0.26)	0.44	-0.1	0.04
c20:5 (EPA)	1.19	(0.32)	1.17	(0.35)	0.61	-0.1	0.1
c22:6 (DHA)	0.68	(0.18)	0.66	(0.17)	0.47	-0.02	0.1
Asthma (N= 47)							
c18:2 (linoleic acid)	51.10	(4.71)	50.86	(4.46)	0.77	-1.4	1.9
c14:0 (myristic acid)	1.03	(0.30)	0.98	(0.27)	0.44	-0.1	0.2
c20:5 (EPA)	1.19	(0.31)	1.22	(0.32)	0.56	-0.2	0.1
c22:6 (DHA)	0.62	(0.17)	0.66	(0.14)	0.18	-0.1	0.02

Development of atopy Examination of the dietary data in 1980 for those who had developed an atopic disease by the year 1986 versus those who stayed healthy showed that the atopic children had consumed less butter, mean 7.7 g/1000 kcal, than the non-atopic children, mean 10.1 g/1000 kcal (p=0.001). The corresponding finding was seen also in 1989 (table 6). The children with atopic diseases in 1989 had also consumed less fish in 1980, mean 3.2 vs 6.6 g/1000 kcal (p<0.001) (table 6).

Table 6. Dietary data (food consumption in g/1000 kcal) in 1980 of those who developed any atopic disease in 1989 versus those who remained healthy.

Variable in 1980	Atopics (-89) N=60		Non-atopics (-89) N=1293		Difference		
	Mean	(SD)	Mean	(SD)	P-value	95%	CI
Margarine	8.2	(6.7)	8.0	(7.4)	0.78	-2.0,	1.5
Butter	8.3	(6.0)	10.2	(7.8)	0.02	0.27,	3.4
Fish	3.2	(6.5)	6.6	(13.0)	<0.001	1.6,	5.2
P/S ratio	0.24	(0.11)	0.24	(0.13)	0.73	-0.04,	0.03

N= number of children participating in the dietary survey in 1980

P/S = ratio of polyunsaturated to saturated fatty acids

5.2 Prevention of common viral or bacterial respiratory and enteric infections and development of atopic diseases (II)

The occurrence of atopic diseases between the intervention and control CDCC attendants did not differ. Asthma was diagnosed by a physician in 48/481 (10%) of the respondents from the intervention CDCC`s with markedly less infections and 46/447 (10%) of the controls (Relative risk (RR) 1.0, 95% confidence interval (CI): 0.7, 1.4). Similarly, no differences were found in the numbers of children who had a diagnosis of other atopic diseases or reported such symptoms (table 7). The mean age at the time of diagnosis of asthma was 7.2 years (SD 4.0) in the intervention group and 7.5 years (SD 4.3) in the control group, that for the onset of atopic dermatitis was 1.8 years in both groups, and that for the onset of seasonal allergic rhinitis was 8.2 years (SD 3.8) in the intervention group and 8.4 years (SD 3.7) in the control group.

In the logistic regression analysis the likelihood of having a diagnosis of asthma up to the age of 15 years increased with the time spent with symptoms of infections as a child (OR 1.2, 95 percent CI: 1.1, 1.4, $p < 0.001$), and the same was true of allergic rhinitis (OR 1.10, 95 percent CI: 1.01, 1.20, $p = 0.03$), but no effect on the likelihood of developing atopic dermatitis was found. The likelihood of having a diagnosis of asthma increased with the time spent on antimicrobials (OR 1.27, 95 percent CI: 1.04, 1.54, $p = 0.02$), and an increased number of episodes of respiratory tract infection increased the likelihood of having diagnosis of asthma (OR 1.1, 95 percent CI: 1.1, 1.2, $p< 0.001$) or atopic dermatitis (OR 1.06, 95 percent CI: 1.01, 1.11, $p = 0.03$).

Table 7. Occurrence of atopic diseases in the population. Data is grouped by the randomised assignment of the participants to either intervention CDCCs (n=481) or control CDCCs (n=447) in the infection prevention trial twelve years earlier.

Atopic disease	Intervention (n= 481)	Controls (n= 447)	RR	95%	CI
Asthma, (%)					
Diagnosed by a physician	48 (10)	46 (10)	1.0	0.7,	1.4
Anti-inflammatory medication (ICSs)					
During life-time (continuous use ≥ 6mo)	17 (4)	15 (3)	1.0	0.5,	2.0
During the last 12 mo (any use)	22 (5)	16 (4)	1.3	0.8,	2.2
Use of β-sympathomimetics					
Any use during the last 12 mo	32 (7)	21 (5)	1.4	0.8,	2.4
Self-reported symptoms:					
Wheezing during the last 12 mo	37 (8)	24 (5)	1.4	0.9,	2.3
Exercise-induced wheezing	29 (6)	20 (5)	1.3	0.8,	2.3
Infection-induced wheezing (last 2yr)	45 (9)	39 (9)	1.1	0.7,	1.6
Atopic dermatitis, (%)					
Diagnosed by a physician	126 (26)	108 (24)	1.1	0.9,	1.4
Self-reported symptoms, (%)	173 (36)	146 (33)	1.1	0.9,	1.3
Seasonal allergic rhinitis, (%)					
Diagnosed by a physician	101 (21)	94 (21)	1.0	0.8,	1.3
Self-reported symptoms					
During life-time	152 (32)	141 (32)	1.0	0.8,	1.2
During the last 12mo	132 (27)	120 (27)	1.0	0.8,	1.3
Cow's milk allergy, (%)					
Diagnosed by a physician	27 (6)	22 (5)	1.1	0.7,	2.0

5.3 RSV exposure in infants under 6 months of age and the use of asthma medication and prevalence of diagnosed asthma later in childhood (III)

There was no difference in the adjusted means of the proportions of children purchasing asthma medication between the unexposed and exposed cohorts (20.5% vs. 20.3%; difference 0.2% [95% CI for difference:-1.2, 1.5]; p=0.8) (Figure 8 a). The adjusted mean number of packages of inhaled corticosteroids purchased per child was 12.7 vs. 12.4 packages in the unexposed and exposed groups, respectively (difference 0.2 [95% CI: -0.4, 0.9]; p=0.5) and the

corresponding figures for inhaled β_2-agonists were 4.6 vs. 4.5 (difference 0.1 [95% CI for difference: -0.1, 0.4]; p=0.4).

The adjusted means of the proportions of the unexposed and exposed children who received special reimbursement for asthma medications were 4.8% and 4.9% (difference -0.1% [95% CI for difference: -0.3, 0.1]; p=0.2) (Figure 8 b). As an overall change in the use of asthma medicines, we found an approximately 1.5-fold increase in purchases from 1995 to 2002.

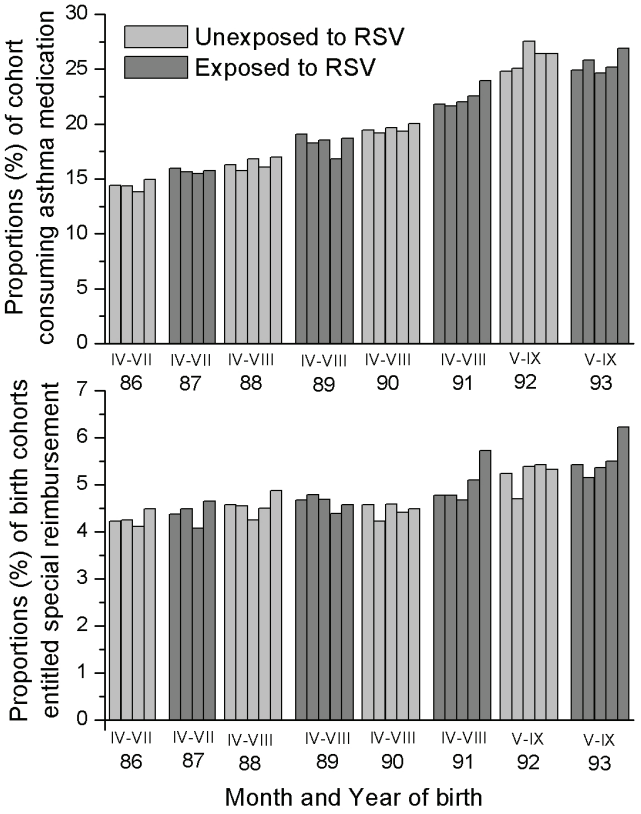

Fig. 8. a) Proportions of the paired child cohorts consuming asthma medication (children over 3 years of age), and b) proportions of the child cohorts entitled to special reimbursement for asthma medication costs, grouped as exposed or unexposed to RSV epidemics at 0-6 months of age in the years in question. Roman numerals on the bars refer to months of the year (i.e. I = January etc).

5.4 Hospital admissions and readmissions for asthma in two areas with different practices used for maintenance medications of steady-state asthma in children 2 to 15 years of age (IV).

The admitted children were older in Kuopio (median 5.0 years, range 2.0 – 15.4) than in Oulu (3.3, 2.0 – 15.8) ($p < 0.001$). In both hospitals, two-thirds of the patients were boys, and inpatient treatment times were short (median 3 days in Kuopio, 2 days in Oulu). In the district of Oulu, 93% of the children with asthma on had inhaled steroid as a regular maintenance medication, whereas in Kuopio the respective figure was 51% (figure 9).

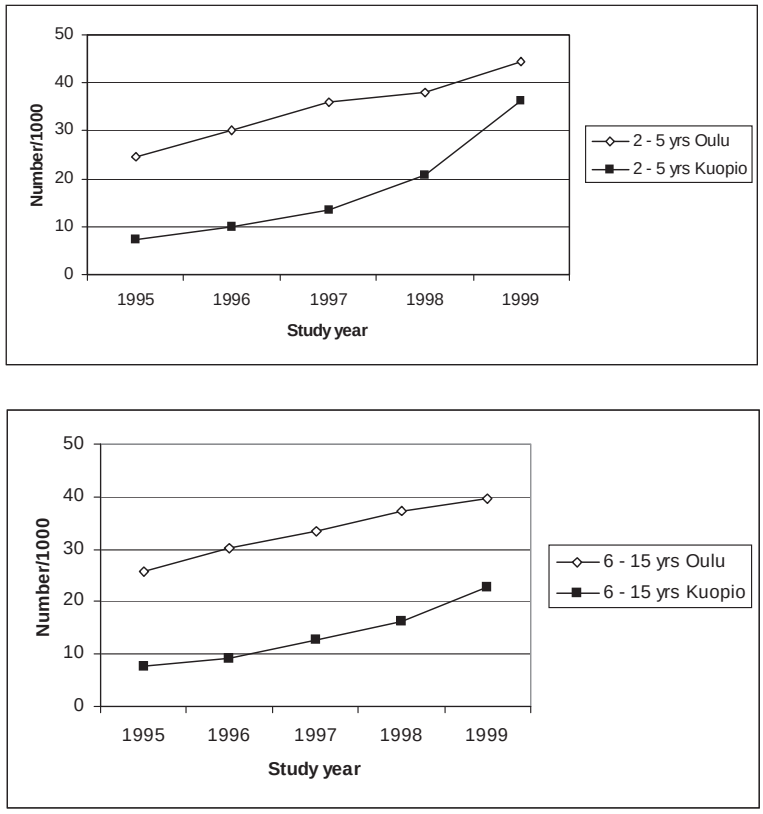

Fig. 9. Prescription of inhaled steroids as an anti-inflammatory medication for asthma among children 2-5 y of age (upper panel) and among children 6-15 y of age (lower panel) in the two study areas, the Kuopio and Oulu districts, from 1995 to 1999.

Children aged 2-5 years. The average total admission rate was 5.1/1000 in Kuopio and 2.0/1000 in Oulu during the study period, from 1995 to 1999 ($p<0.001$). The rates of first admissions (i.e. number of children) being 4.2/1000 and 1.6/1000 ($p<0.001$), respectively. The average numbers of hospital day, were 13.8/1000 and 5.9/1000 ($p<0.001$), respectively (Figure 10).

Children aged 6-15 years. The average total admission rate was 1.2/1000 in Kuopio and 0.3/1000 in Oulu during the study period, ($p<0.00)1$. The rates of first admissions (i.e. number of children) being 1.0/1000 and 0.2/1000 ($p<0.001$). The average numbers of hospital days, expressed as related to child population, were 3.8/1000 and 0.7/1000 ($p<0.001$), respectively (Figure 10).

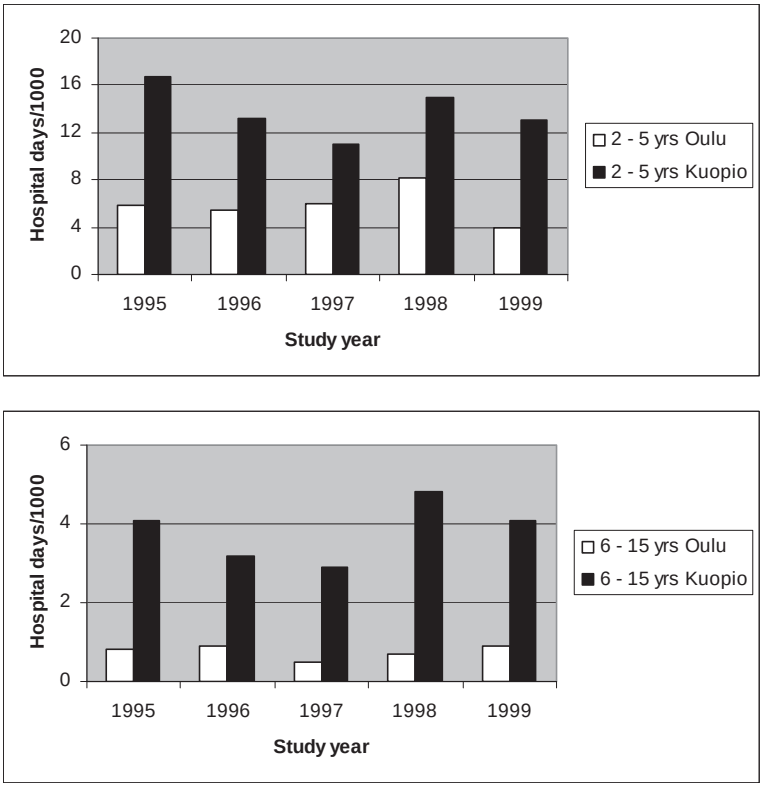

Fig. 10. Hospital days per 1000 children 2-5 y of age (upper panel) and among children 6-15 y of age (lower panel) in the two study areas.

Readmission rates were lower in Oulu area than in Kuopio area, the difference being significant among the children aged 6-15 years ($p<0.05$) (Table 8).

Table 8. Proportions of readmissions.

Age group	Kuopio	Oulu	Sig.
2-5 y	16.5[a]	19.3	n.s.
	(0.8/1000)[b]	(0.4/1000)	
6-15 y	19.6	6.3	P < 0.05
	(0.2/1000)	(0.02/1000)	

[a]Mean percentage of total admissions between 1995 to 1999

[b]Mean number of readmissions/1000 children in the age-specific population in the area between 1995 to 1999

n.s.: not signicicant

6 Discussion

6.1 The effect of dietary fats, common infections and asthma treatment practices on asthma and allergy morbidity rates

Several other studies are comparable with our finding of the association between margarine consumption and atopic disease (von Mutius *et al.* 1998, Bolte *et al.* 2001, Bolte *et al.* 2005). High intake of PUFAs has been associated with wheezing and asthma in children (Haby *et al.* 2001, Murray *et al.* 2006a). The consumption of margarines which are rich in n-6 polyunsaturated fatty acids has been increasing over the past three decades in the diet of the western world in order to reduce coronary heart disease (Viikari *et al.* 1991). In a recent large cohort study (PIAMA) daily intake of foods containing milk fat at 2 years associated with reduced likelihood of asthma and wheezing at the age of 3 years (Wijga *et al.* 2003).

The n-3 fatty acids EPA and DHA were significantly lower in the children with atopic dermatitis both in 1980 and 1986. This is in agreement with earlier findings both in children and adults with atopic dermatitis (Manku *et al.* 1982, Manku *et al.* 1984, Morse *et al.* 1989, Biagi *et al.* 1993). The dietary source of these fatty acids is fish, but we did not find any significant difference in the consumption of fish between the atopic and non-atopic children, although we did find the consumption of fish to be higher among those who remained healthy during the follow-up. In a randomised trial of school aged children the dietary enrichment of n-3 fatty acids did increase the plasma levels of these fatty acids and reduced stimulated tumour necrosis factor α production but had no effect on the clinical severity of asthma (Hodge *et al.* 1996, Hodge *et al.* 1998). Another placebo controlled intervention trial of n-3 PUFA rich fish oil supplementation in infancy reduced the likelihood of early wheeze but had no effect of the likelihood of asthma, wheeze and atopic disease in later childhood (Mihrshahi *et al.* 2003, Peat *et al.* 2004, Marks *et al.* 2006, Almqvist *et al.* 2007).

Three recent observational trials have found that maternal intake of oily fish during pregnancy associated with reduced likelihood of asthma or atopic sensitization to food allergens (Salam *et al.* 2005, Calvani *et al.* 2006, Willers *et al.* 2007). Umbilical cord PUFA concentrations have been related to development of childhood atopic disease (Galli *et al.* 1994, Yu *et al.* 1996, Newson *et al.* 2004). There is evidence from a randomised controlled trial of fish oil supplementation

during pregnancy that n-3 PUFAs influence neonatal immune responses to allergens. This trial was not powered for clinical outcomes but, however, the supplementation group was less likely to be sensitized to egg and had milder eczema in 1 year old children. However, the long-term clinical effects are yet to be seen (Dunstan *et al.* 2004).

The successful prevention of respiratory and enteric infections during early childhood in child day care centres did not increase later allergic morbidity. No differences were found here in the development or clinical course of asthma, allergic rhinitis or atopic dermatitis in adolescence between those who had been exposed to fewer infections and those who had experienced markedly more infections. An increased number of episodes of respiratory tract infection increased the likelihood of having diagnosis of asthma. This is comparable with earlier findings of the increased frequency of respiratory tract infections in early childhood and later diagnosis of asthma (Bodner *et al.* 1998, Nafstad *et al.* 2000, Klinnert *et al.* 2001, Hagerhed-Engman *et al.* 2006). Our results are comparable to those of two recent cohort studies that show no inverse association between the numbers of infection episodes and the occurrence of atopic diseases later in childhood (McKeever *et al.* 2002, Benn *et al.* 2004)(Study II).

The exposition to the single most important cause of lower respiratory tract infection during infancy, RS-virus, during epidemic early in their life did not increase the purchase of asthma medicines as compared to not exposed. Special reimbursement for asthma medication costs did not differ between the exposed and unexposed children. These results may indicate that the exposure to RSV in infancy most probably does not affect the clinical severity of asthma in childhood. Our findings are comparable with recent data suggesting that an RSV infection merely increases the risk of asthma-like symptoms up to the age of 6 years but these symptoms resolve by adolescence (McConnochie & Roghmann 1989, Murray *et al.* 1992, Stein *et al.* 1999, Turner *et al.* 2002, Korppi *et al.* 2004)(Study III).

In the study of different asthma treatment practices in children, the area with active use of ICSs was Oulu. The readmission rates reflect the success of asthma control and applied interventions, like maintenance medication (Wennergren *et al.* 1996, Donahue *et al.* 1997, Bisgaard & Moller 1999, Minkovitz *et al.* 1999). The readmission rates were significantly lower in the area with active use of ICSs as maintenance medication. Thus we concluded that the different admission rates between these two hospitals more probably reflect differences in maintenance therapy than differences in hospitalisation practice. This is comparable with

previous studies on asthma maintenance therapy in children (Wennergren *et al.* 1996, Donahue *et al.* 1997). After the initiation of the National Asthma programme the differences in maintenance medication practices decreased in Finland (Haahtela & Laitinen 1996). We found in study III that annual sales of asthma medicines to children born between 1986 and 1995 increased by approximately 1.5-fold overall from 1995 to 2002. It is most likely that this reflected changes in the policies of treating asthma and asthma-like symptoms, and also the availability of better asthma medicines and devices for children. However, according to the Social Insurance Institution's registers the total number of users of asthma medications has reached its peak and turned into a decreasing trend during recent years (Haahtela *et al.* 2006)(Study III).

Inhaled corticosteroids decrease symptoms as long as they are consumed but well-done controlled trials have failed to show any subsequent long-term beneficial effects after the discontinuation of ICSs in young children (Bisgaard *et al.* 2006, Guilbert *et al.* 2006, Murray *et al.* 2006b). In young children there is a risk for both over-treatment, leading to side-effects and costs, and under-treatment leading to insufficient control of asthma (Wennergren & Strannegard 2002, Valovirta *et al.* 2002, Kocevar *et al.* 2004, Bisgaard & Szefler 2007). In order to optimize the benefit-risk ratio the patient selection, start and duration of asthma treatment are currently advised to be based on clinical index risk and/or findings of abnormality in lung function measurements (Castro-Rodriguez *et al.* 2000, Guilbert *et al.* 2004, Current Care Summaries 2006). The follow-up of hospitalisation patterns can give useful information on improvements of the level of asthma control in children also in the future.

6.2 Methodological considerations

6.2.1 Strengths of the study designs

The study I has two different setups, the cross-sectional and prospective follow-up. Both outcomes in this cohort, the exposure (diet) between the matched pairs and the occurrence of atopic disease in the unmatched data are relevant. The association between dietary fatty acids and occurrence of atopic diseases was analysed together with nutrient intake analysis. Differences supporting these dietary findings were similarly found in the serum fatty acid data. From the methodological point of view, one benefit in this study is that the serum fatty acid

compositions in cholesteryl esters were made both in 1980 and 1986. Furthermore, in 1986 the fatty acid composition of serum phospholipids was analysed together with cholesteryl esters and they both correlated to the dietary P/S ratio, linoleate and fish and fish products (Moilanen *et al.* 1992).

Analysis of the association of asthma, allergic rhinitis and atopic dermatitis with infections in the randomised study design enabled us to avoid both misclassification and reporting biases. Most importantly, it was also possible to make comparisons between responders and non-responders among the intervention and control groups. We found that none of the differences were statistically significant and we could conclude that the groups are representative of their initial intervention group. The differences in the clinical courses of respiratory viral infections in allergy-prone children can easily lead to different treatments and clinical diagnoses, resulting in misclassification biases in observational surveys aimed at evaluating the association of allergic diseases with infections. When ignoring the unbiased randomised set-up and analysing the data as in an observational survey, the time with infection symptoms was associated with an increased likelihood of an asthma diagnosis and allergic rhinitis but no effect on the likelihood of developing atopic dermatitis was found (Study II).

The two-year epidemiological pattern in RSV epidemics in Finland offers a special opportunity to compare children who are 0 – 6 months old in the same calendar months with and without RSV exposure. The numbers of children born in Finland in 1986 - 1995 were obtained from the Population Register Centre at Statistics Finland and data of all purchases of asthma medicines and the granting of reimbursements for asthma medication for each individual were obtained from the Social Insurance Institution. If exposure to RSV in infancy were an important risk factor for the development of asthma or asthma-like symptoms, it should have been reflected in an increase in the consumption of asthma medication at the population level. All the asthmatics that required continuous medication would have been included in the special reimbursement data, because the costs of regular asthma medication are high and special reimbursement allows a 75% discount. There were no differences between the exposed and unexposed cohorts in the amounts of inhaled corticosteroids or β_2-agonists purchased, these being the most frequently prescribed asthma medicines in Finland (Study III).

The study IV was based on medical records of two hospitals with different practices for maintenance therapy for asthma in children. The strengths of the study are that the patients were screened from the register not only by the diagnosis of asthma, but also by obstructive bronchitis (Wennergren &

Strannegard 2002). All cases were reviewed from patient-specific medical records using identical protocols in order to confirm consistent diagnoses. The population in the Oulu area has been increasing and in the Kuopio area slightly decreasing in the last 2 decades. This was taken into account. The annual community-based size of the child population in both hospitals districts obtained from Finnish Official Statistics and the annual number of first and readmissions were expressed as rates per 1000 children of the same age group. The data on the use of inhaled steroids and cromones was purchase-based and obtained from the drug dispensing register of the Social Insurance Institution of Finland.

6.2.2 Limitations of the study designs

There was no validated questionnaire for atopic diseases in the survey evaluating dietary fats and occurrence of atopic diseases. There is no information on skin prick tests or IgE antibodies of the study population. The exact number of the doctors who had made the diagnosis of the atopic disease is not known. However, in order to minimise the effect of possible regional differences in the diagnosis and in diet the pairs were matched by the place where they lived. The dietary surveys have specific limitations. Our survey was carried out by trained nutritionists using a 48-h method. The intakes of dietary constituents were calculated from the food composition files of the Department of Nutrition, University of Helsinki. This method like semi-quantitative questionnaire method is a snap-shot of current diet. Both these methods rely on recall and are as good as the nutritional database that supports them.

The magnitude of our hygiene intervention program in respect to prevent the development of allergy is difficult to assess. We have concluded that, because of the large number of children participating in our survey, a decrease of up to 24% in the occurrence of infections would be sufficient. The decrease was seen both in the number of illness symptoms and use of antimicrobials in the intervention trial. There was a relatively small proportion of children under 6 months in the original intervention trial. However, it is impossible to study infants under 6 months in Finnish child day care because children attend child day care usually after 1 year of age (Study II).

The study III is a register-based ecologic study and identification of those with actual RSV infection was not possible. Even though the actual number of infected children is missing in our data, the infection rate is known to be high during epidemics. In children followed-up from birth, the infection rate has been

70/100 children in infants under 12 months of age (Glezen *et al.* 1986). Also the immigrant children without Finnish ID –number is lacking from the data. The proportion of immigrants in Finland however is small and the exclusion of these persons is not likely to have affected our results.

The study IV is retrospective and register-based. The criteria for hospitalisation in children with acute asthma was checked and found similar in both Oulu and Kuopio Hospital District. The criteria of admittance were checked from the long-term paediatric allergologists working in these two areas. Both Oulu and Kuopio University Hospitals are the only units providing inpatient treatment for pediatric patients in the district. However, we did not have data concerning differences in hospital admissions for other diseases other than asthma and wheezy bronchitis in order to compare the management of acute paediatric patients in these two hospitals. In addition, with the significant difference in the maintenance medication, there was a difference in the dosages of nebulised salbutamol in the emergency rooms of Oulu and Kuopio. The dose of salbutamol in Oulu was half of that used in Kuopio. If the beta-mimetic dosage was important for the admission rates, the results of the admittances should have been the opposite.

7 Conclusion

Diet of the atopic children differed from that of the non-atopic children in the consumption of polyunsaturated fat. The children with atopic diseases consumed more margarine and less butter. We also found that the consumption of fish was higher among those who remained healthy during the follow-up.

Our analysis of the association of asthma, allergic rhinitis and atopic dermatitis with infections in the randomised study design confirmed that decrease in the occurrence of respiratory and gastrointestinal infections did not affect the development of allergic disorders. Reference to the whole follow-up cohort regardless of the intervention gave positive association between infection symptoms, asthma and allergic rhinitis, demonstrating the effect of biases in observational surveys.

Exposure to an RSV epidemic in early infancy did not increase the proportion of those who purchased asthma medication later in childhood. As the proportions of those receiving special reimbursement for asthma medication costs were the same in the exposed and unexposed children, such an epidemic does not seem to have any clinically significant impact on the severity of asthma.

Different treatment policies in asthma maintenance medication can be seen as differences in hospitalisation rates. In particular, improved asthma control can decrease the risk of repeated hospital admissions. This refers to need for monitoring of hospitalisation rates after renewal of treatment protocols.

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ISBN 978-951-42-8750-3 (Paperback)
ISBN 978-951-42-8751-0 (PDF)
ISSN 0355-3221 (Print)
ISSN 1796-2234 (Online)