CHILDHOOD ASTHMA
Epidemiology, prevalence and risk factors

Frida Strömberg Celind

Department of Paediatrics
Institute of Clinical Sciences
Sahlgrenska Academy, University of Gothenburg

UNIVERSITY OF GOTHENBURG

Gothenburg, 2023

Supervisor:
Emma Goksör, MD, Associate Professor

Co-supervisors:
Göran Wennergren, MD, Professor
Bernt Alm, MD, Associate Professor

Cover illustration: L'enfant au pigeon by Pablo Picasso 1901, from his blue period

Childhood asthma - Epidemiology, prevalence and risk factors

frida.stromberg@vgregion.se

ISBN 978-91-8069-203-8 (PRINT)
ISBN 978-91-8069-204-5 (PDF)

Printed in Borås, Sweden 2023
Printed by Stema Specialtryck AB

Till Jimmy, Jon, Arvid och Ingrid

ABSTRACT

Background and aim: Asthma is one of the most common chronic diseases among children often resulting in medical treatment, morbidity and reduced quality of life. It is therefore important to study factors associated with asthma development. Long-term follow-up studies within this research field are scarce. One aim of this thesis was to examine the prevalence of asthma and uncontrolled asthma in a long-term follow-up (12-year-olds). Furthermore, we wanted to study the risk factors for asthma development as well as the risk factors for having an uncontrolled asthma. We also aimed to investigate whether people's behaviour regarding known factors associated with the risk of asthma changed over time. Finally, we aimed to assess the agreement between our questionnaire-based data compared with Swedish national registers.
Methods: Data for the first three, and partly four, papers in this thesis were obtained from a prospective, longitudinal cohort study of children born in 2003 in the region of western Sweden. The parents answered questionnaires at six months and one, four, eight and 12 years of age. The response rate was 68.9% (4,987/7,241) at one year and 76.1% (3,637/4,777) at 12 years. Personal identity numbers (PIN) linked 3,634 children to the Swedish Prescribed Drug Register (SPDR) and the National Patient Register (NPR). Data for the fourth paper in this thesis were obtained from a prospective, longitudinal cohort study of children born in 2018 in the region of western Sweden. The parents answered questionnaires at six months and one year of age. The response rate was 41.5% (3,936/9,475) at one year of age. The questionnaires for both cohorts (2003 and 2018) were based on well-established validated questionnaires.

Results: At 12 years of age, 6.4% reported current asthma and 15% of the asthmatic children were labelled as having uncontrolled asthma. Antibiotic treatment early in life was a risk factor for atopic asthma (OR 2.2, 95% CI 1.2-4.2) while a higher parental educational level was associated with better asthma control (OR 0.3; 95% CI 0.1–0.8) among the children at 12 years of age. The introduction of complementary feeding to infants of eggs, fish and gluten was made significantly earlier in the 2018 cohort compared with the 2003 cohort ($p < 0.01$).
We found good agreement between questionnaire-based data and SPDR data regarding asthma medication.
Conclusion: The association between antibiotic treatment and an increased risk of atopic asthma suggests an immune mediated effect. A lower parental educational level was a risk factor for uncontrolled asthma and some families might need greater educational effort in order to achieve equivalent health for asthmatic children. The earlier introduction of complementary feeding in children born in 2018 compared with 2003 might possibly reduce the risk of asthma development. Finally, we conclude that parental questionnaires, if well-constructed, can provide reliable data on childhood asthma.

Keywords: Agreement study, antibiotics, asthma, asthma control, atopy, children, cohort study, educational level, food introduction, parental questionnaire

SAMMANFATTNING PÅ SVENSKA

Astma är en sjukdom där luftvägarna periodvis återkommande blir trånga vilket leder till hosta och svårigheter att andas. Det är en av de vanligaste kroniska sjukdomarna hos barn och drabbar 6–8% av barnen i Sverige. Astma medför medicinering, behov av sjukvård, sänkt livskvalitet och skolfrånvaro. Ökad kunskap om riskfaktorer ger möjlighet att arbeta preventivt och därigenom minska antalet barn som får astma och svårighetsgraden av sjukdomen hos de barn som ändå drabbas.

Den övergripande målsättningen med doktorandprojektet var att undersöka förekomst av astma samt riskfaktorer för astma hos barn. Syftet var också att jämföra skillnader mellan barn födda med 15 års mellanrum (2003 och 2018) för att studera eventuell förändring av riskfaktorerna för astman över tid. Vi fann att sex procent av 12-åringarna födda 2003 hade astma. Barnen födda 2003 hade en ökad risk för att ha astma vid 12 års ålder om de hade fått antibiotikabehandling tidigt i livet. Mekanismen bakom detta fynd kan vara att antibiotikan stör tarmfloran och på så sätt leder till en negativ påverkan på immunsystemets normala mognadsprocess vilket i sin tur gör att risken för att få astma ökar. När vi studerade 12-åringarna som hade

astma fann vi att det var det lägre risk att deras astmasjukdom var okontrollerad om någon av föräldrarna var högutbildad.
Mycket av kunskapen kring astma och dess riskfaktorer kommer från frågeformulär och det gör också en stor del av datainformationen i detta avhandlingsprojekt. Tillförlitligheten till den här typen av data har ifrågasatts och vi ville därför jämföra svar från våra frågeformulär med data från Socialstyrelsens register. Det visade sig finnas en god överensstämmelse mellan frågeformulärsdata och data från Socialstyrelsens läkemedelsregister. Slutsatsen vi drog var att studier baserade på välgjorda frågeformulär kan vara tillförlitliga och användbara.
En faktor som har blivit alltmer tydlig på senare år för att minska risken för astma- och allergiutveckling är att introducera smakportioner till spädbarn redan mellan fyra och sex månaders ålder. Vi studerade barn födda 2018 och såg att råden gällande matintroduktion till stor del följs. När vi jämförde åldern för introduktion av olika födoämnen genom att studera både barnen födda 2003 och 2018 så såg vi att föräldrar introducerade smakportioner klart tidigare 2018 jämfört med 2003.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Strömberg Celind F, Wennergren G, Vasileiadou S, Alm B, Goksör E.
Antibiotics in the first week of life were associated with atopic asthma at 12 years of age.
Acta Paediatr. 2018;107(10):1798-1804

II. Strömberg Celind F, Wennergren G, Vasileiadou S, Alm B, Åberg N, Goksör E.
Higher parental education was associated with better asthma control.
Acta Paediatr. 2019;108(5):920-926

III. Strömberg Celind F, Vasileiadou S, Goksör E.
Parental questionnaires provided reliable data on childhood asthma compared with national registers.
Pediatr Allergy Immunol. 2021;32(5):917-924

IV. Strömberg Celind F, Goksör E, Carlén E, Schilling B, Alm B, Wennergren G. **Infants were introduced to complementary feeding earlier in 2018 compared with 2003.** Acta Paediatr. 2023;00:1–8.

ABBREVIATIONS

ACT	Asthma control test
ATC code	Anatomical Therapeutic Chemical code
CI	Confidence interval
DNA	Deoxyribonucleic acid
FEV_1	Forced expiratory volume during the first second
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GINA	Global Initiative for Asthma
HPA-axis	Hypothalamic-Pituitary-Adrenal axis
HR	Hazard ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
ICS	Inhaled corticosteroid
IgE	Immunoglobin E
LABA	Long-acting $beta_2$ agonist
LAMA	Long-acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
MBR	The Swedish Medical Birth Register
NPR	National Patient Register
OCS	Oral corticosteroids
OR	Odds ratio
PEF	Peak expiratory flow
PIN	Personal identity number
RTI	Respiratory tract infection
SABA	Short-acting $beta_2$ agonist
SGA	Small for gestational age
SPDR	Swedish Prescribed Drug Register
URTI	Upper respiratory tract infection

CONTENTS

ABSTRACT		
SAMMANFATTNING PÅ SVENSKA		
LIST OF PAPERS		I
ABBREVIATIONS		III
CONTENTS		IV
1. INTRODUCTION		**1**
1.1	Background	1
1.2	Pathophysiology	1
1.3	Symptoms of asthma in children	1
1.4	Diagnosis of asthma in children	2
1.5	Different types of asthma in children	4
1.5.1	Non-atopic asthma/recurrent wheeze	5
1.5.2	Atopic asthma/chronic asthma	5
1.6	Differential diagnoses of asthma in children	5
1.7	Treatment of asthma in children	7
1.8	Assessment of asthma in children	7
1.9	Risk factors for asthma in children	10
1.9.1	Genetics/epigenetics	10
1.9.2	Heredity for asthma/atopic disease	10
1.9.3	Own atopic disease	11
1.9.4	Gender	11
1.9.5	Prematurity and being born small for gestational age	12
1.9.6	Obesity	12
1.9.7	Tobacco smoke	13
1.9.8	Air pollutants	13
1.9.9	Infections	14
1.9.10	Antibiotics	14

1.9.11 Paracetamol 15
1.9.12 Nutrition 15
1.9.12.1 Mothers diet during pregnancy 15
1.9.12.2 Breastfeeding 15
1.9.12.3 Introduction of complementary feeding 16
1.9.13 Stress and psychiatric health 16
1.9.14 Socioeconomic factors 16
1.9.15 Allergens 17
1.9.16 Avoiding asthma 18
1.10 Knowledge gap 18

2. AIM 21

3. EPIDEMIOLOGY 23

3.1 Birth of epidemiology 23
3.2 Study design overview 26

4. METHODS 27

4.1 Ethical considerations 29
4.2 Participants and study design 30
4.3 The Children of Western Sweden cohort 31
4.4 The Children of Western Sweden – 15 years later cohort 32
4.5 Definitions from questionnaires 35
4.6 Register linkage 36
4.6.1 Medical Birth Register 36
4.6.2 National Patient Register 36
4.6.3 Swedish Prescribed Drug Register 37
4.7 Definitions from registers 38
4.8 Statistical analyses 38
4.8.1 Chi-2 test 38
4.8.2 Chi-2 test for trend 38

4.8.3 Logistic regression 39
4.8.4 Cohens kappa 39
4.8.5 Cox regression 39

5. RESULTS 41

5.1 Paper I 41
5.2 Paper II 43
5.3 Paper III 44
5.4 Paper IV 47

6. DISCUSSION 51

6.1 Methodological considerations 51
6.1.1 Errors 51
6.1.2 Validity and reliability 52
6.1.3 Statistical significance 53
6.2 Paper-specific discussions 54
6.2.1 Paper I 54
6.2.2 Paper II 55
6.2.3 Paper III 55
6.2.4 Paper IV 56
6.3 Strengths and limitations 57

7. CONCLUSIONS 59

8. FUTURE WORK 61

9. ACKNOWLEDGEMENTS 63

10. REFERENCES 67

1

INTRODUCTION

1.1 Background

Asthma is a common chronic disease, causing problems worldwide. The prevalence varies between different countries, affecting 2-22% of the population. (1-9) Half a million deaths due to asthma (10), as well as 26 million lost disability-adjusted life years (DALYs) per year have been estimated. (11) Asthma causes a major social and economic burden affecting individual children and adults as well as healthcare systems worldwide. (1,12)

1.2 Pathophysiology

Asthma is a chronic inflammatory disorder of the airways, resulting in variable airway obstruction and affected airflow. (13,14) Common exposures, e.g. allergens, exercise or viral upper respiratory tract infections (URTI), stimulate immune responses and induce chronic airway inflammation which, through diverse mechanisms, causes hyper-responsiveness and obstructed airways. Bronchospasm occurs when the muscles encircling the bronchi tighten, and restrict airflow. The chronic inflammation induces airway oedema as well as exudates and inflammatory infiltrates in bronchi resulting in mucus plugging of the airway lumen and obstructed airflow. (13-15) Airway remodelling, a result of asthma pathophysiology, is a process driven by fibroblast activation, epithelial cell apoptosis, basement membrane thickening, and smooth-muscle hypertrophy, leading to permanent structural changes. (16)

1.3 Symptoms of asthma in children

Asthma presents differently between children in the population based on factors such as age, level of severity, individual asthma triggers and medical history. The airway obstruction in asthma is intermittent and the symptoms therefore vary over time. The most common symptoms of asthma in children are a cough and expiratory wheezing, but heavy breathing, rapid breathing, shortness of breath, chest pain, general fatigue and limited physical activity are all symptoms reported among children with asthma. Respiratory symptoms are often reported to be

worse at night, especially during exacerbations due to respiratory infections or inhalant allergens. Children with asthma report symptoms triggered by physical activities and this is more frequently reported among children than in the adult population. (14,17)
During episodes in which the airways are obstructed to a greater extent, severe exacerbations, the children present varying symptoms of respiratory distress including inspiratory and expiratory wheezing, prolonged exhalation, retractions, dyspnoea, accessory muscle use, tachypnoea, cyanosis, changes in mental status and silent chest. (17,18)

1.4 Diagnosis of asthma in children

A medical history, based on symptoms as stated above, is essential for an asthma diagnosis. (14,17) Asking about known risk factors, such as a personal history of other atopic diseases (eczema, allergic rhinitis, food allergy), heredity, particularly with parental asthma, and environmental exposure (tobacco smoke) is important and a positive answer supports the asthma diagnosis. Gaining information on known risk factors is important not only because it supports the asthma diagnosis and helps differentiation regarding differential diagnoses, but also because it is part of the treatment to minimise removable risk factors. Co-morbidity such as obesity, gastroesophageal reflux disease (GERD) and sleep apnoea should be noted. Information regarding the correlation between events or exposures and symptoms is important in order to obtain an optimal overview of the disease; viral respiratory tract infections, physical exercise, aeroallergens, irritants or emotions are all well-known asthma triggers (see Table 1). (11,14,17) The previous use of bronchodilator treatment may provide important information; clinical improvement is suggestive of asthma while no effect of medication is inconsistent with asthma. In these cases, more consideration is needed to exclude differential diagnoses.
During episodes free from exacerbation, children with asthma usually present with a normal physical examination, including auscultation of the lungs. Asking the patient to take deeper breaths can, in some cases, elicit wheezing. During an exacerbation, the child commonly has a prolonged expiratory phase and expiratory wheezing. Rhonchi are often heard and sometimes also crackles. Focal decreased breath sounds can sometimes be detected. (14,17)
In younger children, the asthma diagnosis is based on the medical history, together with a positive response to asthma medication. A

sensitisation allergy test (blood or skin) is performed. It is carefully interpreted and used to facilitate further categorisation of the asthma, and to eliminate offending allergens. Lung function tests are rarely used among the younger children as they are often difficult to perform in pre-school children. (19)

Table 1. Examples of factors triggering asthma

Trigger	**Specific examples**
Viral infections of the respiratory tract	Respiratory syncytial virus, metapneumovirus, rhinovirus, parainfluenza virus, influenza virus
Allergens	Animal dander, pollens (trees, grasses), dust mites, moulds, food items
Activity	Physical activity; running. Laughing
Irritants	Tobacco smoke, cold or dry air, strong smells, perfumes, cleaning fluids, air pollutants (ozone and NO_2)
Emotions	Anger, fear, stress, anxiety
Occupational exposures	Paint fumes, formaldehydes

In Sweden, a child below three years of age is diagnosed with asthma when it is affected by an obstructive episode for the third time. If the child has an allergic disease (e.g. eczema, food allergy) or is at least three years old the asthma can be diagnosed during the first obstructive episode. (20)
From around six years of age, lung function tests such as spirometry commonly complement the medical investigation of an asthma diagnosis. Spirometry is helpful in diagnosing asthma and in determining the severity of the disease. Airflow obstruction is likely to be present when the spirometry shows a decrease in the forced expiratory volume during the first second (FEV_1), with a normal or decreased forced vital capacity (FVC). An improvement in the FEV1 of >12 percent and >200 ml after the inhalation of a short-acting $beta_2$ agonist (SABA) proves variable airway obstruction and is consistent with asthma while supporting the diagnosis. For patients with an uncertain diagnosis, or when the spirometry shows normal results, bronchoprovocation challenges (methacholine, histamine, mannitol, dry

air, exercise) are considered. The measurement of exhaled nitric oxide can be used to assess the treatment of asthma and also to help diagnose asthma. Peak expiratory flow (PEF) monitoring can be helpful in monitoring asthma during longer periods of time in order to prove the variability of the asthma disease and to take early notice of worsening episodes. Radiology, i.e., chest radiographs and computed tomography, are used primarily in infants, or to identify asthma masqueraders and complications occurring during severe asthma exacerbations (pneumothorax, atelectasis, pneumomediastinum). (14,21-22)

1.5 Different types of asthma in children

With accumulating knowledge asthma has been found to be a complex and heterogeneous condition. Several classifications have been used to distinguish different types of asthma, and there are various factors that contribute to the difficulty involved in defining asthma and its sub-groups. Comorbidities, atopic sensitisation, the level of eosinophils, asthma triggers, age of onset, asthma severity, asthma control and the results of lung function tests can all be argued to play a role in sub-grouping asthma correctly. (23,24)

In the papers in this thesis we have used the traditional sub-groups of atopic asthma and non-atopic asthma. This is in line with the Swedish classification system ICD-10-SE, derived from the international ICD (International Statistical Classification of Diseases and Related Health Problems). (25). Not all countries use the same stratification regarding asthma diagnoses in the ICD. In the United States ICD-10 codes are stratified by asthma severity. (26) However, wheezing preschool children constitute a mixed group with a diverse pathogenesis, where some develop allergic features and chronic/atopic asthma, while others present a more isolated wheezing symptomatology. Children can be categorised as having recurrent wheeze during infancy and after a few years instead have an asthma sub-grouped as atopic. The groups are not always distinct from one another, they overlap, and children often also react to other triggers, such as exercise.

The term “atopy” refers to an hereditary susceptibility to an immune response to common allergens, e.g. pollen, resulting in the overproduction of immunoglobulin E (IgE). The clinical reaction is an increased tendency towards allergic disease.

1.5.1 Non-atopic asthma / recurrent wheeze

A recurrent wheeze typically appears during the first years of life, often during infancy. The symptoms are triggered by viral respiratory tract infections and in between infections the child is symptom free. Immaturity of the small airways during the first years of life contributes to poorer airway function and therefore leads to obstructed airflow when triggered by infection. At the age of four the airway function is more stable and symptoms of asthma are usually no longer present among children with no atopic disease. For the majority of these children, wheezing is not correlated to future asthma during adolescence or adulthood. In Swedish literature as well as clinical practice this condition is referred to as "förkylningsastma" (asthma in combination with viral respiratory tract infection). (27,28)

1.5.2 Atopic asthma / chronic asthma

Atopic asthma is associated with sensitisation to aeroallergens and underlying allergy leading to airway inflammation. After the first years of life, where recurrent wheeze dominates, atopic asthma is more common and often persists into adulthood. Atopic asthma is often accompanied by other comorbidities, e.g. allergic rhinitis, atopic dermatitis or food induced allergy. (29,30)

1.6 Differential diagnoses of childhood asthma

Several conditions in childhood can present with signs and symptoms similar to asthma and in the youngest age group in particular, awareness is important if the response to treatment is unsatisfactory. The differential diagnoses must be considered and must not be forgotten even when the child has a past history of asthma. Table 2 (page 6) presents an overview of some the differential diagnoses of childhood asthma. (11,14,31-40)

Table 2. Differential diagnoses of childhood asthma.

Differential diagnosis	**Examples of symptoms or signs**
Foreign body aspiration	Sudden onset of cough, unilateral examination sounds, recurrent chest infections
Bronchopulmonary dysplasia	Prematurity, low birth weight, extra oxygen, mechanical ventilation
Aspiration or tracheoesophageal fistula	Wheeze/cough associated with feeding
Cystic fibrosis	Chronic respiratory symptoms, failure to thrive, steatorrhea, digital clubbing
Vascular ring or tumour compressing the airway	Stridor, respiratory distress, apnoea, cyanosis
Heart disease	Cardiac murmur, failure to thrive, cyanosis, hepatomegaly
Gastroesophageal reflux	Chronic cough, often cough when feeding, vomiting, recurrent chest infections
Vocal cord dysfunction	Intermittent sudden daytime stridor/wheezing, severe dyspnoea (but no hypoxia or increased work of breathing)
Infection (pneumonia, viral bronchiolitis, laryngotracheobronchitis)	Cough, difficulty breathing, fever, no symptoms between infections, often symptoms <10 days
Laryngotracheobronchomalacia	Stridor/cough/wheeze especially during crying, eating, airway infections), symptoms often present since birth
Sinusitis	Chronic cough
Immune deficiency	Failure to thrive, recurrent fever and infections (also non-respiratory)
Primary ciliary dyskinesia	Cough, recurrent chest infections, neonatal respiratory difficulties, ear infections (chronic)
Tuberculosis	Chronic cough, fever/infections not responding to traditional antibiotics, lymph node enlargement, close contact with person with tuberculosis

1.7 Treatment of asthma in children

The treatment goals regarding asthma in children are to maintain a normal level of physical activity, regular school/daycare attendance, normal lung function, an asthma control test (ACT) >19, SABA ≤ 2 times a week, experience few or no side-effects, symptom free nights, prevent exacerbations and to minimise the future risk of mortality related to asthma. (11,41-43)

The aim is to treat the children with the lowest possible dose while still achieving a well-controlled asthma and fulfilling the treatment goals. The medication can be taken daily or during episodes (e.g. during respiratory tract infections or during the allergy season). In clinical practice, the asthma should be continuously monitored and the treatment should be adjusted based on the response to therapy. In case of suspected treatment failure; inhaler technique, adherence, remaining triggers and untreated comorbidities need to be addressed and ruled out before stepping up asthma treatment. The Global Initiative for Asthma (GINA) has updated the recommendations for medical asthma treatment with the aim of preventing exacerbations and controlling symptoms. These new recommendations will soon be part of the Swedish national recommendations. The Swedish treatment recommendations, from 2015, differ between age-groups but the basics are alike. The first step in asthma-treatment is the use of as-needed relief of symptoms, a short-acting beta$_2$-agonist (SABA) reducing bronchoconstriction. If the asthma remains un-controlled the next step regarding asthma treatment is the use of a controller, sometimes in episodes and sometimes used as daily treatment. The first choice of controller is an inhaled corticosteroid (ICS), which is used to reduce airway inflammation. If this is not enough, additional treatment is included; leukotriene receptor antagonists (LTRA), long-acting beta-agonists (LABA), high doses of ICS and finally add-on therapies with LAMA or monoclonal antibodies are recommended. Once the patient fulfils the criteria for good asthma control and it has been maintained for a few months, the gradual stepping down of asthma treatment should be considered. (41-43).

1.8 Assessment of asthma in children

The assessment of asthma is an important part of clinical asthma care and is based on different definitions and measurements and the use of various methods (11). The definition of asthma control is the degree to which the asthmatic features (e.g. symptoms, functional limitations and

risk of adverse events) are observed or have been removed by using treatment. Asthma severity is instead based on how much treatment the child requires in order to maintain symptom-free and not affected by exacerbations. Severity can be referred to as the intrinsic intensity of the asthma process. (11)

In clinical practice, it is important to distinguish asthma that is uncontrolled due to poor adherence or problems with the inhaler technique from a severe asthma. Severe asthma requires heavier treatment, while poorly controlled asthma on the other hand necessitates other approaches such as the evaluation of adherence and inhaler technique or the assessment of potential co-morbidities and triggers. (11,44,45)

Both national and international asthma guidelines stipulate that optimal asthma control should be a part of the treatment goal. (11,41,43) The absence of a fast, uncomplicated method for assessing asthma control led to the development of the asthma control test (ACT™) in 2004. (44,45). The ACT for children from 12 years of age and adults is a short questionnaire including five questions covering symptoms, limitation of activities and the need for rescue medication during the past four weeks. The questions in the ACT for children four to 11 years have been slightly modified and require a parent as well as the child to participate. (46)

In Sweden, the ACT is the method that is commoly used to assess asthma control and it is also recommended in the Swedish national guidelindes. (41) An ACT level of >24 corresponds to well-controlled asthma, 20-24 to somewhat controlled asthma and $\leq$19 to poorly controlled asthma.

By combining ACT level and treatment step the classification system in Figure 1 is used. (47) Lung function tests, commonly spirometry, are an important complement for the assessement of asthma during follow-ups in clinical practice. Other tests to assess asthma control excist; they include the validated Asthma Control Questionnaire (ACQ) where spirometry results are included, in addition to questions on asthma control and asthma symptoms. GINA recommends the assessement of both symptom control and the future risk of adverse outcomes to conclude the level of asthma control. A lung function test is recommended by GINA as a part of monitoring asthma control. (11)

Severity / treatment step		Asthma Control, based om ACT		
Step	Definition	A: ACT >24 Well-controlled asthma	B: ACT 20-24 Somewhat controlled asthma	C: ACT <20 Poorly controlled asthma
1 Very mild	SABA as reliever +/- ICS or LTRA ≤ 3 w during URTI			
2 Mild	SABA as reliever + ICS low or medium dose or LTRA			
3 Moderate	SABA as reliever + ICS low or medium dose + LABA and/or LTRA			
4 Severe	SABA as reliever + ICS high dose + LABA and/or LTRA			
5 Very severe	One or more of: Anti-IgE, Anti-IL5, Airsonett, oral corticosteroids, theofylline, azithromycin or long acting muscarinic antagonists			

Figure 1. Asthma classification based on the level of asthma control and asthma severity level. Adopted from: Barnläkarföreningen, barnallergi-sektionen, Klassificering av astmasvårighetsgrad med hänsyn till medicinering och symptom hos barn över 4 års ålder, rev 2017. ICS: inhaled corticosteroid; LABA: long-acting beta$_2$-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta$_2$-agonist; URTI: upper respiratory tract infection

1.9 Risk factors for asthma in children

Asthma is a heterogenous disease where gene-environment interactions are likely to influence the risk of developing asthma. Many of these interactions are likely to occur in utero and during the first period of life. (11) Risk factors for asthma are presented below.

1.9.1 Genetics / epigenetics

The genetic code of humans and all other living organisms, is the hereditary material we call deoxyribonucleic acid (DNA). DNA information is stored as base pairs attached to a backbone with the form of a spiral called a double helix. The DNA code exists of base pairs build of adenine, thymine, cytosine, and guanine. The vast majority of these bases are the same in all humans; more than 99% of the three billion base pairs that our genome consists of are the same. The DNA is able to multiply in a process called replication, thereby creating a copy of itself, a critical quality because each newly divided cell needs to have exactly the same DNA as its precursor. The DNA is twisted around proteins called histones, forming the chromosomes located inside the cell nucleus. Genes are built by DNA sequences and the genetic material in many of the genes contains the code for producing a specific protein. Epigenetics - our environment, like diet, activity level, pollutants and tobacco smoke, is able to induce changes that affect the activity level in the genes, has been further studied and understood in the last few decades. (48-50) Genetic changes affect which protein is produced in the organism. Epigenetic changes on the other hand affect whether/how much of the protein that is made; it turns genes on and off. Examples of epigenetic regulation includes methylation where a methyl group is added to the DNA-strain, turning genes off. Genes can be activated by after modification of the packaging of histones. It has been discovered that epigenetic variations do not always emerge from environmental influence but sometimes can be inherited, revolutionising the concept of the former clear distinction between environmental influence and genetic inheritance. (51) Epigenetics is likely to interact with the risk factors reviewed below (52) and in the future the mechanisms will hopefully be fully elucidated.

1.9.2 Heredity for asthma / atopic disease

Heredity for asthma in particular but also for other types of allergic disease is a major risk factor for developing asthma. (53-55) If one

parent has asthma there is a 25% risk that the child will receive this disease while 50% of the children with two asthmatic parents develop asthma. Most children have parents without any asthma and for these children the overall risk of becoming asthmatics is about 5%. (56,57)
Twin-studies studying the heredity for asthmatics show that among dizygous twins, the risk of asthma is three times greater compared with the general population if one of the twins has asthma. A monozygous twin has a six-fold increase in the risk of asthma. (56)
The mechanisms regarding heredity as a risk factor are complex and yet not fully understood. For example, genes involved in asthma development are believed to interact with other genes but also with environmental factors to regulate asthma susceptibility. Researchers in this field have searched for genes connected to the production of allergen-specific immunoglobin E (IgE) antibodies (58). Others groups have studied the immune response by searching for genes programming T helper cells (Th) and the ratio between Th1 and Th2. (59-60) Moreover, genetic research on inflammatory mediators such as cytokines is being performed. (61)

1.9.3 Own atopic disease

Atopic diseases such as eczema, asthma, allergic rhinitis and food allergy often coexist and having one of these conditions increases the risk of receiving one of the others. (62-67)
These children often first present with their conditions in a time-based order. First, during early infancy, atopic dermatitis occurs and food-induced allergy then appears. During later stages of childhood these children develop allergic rhinitis and asthma. This process is referred to as “the atopic march”. (68-70)
Many children have one or two of these manifestations and not all four of them. The mechanisms behind the association between these conditions and the time-based order in which they often occur are multifactorial. Several factors affect the risk of developing atopic disease; they include environmental stress with pollutants, allergen exposure, skin barrier dysfunction caused by filaggrin mutation, microbiome alteration and epigenetic variations, for example. (71-74)

1.9.4 Gender

In childhood, there is a predominance of asthma in boys (65%), (75,76) while female gender is a risk factor for adult asthma. When entering

adolescence, the gender difference in asthma rates narrows and then become higher for girls. (75,77) Among adults, 65% of the asthmatics are female, and they also are more likely to develop severe asthma compared with males. (78,79)
The reasons for the difference in asthma prevalence between the sexes are still not fully understood but a likely contributor is the fact that infant males have smaller lungs and airways compared with their female counterparts. (80) In adulthood the ratio is inversed. (81)
Other factors affecting the sex differences in asthma prevalence are sex hormone change during puberty and the menstrual cycle, where oestradiol has been shown to induce inflammation. (82-84) Social factors such as occupation (85) as well as genetic and epigenetic factors (86,87) have been suggested.

1.9.5 Prematurity and being born small for gestational age

Factors such as, preterm birth and being born small for gestational age (SGA), are risk factors for childhood asthma. (88-90) Children born preterm and SGA have been studied and shown to have a lower FEV_1 and FEV1/FVC ratio compared with children born appropriate for gestational age (AGA) and after full-term pregnancies. (88,89) Affected growth in utero and during infancy have been suggested to lead to impaired lung growth as well as smaller airway calibre and affected lung volume resulting in an increased risk of asthma. (91)

1.9.6 Obesity

Obesity is a risk factor for childhood asthma. (92,93) The association is particularly strong in girls and obese asthmatic children are more likely to have severe disease. (93) A so-called obesogenic diet (high fat, low fibre) leads to alterations in the gut microbiota and also reduces the levels of circulating short-chain fatty acids. These changes are associated with increased airway inflammation in mouse models. (94,95) On the other hand, a high-fibre based diet inhibits airway inflammation in a mouse model and a mechanism for the association between obesity and asthma is therefore suggested. (96,97) A systematic review found that maternal obesity increases the risk of asthma in children. (98)

1.9.7 Tobacco smoke

Being exposed to tobacco smoke, from either maternal smoking during pregnancy or second-hand smoke during infancy, is a risk factor for childhood asthma. (79,99,100)

Nicotine has prenatal effects since it passes over the placenta in utero. Postnatally nicotine affects the child via breastmilk and via inhaled air. The consequence of exposure to maternal smoking in utero and also second-hand-smoke is an influence on lung development, decreased FEV_1 and decreased passive respiratory compliance. (101-102) The children of mothers smoking during pregnancy run a four times higher risk of developing asthma during infancy compared with children without smoking mothers. Being exposed to tobacco smoke during pregnancy appears to have a stronger effect regarding asthma development in children compared with postnatal exposure. (99) The results relating to whether maternal smoking affects allergic sensitisation are contradictory. (103-108) Epigenetics with DNA methylation appears to be involved in the association between tobacco smoke and pediatric asthma (52,107) and trans-generational epigenetic changes have been suggested. (108)

1.9.8 Air pollutants

A well-known risk factor for diminished lung function in children, especially globally, is exposure to outdoor pollutants. These are often traffic related but air pollution from factories, for example, (109-112) is important and it has been suggested that 13% of the global incidence of new cases of childhood asthma are associated with long-term exposure to traffic-related air pollution. (113-116) Pollutants from traffic and factories such as NO_2, SO_2, and PM10 are all risk factors of asthma in childhood. (117) Genetics and epigenetics appear to be involved in the mechanism. (52,118)

Globally, indoor pollutants such as smoke and pollution from gas or biomass fuels used for heating and cockroach infestations have been shown to increase the risk of asthma. (117) Several systematic reviews found an association between asthma and long-term exposure to dampness and moulds, especially among adults but also in children. (119-122) However, a weakness in the studies was the risk of response bias, mould exposure was often self-reported and data were collected retrospectively.

1.9.9 Infections

The 'hygiene hypothesis' from 1989 (123,124) proposes that interaction between humans and microbiota may contribute to preventing asthma, as well as other allergic and autoimmune diseases. The suggested mechanism is an influence of microbial exposure and infections appearing early in life and affecting the development of the infant's immune system. For example, there is a lower risk of asthma among children who attended daycare centres, were raised on farms, had several older siblings, slept in bedrooms with raised levels of bacterial-derived lipopolysaccharide endotoxin or were delivered vaginally. (11,123,125-130)

Since infections early in life exposes the children to microbes, the risk of asthma could be reduced, according to the 'hygiene hypothesis'. Some studies found an association between exposure to infectious agents, such as Helicobacter pylori, measles, hepatitis type A, and a reduced risk of asthma. (131-133)

However, on the other hand, infections during infancy with respiratory syncytial virus (RSV), parainfluenza and rhinovirus are clearly associated with an increased risk of future asthma, and approximately 40% of infants admitted to hospital due to viral respiratory tract infection (RTI) will develop asthmatic disorder remaining at least into later childhood. (134-136) The scientific community has widely debated the subject of causality, whether it is the early RTIs that causes asthma development or whether these children are predisposed to both asthma and for more severe symptoms of RTIs. To summarise the results of several studies, for example twin studies, indicate that early viral RTIs appear to trigger asthma development in already fragile individuals. (137-139)

1.9.10 Antibiotics

An association between antibiotic treatment during infancy and an increased risk of asthma has been shown. (140-142) Difficulties relating to causal relationships and the risk of reversed causation led to further studies and, also when excluding children who did have symptoms of wheezing during an episode of antibiotics, an association was still found (143). The research group in which the author is included has found that antibiotic treatment during the first week of life increases the risk of asthma in one-years-old's and also in four- and eight-year-old children.

(144-146) Whether or not prenatal antibiotic treatment is a risk factor for asthma or not is uncertain. (141,147)

1.9.11 Paracetamol

Studies have found an increased risk of paediatric asthma in children exposed to paracetamol prenatally or during childhood (148-151). It has been difficult to interpret the results since paracetamol often is used for RTI´s which, as described earlier, can contribute to asthma development or be a manifestation of asthmatic disorder. Pregnant women using paracetamol frequently run an increased risk of giving birth to children who develop asthma. Causality has not been able to be determined. (151-153) One proposed mechanism is that paracetamol reduces the levels of pulmonary glutathione, thereby reducing the capacity to resist oxidative stress in the airways. (154)

1.9.12 Nutrition

1.9.12.1 Mothers diet during pregnancy

The mother's diet during pregnancy has been studied in terms of the development of paediatric asthma. Dietary restrictions and avoiding food items do not appear to increase the risk of asthma in the child. (155-157) On the other hand, a reduced risk of asthma has been shown in children whose mothers had an intake of "allergenic" food such as milk, peanuts and fish. (158-161) A dose-dependent association was found; the mothers who ate the largest amounts of peanuts and tree nuts, gave birth to children who developed asthma with a lower frequency compared with the mothers who ate smaller amounts of peanuts and tree nuts. (162)

1.9.12.2 Breastfeeding

Breastfeeding has many favourable effects for both mother and child, but the results are conflicting regarding the possible effect of breastfeeding on the risk of asthma development. Breastfeeding has been shown to decrease the risk of infections with following wheezing episodes during the first years of life. (163-166) Some studies indicate a long-term protective effect of breastfeeding. (167) However, no strong evidence regarding a reduction in the risk of persistent asthma has been found. (168,169) A review article concludes that there is no long-term protection from breastfeeding on asthma development. (170) When comparing infants who were breastfed with infants receiving only

formulas (based on cow's milk or soy protein) there is a higher risk of wheezing condition in the formula fed group. (171) Formulas containing hydrolysed protein compared with breastfeeding did not show any protective effect regarding allergy in the whole population of children. (172) In cases with a very high risk of allergic disease formulas containing hydrolysed protein might have a protective effect on atopic dermatitis. (173-174)

1.9.12.3 Introduction of complementary feeding

The introduction of new food items early in life appears to be protective regarding the risk of developing allergic diseases. (175-183) The risk of food allergy as well as eczema and asthma appear to decrease when food items are introduced at an early stage, around four to six months of age. Fish, eggs and peanuts are examples of food items that have been studied with regard to introduction-time and allergic outcomes. (175-183) Data from animal models consistently show an association between the enteral exposure to antigens early in life and the prevention of sensitisation to the presented antigen (184). This is called oral tolerance and is the suggested mechanism regarding early food introduction and a reduced risk of allergic disease. (185,186) The phenomenon has also been described in humans. (178,187)

1.9.13 Stress and psychiatric health

A social situation with high parental distress (188,189) as well as a child's own affected psychiatric health (190,191) increases the risk of asthma. Stress has been shown to affect the immune response and the balance between the production of different cytokines involved in allergy and asthma development, thereby increasing atopic reactions. The suggested mechanism is that stress affects the hypothalamic-pituitary-adrenal axis (HPA-axis) resulting in increased levels of glucocorticoids. (192) The immune response reacts to increased glucocorticoid levels and stimulate Interleukin 4 and 5 production, leading to a Th2 dominance and therefore an increased risk of asthma. (193,194) This immunologic response to stress has been shown to be stronger among atopic persons compared with non-atopics. (195)

1.9.14 Socioeconomic factors

Poverty is a major risk factor for poor health all over the world. (196) The risk of asthma, on the other hand, has been more common in affluent

countries. (197) Recently, studies have found results challenging this general pattern. Several studies present data in which a lower socioeconomic status increase the risk of wheezing. (198,199) Stress, leading to effects on the hypothalamic-pituitary-adrenal axis and changes in glucocorticoid levels then driving the immune system towards a Th2 mode has been suggested as a mechanism, as suggested above. (200-202) Other factors associated with asthma, e.g. parental smoking and obesity are also more common among people with a lower socioeconomic status.

1.9.15 Allergens

It is well known that inhalant allergens are triggers of asthma symptoms in sensitised children with an established diagnosis of asthma. Whether inhalant allergens also affect the risk of asthma development is not fully understood and studies report contradictory results. (203-207) Children already affected by atopic disease run an increased risk of developing asthma as a result of long-term contact with pets, house dust mites or mould, especially if they are sensitised to that specific agent beforehand. (208-212).

Some studies suggest that healthy children with early exposure to cats or dogs may reduce the risk of asthma (213-218) while others indicate an increased risk. (219-221) Work has been done to acquire a greater understanding of this area (222). However, healthy children with allergic heredity do not seem to have an increased risk of developing allergies if the timing of long-term pet exposure is after one year of age. (223) No final conclusion has been drawn regarding recommendations on early life exposures to pets and other common indoor inhaled aero-allergens.

Exposure and sensitisation to outdoor inhaled aero-allergens appear to have less effect on asthma development compared with indoor allergens. Nevertheless, some studies show that early exposure of birch or grass pollen in children with allergic heredity increases the risk of sensitisation and also an increased risk of asthma among the children who had been in contact with pollen. (224)

1.9.16 Avoiding asthma

First of all, choose your genome carefully. You can also try to make sure that your parents do not have any asthma or allergies. After that, gain an appropriate amount of weight when you are growing in your normal weight mothers' uterus. Stay there until you are full term and try to take the vaginal way out. Hopefully you can avoid antibiotic treatment, at least initially. The best thing for you is simply to move in with your family at their farm, preferably with cows and other animals, right away. You can breastfeed of course, it is really good for many reasons, but we are not sure whether it effects your chances of avoiding asthma, at least not in the long run. Hopefully the farm is located far away from heavily trafficked roads and factories. If anyone has a runny nose or complains of a cough or fever, stay away. Do not be afraid to try new food items, start with a small amount and then increase. Stay away from tobacco smoke and do not pick up any other allergic diseases. Eat healthy food, maybe even from the farm. Do not stress but stay active. Regarding your gender, it is a bit tricky, pros and cons, so I am not going to force you in any direction.

These tips are absolutely no guarantee of avoiding asthma, but they are always a start!

1.10 Knowledge gap

Knowledge of the epidemiology of asthma is important for effective prevention and to identify individuals to target for treatment efforts. Considerable efforts have been made within the research community to determine asthma epidemiology. Much of the current knowledge originates from questionnaire-based data, but the validity of questionnaire-based data has been questioned. Increased knowledge of the reliability of questionnaire-based data is of great relevance. Since questionnaire-based studies are time-efficient, of low-cost, and allow large sample sizes, they are an important complement to clinical data collections when they are valid and accurate.

Much is known regarding the risk factors and protective factors for asthma, but studies of long-term follow up are scarce, indicating a gap of knowledge. Moreover, since asthma is a heterogenous disease with different subgroups, it is of great value to study the specific epidemiology regarding subgroups, e.g. atopic asthma, non-atopic asthma and also uncontrolled asthma. As we live in an evolving society, with an increasing urbanisation and significant demographic changes in

in the population, the epidemiology is also evolving and changes. As a result, we are unable to fully rely on 20-year-old epidemiological studies of childhood asthma or its subgroups and access to updated epidemiological data is of considerable importance.

2

AIM

The overall aim of this thesis was to improve the current knowledge regarding the epidemiology of childhood asthma; prevalence, risk factors and protective factors. The objectives of each study are as follows.

→ To examine the prevalence of, and risk factors for asthma at 12 years of age and to analyse the associations with atopic and nonatopic asthma. In particular, we wanted to investigate whether antibiotic treatment early in life affected the risk of asthma during long-term follow-up. **(Paper I)**.

→ To study the prevalence of uncontrolled asthma and hospitalisation due to asthma and to analyse factors that affect asthma control and hospitalisation due to asthma among 12-year-old asthmatics. **(Paper II)**

→ To analyse the agreement between asthma data based on questionnaires and asthma data delivered from Swedish registers, the Swedish Prescribed Drug Register (SPDR) and the National Patient Register (NPR). We also aimed to study the pattern of asthma medication during childhood **(Paper III)**

→ To study adherence to current advice relating to food introduction. We also wanted to examine whether the timing for introducing complementary foods changed between children born in 2003 and in 2018. **(Paper IV)**

3

EPIDEMIOLOGY

Epidemiology is *"the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems."* (225)

3.1 Birth of epidemiology

In 1813 a boy named John Snow was born. The family lived in York, England, where the father worked as a coal-yard labourer. During the 19th century the infectious disease of cholera became a major threat that killed hundreds of thousands of people in Europe due to dehydration because of profuse diarrhoea. John grew up and wanted to become a physician and he therefore moved to London for further studies. He became interested in the cholera disease and reasoned that it might be caused by an infectious agent in food or water. He was not the first to introduce this hypothesis but the prevailing theory at the time was that cholera was spread by miasma (inhaled poison from polluted air) and John's theory met with doubt and resistance. To improve his understanding of the cholera disease he conducted studies during one of the cholera outbreaks in the mid 19th century. He collected data on 350,000 persons and recorded many different variables such as the source of drinking water for each case. Snow discovered that the vast majority of the cholera cases obtained their drinking water from sources where sewage contaminated the drinking water. Only a small minority of the cases received their drinking water from pumps upstream of the sewage contamination. Snow did not find any other differences between the people who had received contaminated water and the ones who had not. Both groups included rich and poor people and people of different genders, ages, household sizes, conditions and occupations. The households with contaminated drinking water were 14 times as common among cases that died from cholera compared with households without contaminated drinking water.

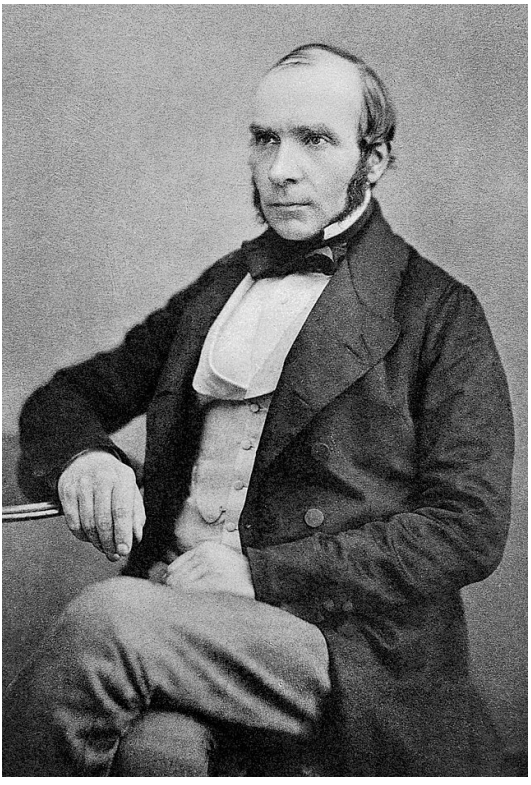

Figure 2. John Snow

John Snow presented his findings to the authorities and suggested closing the pumps with contaminated water but this was denied and met with the argument “this is purely statistical evidence”. Later on, these pumps were removed and the cholera outbreak ended. (226,227)

Snow (Figure 2) is often referred to as one of the pioneers of epidemiology. His work illustrates the core of epidemiology; revealing patterns and associations leading to an increased understanding of a disease, in this case cholera.

John Snow died in 1858 at 45 years of age.

3.2 Study design overview

Asthma epidemiology can be investigated from various perspectives and by using studies of different types. A schematic overview of the types of study design is shown in Figure 3.

The appropriate choice of study design depends on the research question. In *experimental* studies, the research team introduces an intervention and, in that way, interferes with the natural course. There is usually a control-group, where the study subjects are not exposed to the intervention, but in "all" other respects are equal to the intervention-group. The study subjects are randomised to either an intervention or control-group and the intention with the study is to determine the effect the intervention has on the participants compared with the natural course. In well-performed experimental studies, the main advantage is satisfactory control of confounders and mediators, opening up the opportunity to determine causal relationships between exposure and outcome. However, when the exposure is dangerous or unethical or when the time from exposure to outcome is long, experimental studies are often not suitable or impossible to perform.

In *observational* studies, the research team does not interfere with the natural course. The study design, where data occurring at a single/specific point in time are used, is called a cross sectional-study. If the study includes follow-up time and changes that might occur over a period of time, the study is called longitudinal. Observational studies can be further categorised as descriptive or analytical. In a descriptive study the characteristics of the study subjects is only described. An analytical study is used to quantify an association between exposure and outcome. Cohort studies are observational, longitudinal, analytical studies that follow participants who share a common characteristic. In birth cohorts the same common characteristic could be such as being born in the region of western Sweden in a specific year.

Since cohort studies do not interfere with the natural course, dangerous exposures and risk factors can be studied. Several outcomes can be analysed, large numbers of participants can be included, incidence-calculations can be made and associations with long latency periods can be investigated. Adjustments for confounders can be made. However, the effect of potential confounders cannot be eliminated and causality cannot be fully determined in a cohort study.

Cohort studies can be categorised as retrospective or prospective. If the exposure information is collected after the outcome has occurred, the

study is retrospective. This can be advantageous in cases with long latency periods but leaves an increased risk of recall bias, missing data or potential confounders. If the collection of data on exposures is initiated before the outcome has occurred, the study is called prospective. A prospective study design reduces the risk of missing data and confounders.

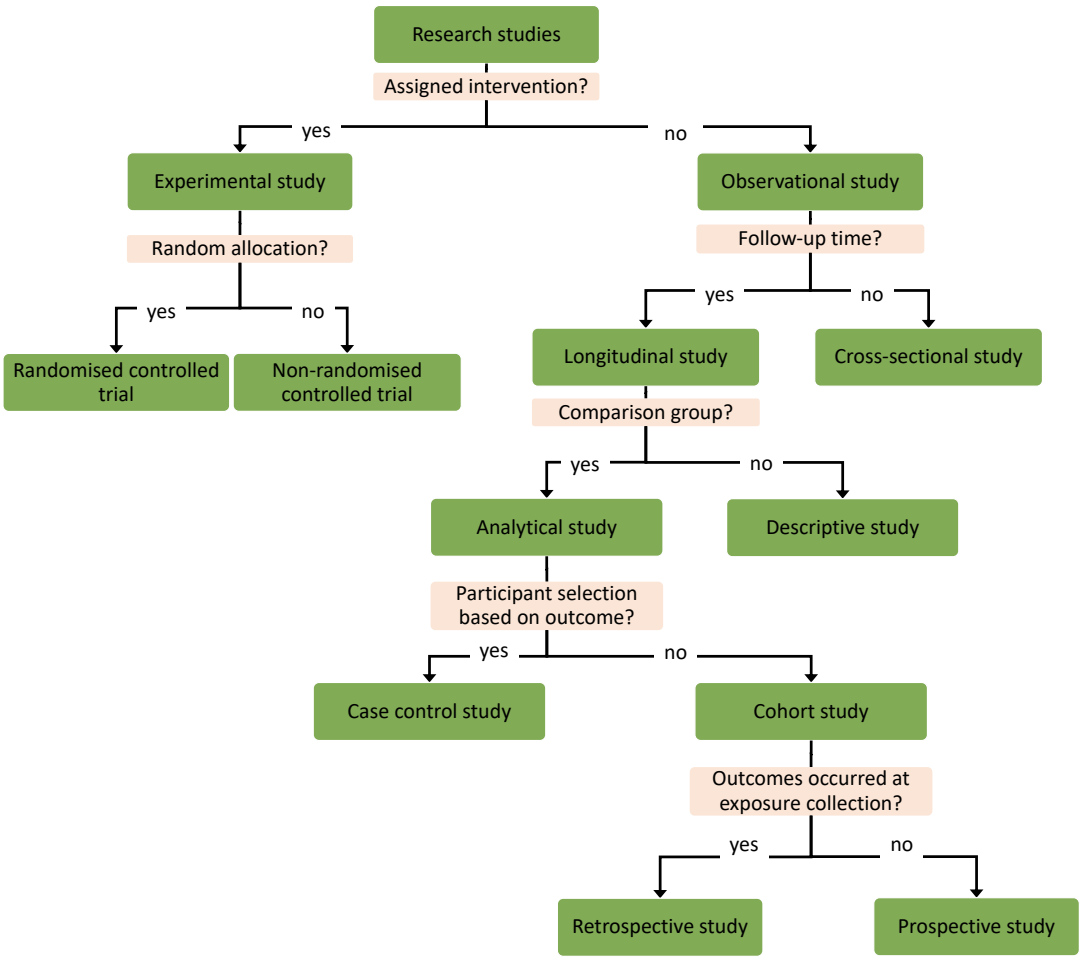

Figure 3. Schematic overview of types of study designs.

4

METHODS

4.1 Ethical considerations

All four papers included in this thesis have ethical approval. The first three papers have been approved by the ethics committee at the University of Gothenburg (registration numbers 846-14 and Ö 524-00) and the fourth, and final, paper has been approved by the Central Ethical Review Board in Gothenburg (registration number 190-18) and by the ethics committee at the University of Gothenburg (registration number Ö 524-00)

For the children and their families, the potential risks when approving participation in the studies in this thesis relate to personal integrity. Data linkage was performed by the National Board of Health and Welfare. The personal identification numbers (PIN) were removed before data delivery and replaced by study identification numbers meaning that data were completely anonymised to the research group. The families were informed that the participation in the study could be withdrawn at any time, even after an informed consent. The research in this thesis conforms to the guidelines stated in the Declaration of Helsinki.

4.2 Participants and study design

A summary of participants and study design is presented in Table 3.

Table 3

	Design	Patients	Outcome
Paper I	Cohort study, children born in 2003 Data from questionnaire and the Swedish Medical Birth Registry	**n = 3637**	**Asthma prevalence and risk factors**
Paper II	Cohort study, children born in 2003 Data from questionnaire	**n = 233**	**Uncontrolled asthma and hospitalisation**
Paper III	Cohort study, children born in 2003 Comparison between data from questionnaire and national registers (the National Patient Register and Swedish Prescribed Drug Register)	**n = 3634**	**Agreement between register-based data and questionnaire-based data on asthma**
Paper IV	Cohort, children born in 2018 compared with cohort of children born in 2003 Data from questionnaires and the Swedish Medical Birth Registry	**n = 4987 (2003)** **n = 3936 (2018)**	**Adherence to recommendations on introduction of complementary feeding**

4.3 The Children of Western Sweden cohort

The first three, and in part the fourth, papers, in this thesis are based on data from a prospective, longitudinal population-based birth cohort called the Children of Western Sweden. The children were born in the Västra Götaland County (see Figure 4) in 2003 in and this thesis uses data from a 12-year-follow-up. The region comprises 49 municipalities and has a population of 1.6 million inhabitants, 17% of the Swedish population. Rural, sub-urban and urban areas are included. The metropolitan area of Gothenburg is included in the study. From the total birth cohort in Västra Götaland in 2003, 16,682, 50% were randomly selected resulting in 8,176 infants.

Figure 4. Map of Sweden and the Västra Götaland County. Edit: Jon Celind

The parents obtained postal questionnaires when their children were six months of age and one, four, eight and 12 years of age. In the first three papers in this thesis we have used data from the 12-year-follow-up. The

response rate at 12 years of age was 64% of the children who entered the study during infancy (3637/5654). This corresponds to 76% out of the 4777 to whom the questionnaires were distributed and 90% of the responders in the eight-year follow-up (3637/4051). An overview of the participation is shown in Figure 5.

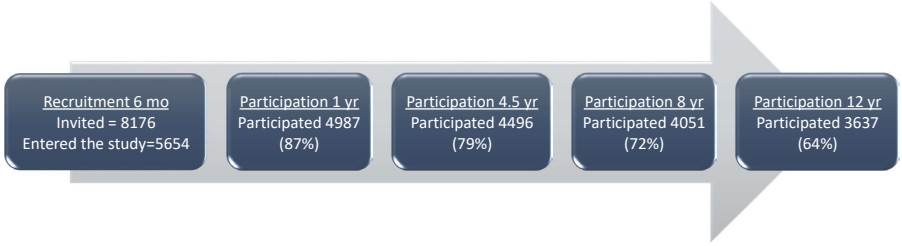

Figure 5. Flowchart of the participation from the 2003 cohort (Paper III).

The questionnaires were based on validated questions from the international ISAAC Study and from the Swedish BAMSE Study. Questions on pregnancy, postnatal factors, admission to a neonatal ward, antibiotic treatment during the first week of life, parental educational level, parental smoking and heredity were asked at six months of age. At 12 months of age, questions were asked regarding breastfeeding and the introduction of complementary feeding, atopic diseases and pets in the home were asked. Questions regarding airway symptoms, asthma medications, triggers of asthma, hospitalisation due to asthma, allergic sensitisation, atopic disease and parental smoking were asked at 12 years of age.

4.4 The Children of Western Sweden – 15 years later cohort

The fourth, and last, paper in this thesis is based on data from a prospective, longitudinal population-based birth cohort called the Children of Western Sweden – 15 years later. The children were born in the Västra Götaland County in 2018. Both rural, sub-urban and urban areas are included. From the total birth cohort in Västra Götaland in 2018, 19,613, 50% were randomly selected resulting in 9,799 infants. The parents were sent postal questionnaires when their children were six months of age and at 12 months of age. The response rate at six months was 48% of the infants who entered the study (4576/9475). At 12

months of age, the response rate was 42% (3936/9475). An overview of the participation is shown in Figure 6.

The questionnaires were based on validated questions from the international ISAAC Study and from the Swedish BAMSE Study and the questions corresponded to the questions for the 2003 cohort.
Questions regarding pregnancy, postnatal factors, parental smoking, parental educational level and heredity were asked at six months of age. At 12 months of age, questions were asked regarding breastfeeding and the introduction of complementary feeding, wheezing and atopic diseases.

Figure 6 (page 34). Flow chart of participants from the 2018 cohort. Q1 = six-month questionnaire (Q1:A = standard version, Q1:B = short version), Q2 = 12-month questionnaire.

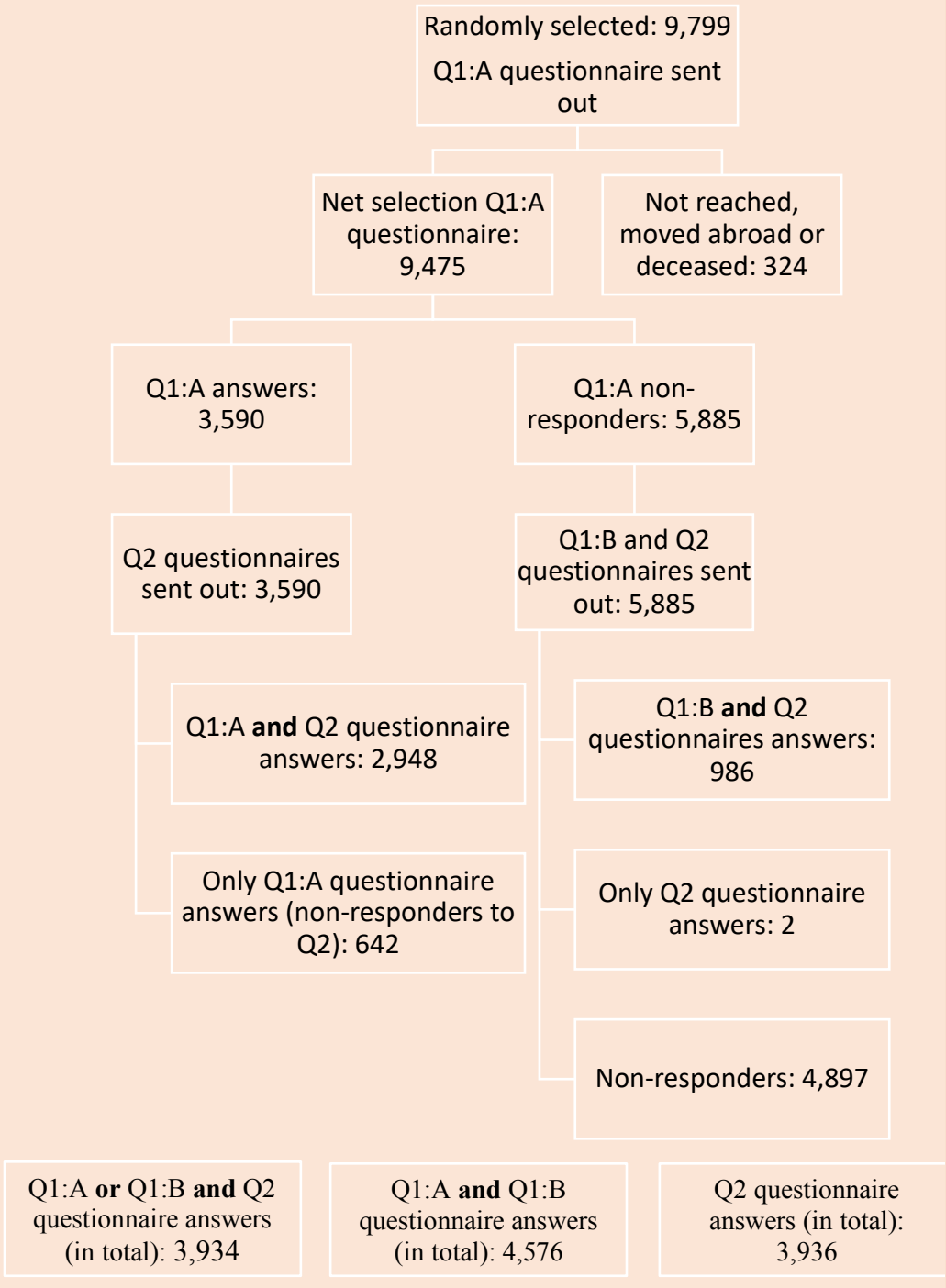
Randomly selected: 9,799
Q1:A questionnaire sent out
Net selection Q1:A questionnaire: 9,475
Not reached, moved abroad or deceased: 324
Q1:A answers: 3,590
Q1:A non-responders: 5,885
Q2 questionnaires sent out: 3,590
Q1:B and Q2 questionnaires sent out: 5,885
Q1:A **and** Q2 questionnaire answers: 2,948
Q1:B **and** Q2 questionnaires answers: 986
Only Q1:A questionnaire answers (non-responders to Q2): 642
Only Q2 questionnaire answers: 2
Non-responders: 4,897
Q1:A **or** Q1:B **and** Q2 questionnaire answers (in total): 3,934
Q1:A **and** Q1:B questionnaire answers (in total): 4,576
Q2 questionnaire answers (in total): 3,936

Figure 6.

4.5 Definitions from questionnaires

Definitions from the questionnaires are presented in Table 4.

Table 4. Definitions based on questionnaires in Papers I-IV.

Variables	Definitions based on questionnaires in Papers I-IV
Paper I	
Current asthma at 12 years of age	Ever reported doctor-diagnosed asthma and either current treatment or current symptoms.
Atopic asthma at 12 years of age	Current asthma, as stated above, plus reported allergic sensitisation and/or current doctor-diagnosed allergic rhinitis, food allergy or eczema (a reported diagnosis of allergic rhinitis, food allergy or eczema and either treatment and/or symptoms during the last 12 months).
Nonatopic asthma at 12 years of age	Current asthma, as stated above, and not having any reported allergic sensitisation or current doctor-diagnosed allergic rhinitis, food allergy or eczema.
Paper II	
Current asthma at 12 years of age	Ever reported doctor-diagnosed asthma and either current treatment or current symptoms.
Hospitalisation due to asthma	Reported admission to hospital due to asthma during the past 12 months.
Asthma control	Reported ACT. Uncontrolled asthma: ACT < 20, Controlled asthma: ACT ≥20
Paper III	
Any wheeze at one year of age	Any parent-reported wheeze during the first year of life.
Recurrent wheeze at one year of age	At least three episodes of reported wheeze during the first year of life.
Doctor diagnosed asthma at one year of age	Reported, doctor-diagnosed asthma during the first year.
Asthma medication	Any reported asthma maintenance treatment or inhaled SABA.
Asthma maintenance treatment	Reported treatment with ICS and/or LABA and/or LTRA.
Current asthma at 12 years of age	Ever reported doctor-diagnosed asthma and either current treatment or current symptoms.
Paper IV	

Age of introducing complementary feeding (e.g. eggs, fish…), in the 2003 cohort	The reported age in number of weeks for introducing different food items was adjusted into months.
Age of introducing complementary feeding (e.g. eggs, fish…), in the 2018 cohort	The reported age in number of months for introducing different food items

4.6 Register linkage

A number of national registers are administered by the Swedish National Board of Health and Welfare. The purpose of these registers is to make scientific analyses and the development of Swedish healthcare possible. These registers are linked to the personal identity number (PIN) of each individual and the registers can be linked to one another and can also be linked to different types of data, for example questionnaire-based data. Data from some of the Swedish national registers were used in this thesis.

4.6.1 Medical Birth Register

The National Medical Birth Register (MBR) was established in 1973. All health care providers in Sweden are obliged to report information from medical records to the register. The information in the register includes prenatal, delivery and neonatal care and yearly reports are published. The reliability of the register is primarily based on the medical records and the administrative routines among the health care providers. The overall quality of the MBR is overall considered to be good. To some extent, the coverage is high, 97-99% of all deliveries in Sweden are included. Information in the MBR is based on self-reported data, which present a possible bias. The reliability can also be negatively affected if bias is introduced when information is transferred from medical journals to the MBR. (228) We used data from the MBR as supplementary information in Papers I and IV.

4.6.2 National Patient Register

The National Patient Register (NPR) was initiated in the 1960s and initially contained information from in-patient care at public hospitals.

Since 1987 NPR has covered all Swedish inpatient admissions and in 2001 outpatient visits to physicians also began to be included.
The information in the register includes patient data, geographical data, administrative data (e.g. date of admission and discharge) and medical data (e.g. main and secondary diagnosis according to the assigned ICD-10 codes from the medical records). Both private caregivers and the county councils provide information to the NPR once a month but primary care is not yet included in the NPR.
Regarding the quality of the data; the underreporting of the data for inpatient care is low, according to the Swedish Board of Health and Welfare, low. The outpatient data have had higher underreporting, but the quality relating to outpatient care has made major improvements since the outpatient register was launched in 2001. Incoming data to the NPR undergo quality controls, e.g. the validity of the main diagnosis. (229) We used data from the NPR in Paper III.

4.6.3 Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register (SPDR) was established in 2005 and provides statistics on all prescribed drugs dispensed at pharmacies in Sweden. Register updates are made monthly with data from the Swedish eHealth Agency based on dispensed drugs. All pharmacies are obliged to report to the Swedish eHealth Agency when a prescribed drug is dispensed and this information is transmitted to the National Board of Health and Welfare. The register includes, for example, patient data and product data (e.g. Anatomical Therapeutic Chemical code (ATC code), medical devices). The overall quality of the SPDR is estimated to be overall very good. The data collection is performed automatically and hence the risk of measurement mistakes is small. Quality checks are performed by the Swedish eHealth Agency. (230) We used data from the SPDR in Paper III.

4.7 Definitions from registers

Definitions from the registers are presented in Table 5.

Table 5. Definitions based on registers in Paper III.

Variables	Definitions based on registers in Paper III
National Patient Register	
Obstructive bronchitis/bronchiolitis	At least one inpatient ICD-10 code of J20 or J21
Asthma	At least one (main or secondary) diagnosis of ICD-10 code of J45. (from outpatient or inpatient register depending on the research question)
Obstructive disease	At least one inpatient ICD-10 code of J20, J21 or J45
Swedish Prescribed Drug Register	
ICS treatment	At least one of the ATC codes R03BA (ICS) or R03AK (ICS and LABA)
Maintenance treatment	At least one of the ATC codes R03BA (ICS), R03DC03 (LTRA), R03AK (ICS and LABA) or R03AC12/13 (LABA)
Any asthma medication	At least one of the ATC codes R03AC02/03 (inhaled SABA), R03AC12/13 (LABA), R03BA (ICS), R03DC03 (LTRA) or R03AK (ICS and LABA).

4.8 Statistical analyses

IBM SPSS Statistics version 23.0, 28.0 (IBM CORP, Armonk, NY, USA) was used for the statistical calculations in all four papers in this thesis. A p-value of <0.05 was used as a cut-off for statistical significance.

4.8.1 Chi-2 test

To statistically compare differences in frequencies between groups for categorical or dichotomous variables we used the chi-2 test.

4.8.2 Chi-2 test for trend

To statistically analyse trends in frequencies between groups for categorical or dichotomous variables we used the chi-2 test for trend.

4.8.3 Logistic regression

We created univariate and multivariate models to analyse risk factors and risk-reducing factors regarding different outcomes. Since our outcome variables were dichotomous, logistic regression models were chosen. The selection process regarding adjustments for potential confounders was made, taking consideration of significant, clinically relevant factors. The results were presented as odds ratios (OR´s) using 95% confidence intervals.

4.8.4 Cohen's kappa

To measure the statistical agreement between categorical variables we calculated the Cohen's kappa coefficient (κ). A 95% confidence interval was used.

4.8.5 Cox regression

We created univariate and multivariate models to compare differences in time regarding the introduction of food items between two cohorts. Since time-to-event was a factor a Cox regression model was chosen. The selection process regarding adjustments for potential confounders was made in a stepwise manner, taking consideration of significantly and clinically relevant factors. The results were presented as hazard ratios (HRs) using 95% confidence intervals.

5

RESULTS

A condensed summary of the results from the papers included in this thesis is presented below.

5.1 Paper I

In Paper I we studied the prevalence of, and risk factors and protective factors for, asthma at 12 years of age. We also wanted to analyse these factors for the subgroups of atopic and non-atopic asthma. The reported prevalence of current asthma was 6.4% (233/3637) and out of these asthmatics, 65% were found to have an atopic asthma. Multivariate analyses were performed and are presented in Table 6 where antibiotic treatment during the first week of life was found to be a risk factor for the total asthma group as well as for the children with atopic asthma. In the non-atopic group, no significant association was found. Breastfeeding for at least four months reduced the risk of nonatopic asthma.

We also analysed the asthma triggers the participants reported and exercise was a trigger for the majority of the children with asthma (59%) as well as colds (59%). Pollen was reported to be a trigger in 27%, furry animals in 22% and mites in 10%. Twenty-eight percent of these 12-year-old children had reported an asthma only occurring during colds.

Table 6. Multivariate analysis for factors affecting the risk of current asthma (n = 233), atopic (n = 151) and non-atopic asthma (n = 82) at 12 years of age. Statistically significant adjusted ORs (aORs) are indicated in bold. (from Paper I)

	Asthma	**Asthma atopic**	**Asthma non-atopic**
Factors	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Parental asthma	**2.6 (1.9-3.7)**	**2.5 (1.7-3.6)**	**3.0 (1.7-5.0)**
Parental rhinitis	1.1 (0.8-1.6)	**1.6 (1.1-2.3)**	0.7 (0.4-1.1)
Parental eczema	1.2 (0.9-1.6)	1.0 (0.7-1.4)	**1.7 (1.1-2.8)**
Male gender	1.3 (0.99-1.8)	**1.6 (1.1-2.3)**	0.9 (0.6-1.4)
Gestational age < 37 weeks	1.0 (0.5-1.8)	0.8 (0.4-1.9)	1.3 (0.6-3.2)
Maternal medication	1.2 (0.9-1.6)	1.1 (0.8-1.6)	1.4 (0.9-2.3)
Small for gestational age	**2.6 (1.1-5.9)**	2.3 (0.9-6.3)	**3.8 (1.1-13.7)**
Antibiotics first week	**1.9 (1.1-3.2)**	**2.2 (1.2-4.2)**	1.4 (0.5-3.4)
Doctor-diagnosed food allergy first year	**2.2 (1.3-3.7)**	**3.0 (1.8-5.1)**	0.6 (0.1-2.5)
Eczema during the first year	**2.1 (1.5-2.8)**	**2.7 (1.9-4.0)**	1.1 (0.6-2.0)
Recurrent wheeze first year	**3.3 (2.1-5.0)**	**2.4 (1.4-4.4)**	**5.1 (2.8-9.5)**
Introduction of egg < 9 months of age	0.9 (0.7-1.4)	1.1 (0.7-1.7)	0.8 (0.4-1.5)
Introduction of fish < 9 months of age	0.8 (0.5-1.1)	0.7 (0.4-1.1)	0.9 (0.5-1.8)
Fish at least once a month or more	1.1 (0.6-1.9)	1.0 (0.5-1.9)	1.4 (0.5-3.7)
Damp mould in the home	**0.3 (0.1-0.9)**	0.4 (0.1-1.2)	0.3 (0.03-2.1)
Cat at home during infancy	0.8 (0.6-1.1)	0.9 (0.6-1.3)	0.7 (0.4-1.2)
Breastfeeding at least four months	1.2 (0.8-1.7)	1.1 (0.7-1.9)	**0.5 (0.3-0.95)**
Smoking during pregnancy	0.6 (0.3-1.2)	1.1 (0.5-2.1)	---
Parental educational level	0.9 (0.7-1.2)	0.7 (0.5-1.1)	1.3 (0.8-2.1)

5.2 Paper II

In Paper II, we examined the prevalence of uncontrolled asthma and factors that affected the risk of uncontrolled asthma (ACT < 20). Among the 12-year-old children with asthma in the cohort, 15% (33/215) had uncontrolled asthma. In the multivariate model a higher educational level (>12 years) in at least one of the parents reduced the risk of uncontrolled asthma. On the other hand, asthma symptoms triggered by exercise, having a cat in the home and current doctor-diagnosed rhinitis increased the risk of uncontrolled asthma. The results from the multivariate model are shown in Figure 7.

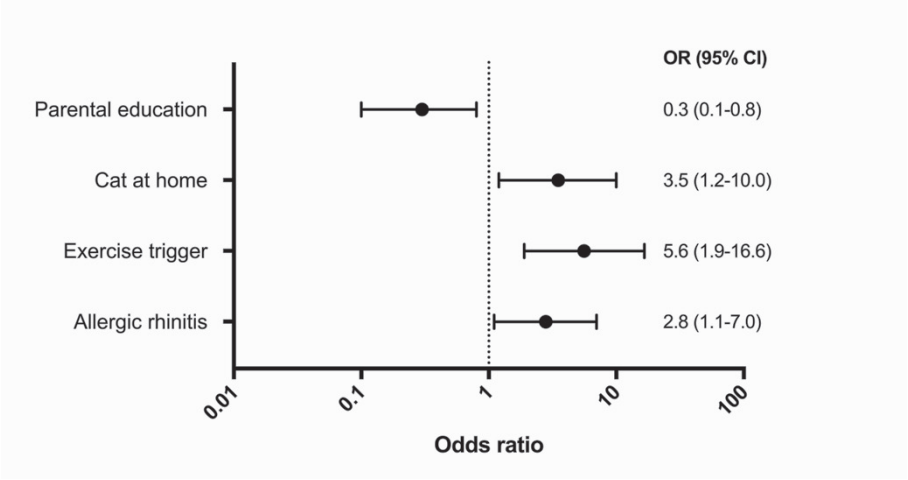

Figure 7. Results from the multivariate analysis. Factors affecting the risk of uncontrolled asthma. (from Paper II)

We wanted to study the children with the heaviest asthma burden and chose to investigate hospitalisation due to asthma. Hospitalisation due to asthma during the last year was reported in only six of the 232 12-year-old children with current asthma. This corresponds to 0.2% out of the total 2003 cohort (6/3,637). Univariate risk factors for hospitalisation were an uncontrolled asthma and having reported mites and pollen as asthma triggers. The hospitalised children reported combination treatment more frequently compared with the asthmatic

children who had not recently been hospitalised due to asthma ($p < 0.05$).

5.3 Paper III

In Paper III we investigated the agreement between questionnaire-based data and data from national Swedish registers regarding dispensed asthma medication, inpatient care and outpatient visits. We also aimed to study the pattern of asthma medication during childhood

The agreement was analysed at 12 years of age and interpreted according to the Landis and Koch criteria. (231) The overall agreement between the SPDR data on any asthma medication as well maintenance treatment and the questionnaire data on asthma medication was substantial (see Table 7). Substantial overall agreement was also shown regarding current asthma from the questionnaire and maintenance treatment from the SPDR.

Table 7. Agreement at 12 years of age between the questionnaire data and the drug register data. (from Paper III)

Questionnaire	Register	Overall agreement	Kappa statistics (95% CI)	Strength of agreement
Any asthma medication	Any asthma medication	94.8%	0.71 (0.67-0.75)	Substantial
Any asthma medication	Maintenance treatment	95.3%	0.68 (0.64-0.72)	Substantial
Current asthma	Maintenance treatment	96.0%	0.68 (0.63-0.73)	Substantial

We compared inpatient care data in the NPR with inpatient care data from the questionnaire. In the questionnaire among the one-year-old children, 661 children were reported with any wheeze, 173 with recurrent wheeze and 69 with doctor-diagnosed asthma. Of the children with reported any wheeze, 12.6% received inpatient treatment due to obstructive disease during the first two years of life according to the NPR. In comparison, 20.8% of the children with recurrent wheeze and 36.2% of the children with doctor-diagnosed asthma were hospitalised due to obstructive disease during the first two years of life according to NPR data (P for trend < 0.01).

When studying outpatient care data, comparing our questionnaire-based data with the NPR, we found that the NPR included outpatient asthma diagnoses for only 30.5% of the study subjects with current asthma in the questionnaire at 12 years of age and 32.8% of the children dispensed with any asthma medication at 11-13 years of age according to the SPDR. The comparison between NPR outpatient care and questionnaire-based data is shown in Figure 8.

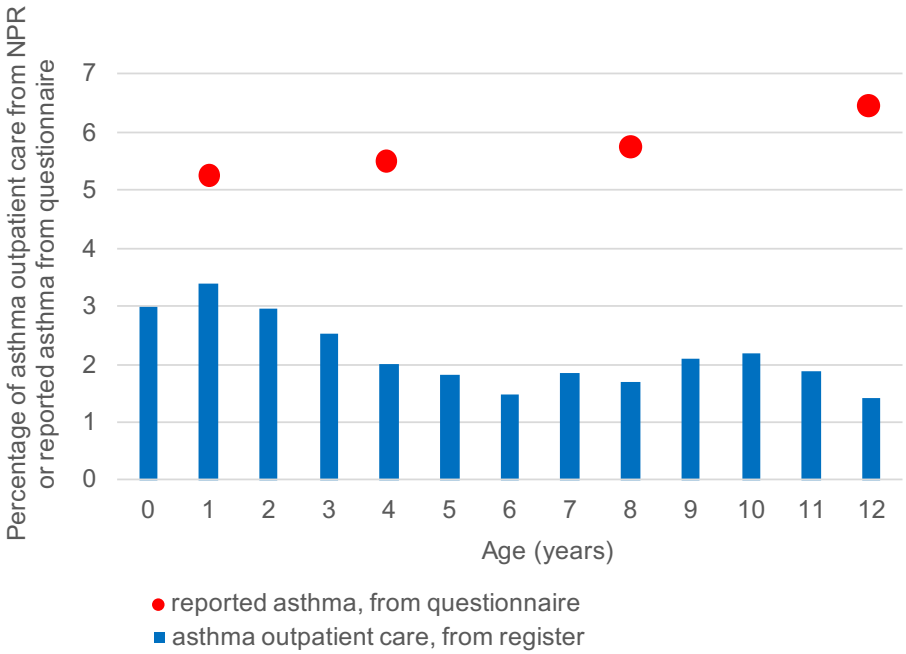

Figure 8. The percentage of children in the NPR who received a diagnosis of asthma for each year from 0 to 12 years of age. The red dots represent the percentage of asthma at one, four, eight and 12 years of age according to questionnaires. (from Paper III)

In Paper III we also studied the changing pattern of asthma medication during childhood (Figure 9). Having SABA as the only dispensed

asthma medication was common among the younger children but less common after a few years of age. However, as the children grew older we noticed an increase regarding SABA as the only dispensed asthma medication and at 11-13 years of age, 38% of the children who were dispensed asthma medication received inhaled SABA as their only asthma medication. Asthma treatment with ICS as the only maintenance asthma treatment remained stable during childhood.

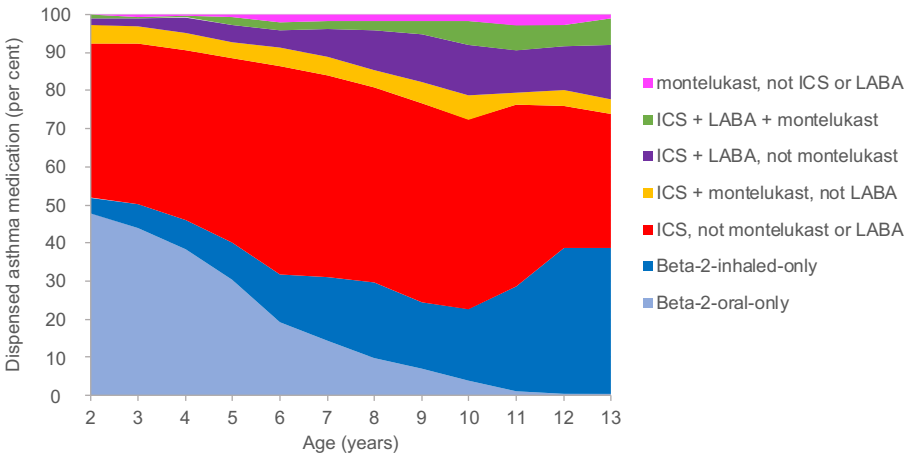

Figure 9. The changing pattern of asthma medication from two to 12 years of age. The figure is based on asthma medication dispensed to the children in the 12-year-old cohort, according to the Swedish Prescribed Drug Register. The total number of children who received medication were: age 2 y, 303; age 3, 403; age 4, 364; age 5, 298; age 6, 243; age 7, 236; age 8, 246; age 9, 229; age 10, 217; age 11, 219; age 12, 223; and age 13, 234. (from Paper III)

5.4 Paper IV

In Paper IV we studied the adherence to current advice regarding the time of introducing new food items. The current advice propose introduction between four and six months of age. We also aimed to investigate whether the timing for introducing complementary foods changed between the two cohorts of children born in 2003 and in 2018.

Eggs

At six months of age, 67.2% (2,446/3,641) of the children born in 2018 were introduced to eggs. Complementary feeding with the introduction of eggs was made significantly earlier for the children in the 2018 cohort compared with the 2003 cohort ($p < 0.001$), even when adjusting for potential confounding factors using a multivariate Cox regression analysis, see Figures 10 and 11.

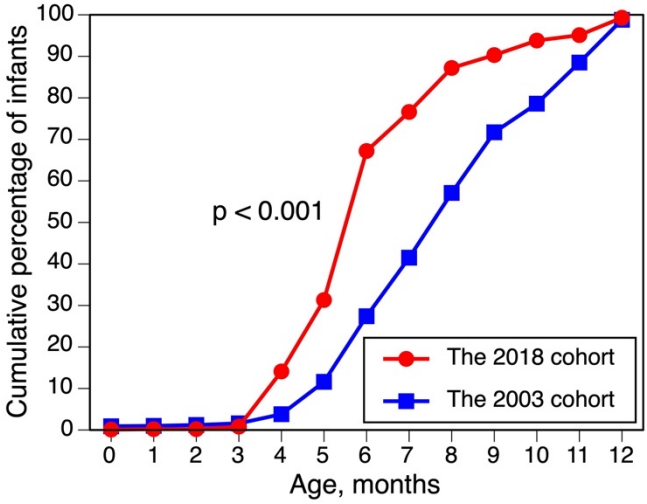

Figure 10. The age, at which the food item of eggs was first introduced to the infant. The p value (from the adjusted Cox regression analysis) refers to the difference in age regarding the introduction of eggs in the two cohorts. (from Paper IV)

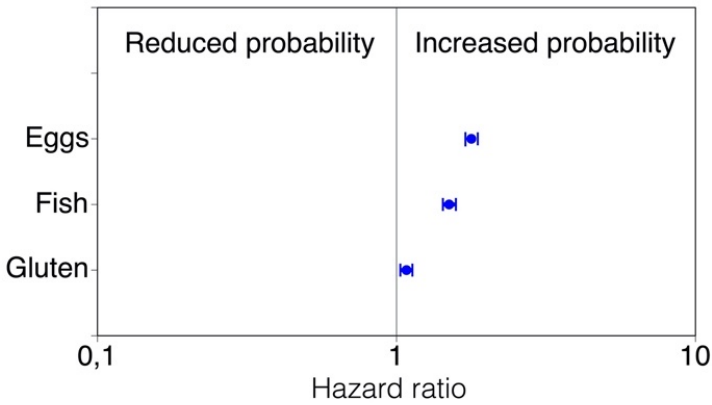

Figure 11. The association between birth year (2003 compared with 2018) and the age of introducing complementary feeding, results shown as hazard ratios. The 2003 cohort was used as the baseline/reference. An increased probability of introducing the specific food item earlier in 2018 is indicated by an HR value above 1 and a reduced probability is indicated by an HR value below 1. (from Paper IV)

Fish

At six months of age, 78.9% (2,909/3,689) of the children born in 2018 were introduced to fish. Complementary feeding with the introduction of fish was made significantly earlier for the children in the 2018 cohort compared with the 2003 cohort ($p < 0.001$), even when adjusting for potential confounding factors using a multivariate Cox regression analysis, see Figures 11 and 12.

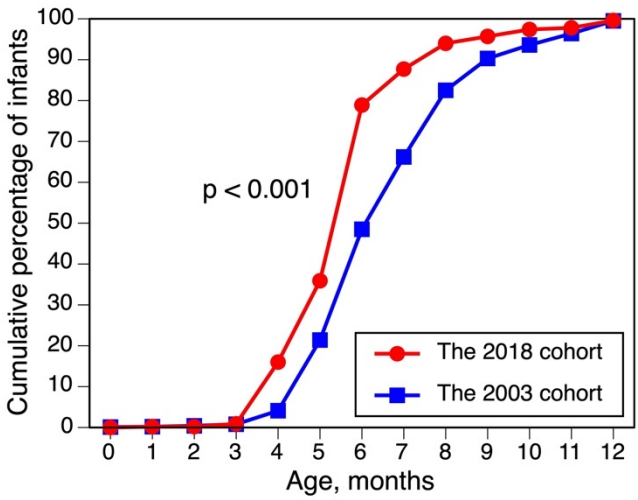

Figure 12. The age, at which the food item fish was first introduced to the infant. The p value (from the adjusted Cox regression analysis) refers to the difference in age regarding the introduction of fish in the two cohorts. (from Paper IV)

Gluten

At six months of age, 89.1% (3,328/3,736) of the children born in 2018 were introduced to gluten. Complementary feeding with the introduction of gluten was made significantly earlier for the children in the 2018 cohort compared with the 2003 cohort ($p < 0.001$), even when adjusting for potential confounding factors using a multivariate Cox regression analysis, see Figures 11 and 13.

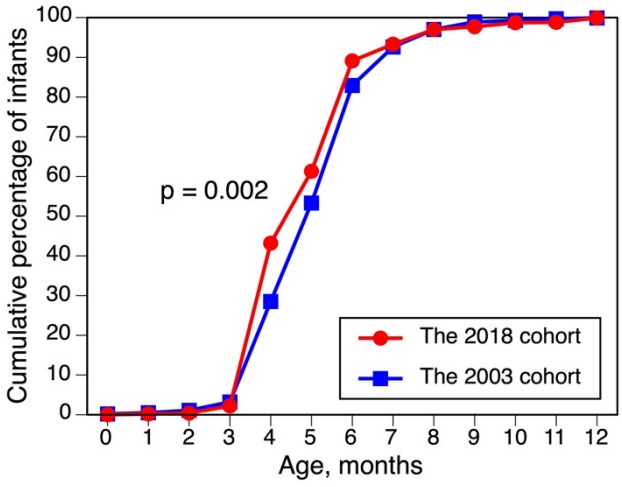

Figure 13. The age, at which the food item of gluten was first introduced to the infant. The p value (from the adjusted Cox regression analysis) refers to the difference in age regarding the introduction of gluten in the two cohorts. (from Paper IV)

6

DISCUSSION

6.1 Methodological considerations

All research is accompanied by the possibility of errors. These potential errors can be random or systematic and it is important to be aware of these potential errors when planning a study or interpreting incoming data.

6.1.1 Errors

Random errors cannot be fully eliminated from a study and the variations in measurements occurs unpredictably/randomly from one participant to another. The results from the measurements cluster around the true value and, in this way, random errors affect precision. One example of a random error could be flaws in the transcription from the questionnaire to the data set. A large number of study participants reduce the effect of random errors.

Systematic errors, sometimes known as biases, are not affected by the size of the study population and can be labelled selection bias, information bias or confounding. Systematic errors are predictable and affect the data in the same direction and not randomly, as is the case for random errors. Accuracy is affected by systematic errors. Selection bias can occur when the research team selects the wrong group, for example only invites people with asthmatic parents to participate in a study, when the aim was a population-based cohort. An information bias (also called measurement bias or mis clarification) can occur when exposure or outcome variables are systematically measured or classified incorrectly. One example could be a question in a questionnaire with the aim of categorising someone as having asthma or not. If the question instead answers whether the children have rhinitis or not an information error has occurred.

A schematic overview is shown in Figure 14.

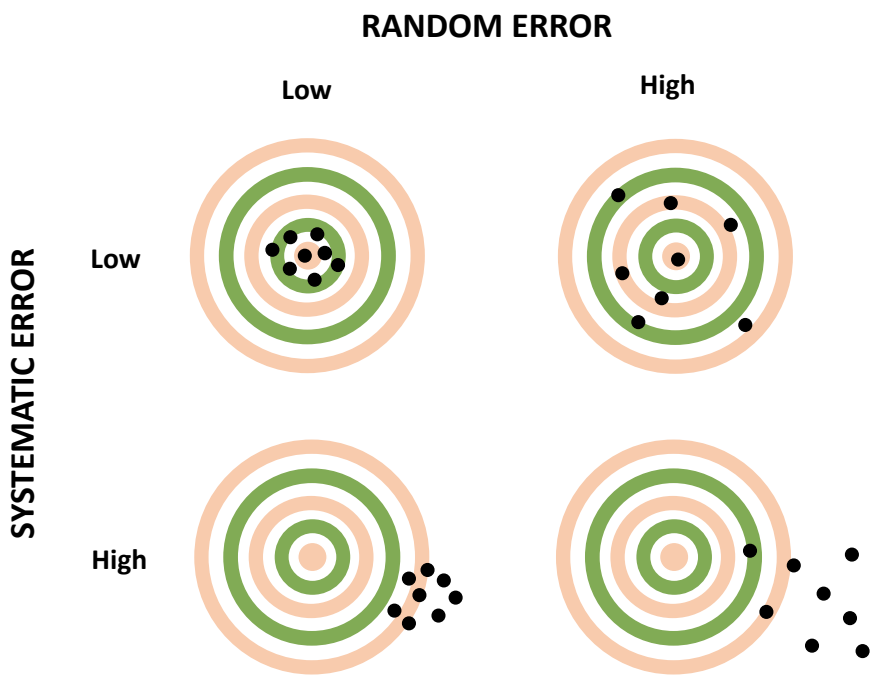

Figure 14. Results due to random and systematic errors

A confounder is a factor that induces bias in a study by affecting both the exposure and the outcome. If a confounder is not adjusted for in the analyses of associated factors, a false association between exposure and outcome can be interpreted as true. A mediator, on the other hand, is the mechanism of the relationship between the independent variable (the exposure) and the dependent variable (the outcome). A mediator is influenced by the exposure and affects the outcome. Knowledge and understanding in your research field is required in order to distinguish a potential confounder from a mediator.

6.1.2 Validity and reliability

Internal validity refers to an expression used to describe whether a study measures what it was meant to measure, the extent to which a causal relationship proposed in a study cannot be explained by systematic errors.

External validity describes the generalisability for a study, if the results from a study can be applied in a broader context. High reliability has high consistency. High reliability in a study is shown if the test repeatedly comes to the same conclusion when performing the same test several times using the same study participants.

6.1.3 Statistical significance

According to the null hypothesis (H_0) there is no significant difference in the exposed group compared with the non-exposed group regarding the risk of a specified outcome event. The alternative hypothesis (H_1) states that there is a significant difference in the exposed group compared with the non-exposed group regarding the risk of the event. A result is called statistically significant when the probability of the received result would be very uncommon if H_0 was accurate. The significance level is defined and chosen before collection of the data and in the field of epidemiology, it is often set at 0.05, resulting in 5% of the analyses where no true effect is present providing a statistically significant result. A false positive finding, falsely rejecting H_0 when H_0 is actually true is called a type-1 error. A false negative finding, not rejecting the H_0 when H_0 is actually false is called a type-II-error. A schematic overview of type-I and type-II errors is shown in Figure 15.

	Decision	
	Not reject H_0	**Reject H_0**
H_0 = true (no difference)	Correct	Type-I error "false positive"
H_0 = false (there is a difference)	Type-II error "false negative"	Correct

Figure 15: Schematic overview of type-I and type-II errors (after inspiration from reference 232).

The power is the probability of rejecting H_0 when H_0 is false, the chance of finding a true effect of the exposure. The strength of the statistical power is affected by sample size, the degree of variability in variables, the frequency of the outcome being studied, the chosen level of significance and the strength of the true effect of an exposure on the outcome. (232)

6.2 Paper-specific discussion

6.2.1 Paper I

The main finding in this paper was that antibiotic treatment during the first week of life was found to be a risk factor for asthma among 12-year-old children. As mentioned earlier, an association between antibiotic treatment during infancy and an increased risk of asthma has been previously shown in other studies. (233,234) However, potential confounders and the risk of reverse causation have indicated difficulties in concluding causal relationships. In this observational study, we are naturally unable fully to determine causality, but the fact that the result of early antibiotic treatment was an independent risk factor for the whole asthma group as well as for the atopic asthmatics but not the non-atopic asthmatics indicates an immune-mediated component. Since we chose to study the exposure to antibiotics during the first week of life we believe that the risk of reverse causation (treatment of early obstructive episodes) and confounding by indication is minimised. The possibility that new-born children in need of neonatal hospital care might be a predisposed group of children that run an increased asthma risk could not be excluded. (235) The proposed mechanism regarding antibiotic and a potential causal relationship with the development of asthma is in line with the hygiene hypothesis discussed above. The disturbing effect on the intestinal flora caused by antibiotic treatment can disrupt the maturation of immunological tolerance for the infant and potentially increase the risk of asthma. (236,237)

Breastfeeding was found to be a risk reducing factor for nonatopic asthma among the 12-year-olds. No effect was seen regarding atopic asthma. In an attempt to further study this association, we analysed whether breastfeeding was associated with asthma in combination with no allergic rhinitis. However, we were unable to find any such association. Our research team found an effect of breastfeeding in the same cohort when the children were 12 months of age (144) but not at four or eight years of age. (145,146) Other studies in the field found a

reduced risk of wheeze due to breastfeeding during infancy and in this young age-group most studies have agreed on the association between breastfeeding and asthma. (238) The suggested mechanism has been a reduction in the risk of infections during the first year of life. (239) Previous studies of the association between breastfeeding and asthma risk during long-term follow ups have presented conflicting results. This might be explained by variations in study design as well as in definitions of exposure and outcome. For example, Paper I shows results relating to the effect of breastfeeding on non-atopic asthma but no effect on atopic asthma. Some studies, instead, observed an association between breastfeeding and atopic asthma, (167) while others did not find any effect of breastfeeding and sensitisation. (240,241)

6.2.2 Paper II

The main results from Paper II showed that a higher parental education level reduced the risk of uncontrolled asthma. On the other hand, children who did not have any parent with a higher educational level ran an increased risk of uncontrolled asthma. Previous studies have published the results relating to socioeconomic factors negatively affecting the level of asthma control and asthma severity. (242,243) The rationale for this association is not yet fully understood but obesity and unhealthy eating habits, for example, are associated with lower socioeconomic status. It can also be argued that highly educated parents are better prepared to ingest and interpret information regarding the asthma disease and the medical therapy. Assessing asthma control should, according to both national and international guidelines, (11,41) be a prioritised part of clinical asthma care. Our result regarding parental educational level therefore opens the door to discussion. Some families perhaps require an extra focus from healthcare providers with the goal of achieving equivalent health for asthmatic children.

6.2.3 Paper III

This study found a good agreement between the questionnaire-based data and data obtained regarding asthma medication from the SPDR. In contrast, the NPR, was incomplete regarding asthma diagnoses.

Epidemiological studies of asthma are commonly observational and questionnaires are often used, as they allow large samples and are often time-efficient and less expensive compared with clinical data collections or experimental designs. The validity of observational, questionnaire-

based studies has been questioned. (244,245) The good agreement between the data from questionnaires and data obtained from the SPDR indicates that solid parental questionnaires can provide reliable data on childhood asthma.
On the other hand, regarding asthma, outpatient data from the NPR, did not correspond with the data from the SPDR or from the questionnaires. Registers are able to provide very valuable information but it is important to analyse their content and then draw conclusions on how to use register-based data. The NPR does not include data from primary care and the asthmatic children who received their asthma care in primary care were therefore missing.
When studying the pattern of asthma medication during childhood we found that surprisingly many, 38%, of the children aged 11-13 years received inhaled SABA as their only asthma treatment. New treatment recommendations are soon to be introduced in Sweden, as mentioned above. SABA as a single treatment will be removed as a treatment option for asthmatic children in this age group. The pattern regarding asthma treatment during childhood is therefore likely and hopefully about to change in the near future.

6.2.4 Paper IV

The main findings in this paper were that complementary feeding with eggs, fish and gluten was introduced at an earlier age in children born in 2018 compared with 2003. We also found that current recommendations from child welfare centres regarding the early introduction of complementary foods appear to be followed.
Advice regarding the time of introducing complementary feeding has undergone major changes. Before 2002, the national Swedish recommendations were to avoid peanuts during the first year in life and that egg and fish introduction was recommended after the age of 12 months among children with a high risk of allergy. Studies showed a reduced risk of allergic disease and asthma with an earlier introduction (175-183) and the suggested mechanism behind the association is oral tolerance. As a result of these presented data, the recommendations changed and the current Swedish advice recommends the introduction of complementary feeding between four and six months of age. The results from Paper IV appear to reflect the fact that parents have accepted and now follow the recommendations.

6.3 Strengths and limitations

The opportunity to adjust for many relevant potential confounders is a major strength in all four papers included in this thesis. This was made possible by collecting the potential confounders in questionnaires as well as by linking the questionnaire-based data to registers. The prospective design reduces the risk of recall bias. We have large cohort sizes in both study cohorts, almost 5,000 children born in 2003 and almost 4,000 children born in 2018. In the 2003 cohort we have a high response rate.

In the 2018 cohort we have a lower response rate compared with the 2003 cohort which presents an opportunity for selection bias affecting both results from the 2018 cohort, as well as bias when comparing the two cohorts. For example, we have a higher proportion of parents who reported a high level of education in 2018 compared with 2003.

We have not clinically tested our cohorts, which can represent a limitation. Clinical examinations could have given the studies higher internal validity regarding the outcome of asthma, for example. Limitations such as the risk of affected validity caused by selection bias or information bias are possible. To minimise these limitations, we used validated questions and a prospective design. Another limitation is that, even though we have adjusted for potential confounders, we are unable to rule out the possibility of missing relevant confounders.

7

CONCLUSIONS

→ Treatment with antibiotics during the first week of life increased the risk of atopic asthma among 12-year-old children, suggesting an immune-mediated effect. As many as a quarter of the 12-year-old children with asthma only reported symptoms during episodes of colds. **(Paper I)**

→ Fifteen percent of the 12-year-old children with asthma had an uncontrolled asthma. A higher parental educational level was associated with better asthma control in the children. Three percent of the asthmatics were hospitalised due to asthma during the last year. Having uncontrolled asthma and having reported mites and pollen as asthma triggers increase the risk of hospitalisation. **(Paper II)**

→ Good agreement was found between questionnaire data and data from the Swedish Prescribed Drug Register (SPDR), indicating that well-constructed parental questionnaires on asthma provide reliable results and can also be used in the future for asthma epidemiology research. The national outpatient register (NPR), on the other hand, was incomplete, probably because the data on children treated in primary care were not included the register. Thirty-eight percent of the 12-year-olds only received SABA, with no maintenance treatment. **(Paper III)**

→ Complementary feeding with eggs, fish and gluten was introduced at an earlier age in children born in 2018 compared with 2003. The current recommendations regarding the introduction of complementary feeding from child welfare centers appear to be followed. This could possibly reduce the risk of allergic disease development. **(Paper IV)**

8

FUTURE WORK

The papers in this thesis have resulted in updated data on asthma epidemiology and, as people's lifestyles are most likely to change also during time ahead the research field needs to pay attention to these changes and investigate their possible impact on childhood asthma.
In the near future I hope to have the opportunity to study the development of asthma prevalence and factors affecting the risk of asthma over time. This is now made possible due to the 2003 cohort and the 2018 cohort.
Hopefully, we will be able thoroughly to study the association between early antibiotic treatment and asthma by using data from the children in the 2018 cohort; by combining questionnaire-based data, register based data, medical records and clinical data.
The Swedish treatment recommendations will soon be altered and it would be interesting to study school-aged children in terms of asthma medication, exacerbations and asthma control and compare eventual differences before and after the changes in recommendations.

9

ACKNOWLEDGEMENTS

Utan alla barn och föräldrar som deltagit i studierna hade detta doktorandprojekt aldrig varit möjligt och var och en av er om deltog har bidragit till att vi kom närmre det där som vi brukar kalla sanningen. Mitt första stora tack går till er.

Mina båda huvudhandledare **Emma Goksör** och **Göran Wennergren**. Tack för att ni tog mig med på turen. Emma, ditt forskningsintresse är smittande. Din klarsynthet och problemlösningsförmåga har besparat mig mycket tid och frustration under denna doktorandresa och jag är tacksam för guidningen genom många statistiska snårigheter. Jag är glad för att du trodde på mig när jag var alldeles ny i forskningen och vågade ge mig utmaningar och ansvar. Allra gladast är jag nog för vänskapen och klokheten – att jag kan ringa dig också när livet bjuder på motgång. Göran. Dina nivåer av arbetskapacitet, medicinsk kunskap, vänlighet, entusiasm, tålamod och tillgänglighet ryms sällan i en och samma person. Jag tycker det är lika inspirerande som imponerande att du har kunnat bibehålla detta genom din långa och framgångsrika karriär. Jag är så tacksam att du alltid tagit dig tid att svara på mina frågor och komma med råd kring hur jag ska komma vidare. Efter några första mer handfasta tips har du ofta avslutat med ett för mig revolutionerande råd ”Börja med den del som är roligast!”

Min bihandledare **Bernt Alm** och forskarkollegorna **Styliana Vasileiadou, Per Möllborg, Nils Åberg, Rolf Pettersson** och **Laslo Erdes**. Ni bjuder alltid på er själva och er kunskap. Ni fick mig att känna mig välkomnad och inkluderad i gruppen från allra första gången vi sågs på forskningsdag på Jonsereds Herrgård.

Mina chefer under doktorandtiden. **Jessica Sommerfors Holm, Helena Collin Alberts, Åsa Ståleby** och **Erica Alinder**. Tack för supporten och acceptansen när jag försvunnit iväg i forskning.

Kompisar. Jag är glad för er och för att ni är alldeles lagom ointresserade av min forskning och istället bryr er om resten av mig.

Mina brorsor. **Jacob** och **Victor.** För att ni är de enda som vågar ge mig de lite mer hårda sanningarna om mig själv. Och för att vi har varann.

Mamma och **Pappa.** För att ni gav oss syskon en så trygg uppväxt. Det finns inget jag hade bytt ut den emot. Tack för omtanken, intresset, stödet och närvaron ni gett och ger men tack också för att ni uppmuntrade mig att ge mig iväg från radhuset på Tre vänners väg för att utforska min väg på egen hand.

Jon, Arvid och **Ingrid**. Jag är lyckligt lottad som fick bli er mamma och det är fantastiskt att få följa er. Jag hade trott att man som förälder skulle visa er vad livet var men det visade sig att det också var tvärtom.

Min man. **Jimmy**. Tack för att du alltid tror att jag ska klara saker. Tack för tålamodet och feedbacken. Tänk att vi blev såna som ibland pratar vetenskap med varann i soffan! Jag är så glad för din grundmurade kärlek och stolthet för våra barn och vår familj.

10

REFERENCES

1. Lodrup Carlsen KC, Haland G, Devulapalli CS, Munthe- Kass M, Pettersen M, Granum B, Lovik M, et al. Asthma in every fifth child in Oslo, Norway: a ten-year follow up of a birth cohort study. Allergy. 2006;61:454-460

2. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 2007;62:758-66.

3. McNeill G, Tagiyeva N, Aucott L, Rsuuell G, Helmes PJ. Changes in the prevalence of asthma, eczema and hay fever in pre-pubertal children: a 40-year perspective. Paediatr Perinatal Epidemiol. 2009;23:506-512.

4. Lai CKW, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. International Study of A, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 2009;64:476-83.

5. Ballardini N, Kull I, Lind E, Hallner E, Almqvist C, Melen E, et al. Development and comorbidity of eczema, asthma and rhinitis to age 12 – data from the BAMSE birth cohort. Allergy. 2012;67(4):537-44

6. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health 2012;12:204.

7. Mallol J, Aguirre V, Mallol-Simmonds M, Matamala-Bezmalinovic A, Calderon- Rodriguez L, Osses-Vergara F. Changes in the prevalence of asthma and related risk factors in adolescents: Three surveys between 1994 and 2015. Allergol Immunopathol (Madr) 2019;47:313–321.

8. Asher MI, Garcia-Marcos L, Pearce NE, Strachan DP. Trends in worldwide asthma prevalence. Eur Respir J. 2020;56(6)

9. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1736-88.

10. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 2017;5:691-706.

11. Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2022. [cited 2023 Jan 14. Available at: https://ginasthma.org/.

12. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59:469-78.

13. James W Mims; Asthma: definitions and pathophysiology. Int Forum Allergy Rhinol.2015;5 (1) 2-6.

14. Nelson textbook of pediatrics R Kliegman, R Behrman, H Jenson, B Stanton, 18th edition

15. Gans M, Gavrilova T. Understandimg the immunology of asthma: Pathophysiology, biomarkers and treatment for asthma endotypes. Pediatr Respir Rev 2020;36:118-127

16. Hough K, Curtiss M, Blain T, Liu R, Trevor J, Deshane J, et al. Airway remodeling in asthma. Front Med 2020;21(7):191 doi 10.3389

17. Papi A, Brightling C, Pedersen S. Asthma Lancet 2018; 391(10122): 783-800.

18. Hoch H, Houin P, Stillwell P. Asthma in children: A Brief Review for Primary Care Providers Pediatrics 2019;48(3):103-109.

19. Moral L, Vizmanos G, Torres-Borrego J, Praena-Crespo M, Totajada-Girbes M, Pellegrini F, et al. Asthma diagnosis in infants and preschool children: a systematic review of clinical guidelines. Allergol Immunopathol 2019;47(2):107-121.

20. Svenska Barnläkarföreningens delförening för allergi och lungmedicin, Astmaterminologi och definitioner, 2020

21. Gaillard E, Kuehni C, Turner S, Goutaki M, Holden K, de Jong C, et al. European Respiratory Society clinical practice guidelines for the

diagnosis of asthma in children aged 5-16 years. Eur Respir J.2021; 58(5)2004173

22. Moral L, Vizmanos G, Torres-Borrego J, Praena-Crespo M, Totajada-Girbes M, Pellegrini F, et al. Asthma diagnosis in infants and preschool children: a systemtic review of clinical guidelines. Allergol Immunopathol 2019; 47(2):107-121.

23. Conrad L, Cabana M, Rastogi D. Defining pediatric asthma: phenotypes to endotypes and beyond Pediatric Research 2021; 90;45-51.

24. Schultz A, Brand P. Episodic viral wheeze and multiple trigger wheeze in preschool children: a useful distinction for clinicians? Paediatr Respir Rev 2011;12(3):160-4.

25. ICD-10-SE

26. ICD-10-CM

27. A Wright. Epidemiology of asthma and recurrent wheeze in childhood Clin Rev Allergy Immunol 2002;22(1):33-44.

28. Martinez FD, Wright A, Taussig L, Holberg C, Halonen M, Morgan W. Asthma wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332(3):133-8.

29. Nissen SP, Kjaer HF, Host A, Nielsen J, Halken S. The natural course of sensitization and allergic diseases from childhood to adulthood. Pediatr Allergy Immunol 2013:24:549– 55.

30. Akar_Ghibril N, Casale T, Custovic A, Phipatanakul W. Allergic Endotypes and Phenotypes of Asthma J Allergy Clin Immunol Pract 2020;8(2):429-440

31. Masters IB, Chang AB, Patterson L, Wainwright C, Buntain H, Dean BW, et al. Series of laryngomalacia, tracheomalacia and bronchomalacia disorders and their associations with other conditions in chidren Pediatr Pulmoniol 2002;34(3)189-95.

32. Eigen H. Differential diagnosis and treatment of wheezing and asthma in young children.Clin Pediatr 2008;47(8):735-43.

33. Farrell P, Rosenstein B, White T, Accurso F, Castellani C, Cutting G, et al. Guidelines for Diagnosis of Cystic Fibrosis in Newborns

through Older Adults: Cystic Fibrosis Foundation Consensus Report. J Pediatr 2008; 153(2):4-14.

34. Grover S, Bansal A, Singhi S. Airway foreign body aspiration Indian J Pediatr 2011;78(11):1401-3.

35. Backer C, Mongé M, Popescu A, Lltayeb O, Rastatter J, Rigsby C Vascular rings Semin Pediatr Surg 2016: 25(3):165-75.

36. Principi N, Di Pietro G, Esposito S. Bronchopulmonary dysplasia: clinical aspects and preventive and therapeutic strategies. J Transl Med 2018;16(1):36.

37. Lee S. Basic Knowledge of Tracheoesophageal Fistula and Esophageal Atresia. Adv Neonatal Care 2018;18(1):14-21.

38. Poddar U. Gastroesophageal reflux disease (GERD) in children. Paediatr Int Child Health 2019 39(1):7-12.

39. Malaty J, Wu V. Vocal Cord Dysfunction: Rapid Evidence Review. Am Fam Physician 2021;104(5):471-475.

40. Singh Y, Lakshminrusimha S. Perinatal Cardiovascular Physiology and Recognition of Critical Congenital Heart Defects. Clin Perinatol 2021;48(3): 573-594

41. Swedish Board of Health and Welfare [Socialstyrelsen]. National guidelines for treatment of asthma and COPD [Nationella riktlinjer för vård vid astma och KOL]. Stockholm: Swedish Board of Health and Welfare 2020. [Cited 2023, January 14]. Available at: http://www.socialstyrelsen.se/nationellariktlinjerastmaochkol.

42. Läkemedelsbehandling vid astma – Behandlingsrekommendation. Information från Läkemedelsverket. 2015.

43. Svenska Barnläkarföreningens delförening för allergi och lungmedicin, Underhållsbehandling av astma, 2018.

44. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li J, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol 2004;113:59-65.

45. Szefler S. Advances in pediatric asthma in 2009: Gaing control of childhood asthma. J Allergy Clin Immunol 2010;125(1):69-78

46. ACT GSK

47. BLF Svenska Barnläkarföreningens delförening för allergi och lungmedicin, Klassificering av astmasvårighetsgrad med hänsyn till medicinering och symptom hos barn över 4 års ålder, rev 2017

48. Kumar V, Aster JC. Robbins basic pathology, Tenth edition. 10th edition ed; 2018.

49. Xu CJ, Söderhäll C, Bustamante M, Baïz N, Gruzieva O, Gehring U, et al. DNA methylation in childhood asthma: an epigenome-wide meta-analysis. Lancet Respir Med. 2018;6(5):379-388.

50. Zhang L, Lu Q, Chang C. Epigenetics in Health and Disease. Adv Exp Med Biol. 2020;1253:3-55.

51. Richards EJ. Inherited epigenetic variation – revisiting soft inheritance. Nat Rev Genet 2006;7(5):395-401.

52. Gruzieva O, Merid SK, Melén E. An update on epigenetics and childhood respiratory diseases. Paediatr Respir Rev. 2014;15(4):348-54.

53. S.H. Arshad, R.J. Kurukulaaratchy, M. Fenn, S. Matthews. Early life risk factors for current wheeze, asthma and bronchial hyper-responsiveness at 10-years of age**.** Chest. 2005;127:502-508.

54. Arshad S, Karmaus W, Raza A, Kurukulaaratchy DM, Matthews S, Holloway J, Sadeghnejad et al. The effect of parental allergy on childhood allergic diseases depends on the sex of the child. J Allergy Clin Immunol. 2012;130(2):427-434.

55. Ferreira MA, Vonk JM, Baurecht H, Marenholz I, Tian C, Hoffman JD. Shared genetic origin of asthma, hay fever and eczema elucidate allergic disease biology. Nat Genet. 2017;49(12):1752-1757.

56. Thomsen SF, van der Sluis S, Kyvik KO, Skytthe A, Backer V. Estimates of asthma heritability in a large twin sample. Clin Exp Allergy. 2010;40:1054–61.

57. Thomsen S. Genetics of asthma: an introduction for the clinician. Eur Clin Respir J. 2015; 2(1).

58. Levin AM, Mathias RA, Huang L, Roth LA, Daley D, Myers RA, et al. A meta-analysis of genome-wide association studies for serum total

IgE in diverse study populations. J Allergy Clin Immunol 2013;131:1176-84.

59. Ober C, Yao T-C. The genetics of asthma and allergic disease: a 21st century perspective. Immunol Rev 2011;242:10-30.

60. Brooks C, Pearce N, Douwes J. The hygiene hypothesis in allergy and asthma: an update. Curr Opin Allergy Clin Immunol 2013;13:70-7.

61. Daley D, Park JE, He JQ, Yan J, Akhabir L, Stefanowicz D, et al. Associations and interaction of genetic polymorphisms in innate immunity gebes with early viral infections and susceptibility to asthma and asthma-related phenotypes. J Allergy Clin Immunol. 2012;130(6):1284-93

62. S.H. Arshad, R.J. Kurukulaaratchy, M. Fenn, S. Matthews. Early life risk factors for current wheeze, asthma and bronchial hyper-responsiveness at 10-years of age**.** Chest. 2005;127:502-508.

63. Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, et al. Rhinitis and onset of asthma: a longitudinal population-based study. Lancet 2008;372:1049-57.

64. Rochat MK, Illi S, Ege MJ, Lau S, Keil T, Wahn U, et al. Allergic rhinitis as a predictor for wheezing onset in school-aged children. J Allergy Clin Immunol 2010;126:1170-5.

65. Kobyletzki L, Bornehag C, Hasselgren M, Larsson M, Boman Lindström C, Svensson Å. Eczema in early childhood is strongly associated with the development of asthma and rhinitis in a prospective cohort. BMC Dermatology. 2012;12(1):11-16.

66. Pinart M, Benet M, Annesi-Maesano I, von Berg I, Berdel D, Carlsen K et al. Comorbidity of eczema, rhinitis and asthma in IgE-sensitised and non-IgE-sensitised children in MeDall: a population based cohort study. Lancet Respir Med; 2014;2(2):131-40.

67. L. Schneider, J. Hanifin, M. Boguniewicz, L.F. Eichenfield, J.M. Spergel, R. Dakovic, et al. Study of the atopic march: development of atopic comorbidities Pediatr Dermatol 2016;33:388-398.

68. Spergel JM. From atopic dermatitis to asthma: the atopic march. Ann Allergy Astma Immunol 2010;105:99-106. Review.

69. Zheng T, Yu J, Oh M, Zhu Z. The Atopic March: Progression from Atopic Dermatitis to Allergic Rhintis and Asthma. Allergy Asthma Immunol Res. 2011; 3(2):67-73.

70. Goksör E, Loid P, Alm B, Åberg N, Wennergren G. The allergic march comprises the coexistence of related patterns of allergic disease not just the progressive development of one disease. Acta Paediatr. 2016 Dec;105(12):1472-1479.

71. Pinart M, Benet M, Annesi-Maesano I, von Berg !, Berdel D, Carlsen K et al. Comorbidity of eczema, rhinitis and asthma in IgE-sensitised and non-IgE-sensitised children in MeDall: a population based cohort study. Lancet Respir Med; 2014;2(2):131-40.

72. D.C. Belgrave, R. Granell, A. Simpson, J. Guiver, C. Bishop, I. Buchan, et al. Developmental profiles of eczema, wheeze, and rhinitis: two population-based birth cohort studies. PLoS Med, 11 (2014) p. e1001748

73. Paller A, Spergel J, Mina-Osorio P, Irvine A. The atopic march and atopic multimorbidity: Many trajectories, many pathways. J All Clin Immunol. 2019; 143(1):46-55.

74. A.S. Paller, H.H. Kong, P. Seed, S. Naik, T.C. Scharschmidt, R.L. Gallo, et al. The microbiome in atopic dermatitis**.** J Allergy Clin Immunol. 2019;143 (1)26-35

75. Horwood LJ, Fergusson DM, Shannon FT. Social and familial factors in the development of early childhood asthma . Pediatrics 1985;(75):859-68.

76. Chowdhury N, Guntur V, Newcomb D, Wechsler M. Sex and gender in asthma. Eur Respir Rev. 2021;30(162):doi:10.1183/16000617.0067-2021.

77. Goksör E, Amark M, Alm B, Gustafsson PM, Wennergren G.. Asthma symptoms in early childhood--what happens then? Acta Paediatr. 2006;95(4):471-8

78. Schatz M, Camargo CA Jr. The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. Ann Allergy Asthma Immunol 2003;91:553–558.

79. Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN et al. Characterization of severe asthma worldwide: data from the international severe asthma registry. Chest 2020; 157: 790–804.

80. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 1995;332:133-8.

81. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948-68.

82. Farha S, Asosingh K, Laskowski D, Hammel J, Dweik RA, Wiedemann HP et al. Effects of the menstrual cycle on lung function variables in women with asthma. Am J Respir Crit Care Med 2009; 180: 304–310.

83. de Oliveira AP, Peron JP, Damazo AS, Franco AL, Domingos HV, Oliani SM, et al. Respir Res. 2010;11(1):115. Female sex hormones mediate the allergic lung reaction by regulating the release of inflammatory mediators and the expression of lung E-selectin in rats. Respir Res. 2010; 24;11(1):115

84. Zhang GQ, Özuygur Ermis SS, Rådinger M, Bossios A, Kankaanranta H, Nwaru B. Sex Disparities in Asthma Development and Clinical Outcomes: Implications for Treatment Strategies. J Asthma Allergy. 2022;18;15:231-247.

85. Moscato G, Apfelbacher C, Brockow K, Eberle C, Genuneit J, Mortz C, et al. Gender and occupational allergy: report from the task force of the EAACI Environmental and Occupational Allergy Interest Group. Allergy 2020; 75: 2753–2763.

86. Loisel DA, Tan Z, Tisler CJ, Gangnon RE, Jackson DJ, Gern JE et al. IFN-G genotype and sex interact to influence the risk of childhood asthma. J Allergy Clin Immunol 2011;128:524–531.

87. Myers RA, Scott NM, Gauderman WJ, Qiu W, Mathias RA, Romieu I, et al. Genome-wide interaction studies reveal sex-specific asthma risk alleles. Hum Mol Genet 2014;23:5251–5259.

88. Tedner SG, Örtqvist AK, Almqvist C. Fetal growth and risk of childhood asthma and allergic disease. Clin Exp Allergy 2012;42:1430–47.

89. den Dekker HT, Sonnenschein-van der Voort AMM, de Jongste JC, Anessi-Maesano I, Arshad SH, Barros H, et al. Early growth characteristics and the risk of reduced lung function and asthma: A meta-analysis of 25,000 children. J Allergy Clin Immunol 2016;137:1026-35.

90. Schultz ES, Hallberg J, N Andersson, Thacher JD, Pershagen G, Bellander T, et al. Early life determinants of lung function change from childhood to adolescence. England: Elsevier Ltd Respiratory medicine, 2018;139:48-54.

91. Canoy D, Pekkanen J, Elliott P, Pouta A, Laitinen J, Hartikainen AL, et al. Early growth and adult respiratory function in men and women followed from the fetal period to adulthood. Thorax 2007;62:396-402.

92. Loid P, Goksör E, Alm B, Pettersson R, Möllborg P, Erdes L, et al. A persistently high body mass index increases the risk of atopic asthma at school age. Acta Paediatr. 2015;104(7):707-12.

93. Deng X, Ma J, Yuan Y, Zhang Z, Niu W. Association between overweight or obesity and the risk for childhood asthma andwheeze: An updated meta-analysis on 18 articles and 73 252 children. Pediatr Obes 2019; 14: e12532.

94. Marsland BJ, Gollwitzer ES. Host-microorganism interactions in lung diseases. Nat Rev Immunol 2014;14:827-835.

95. Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger NC. Ngom-Bru, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis Nat Med 2014;20:159-166.

96. Thorburn AN, McKenzie CI, Shen S, Stanley DL, Mason M, et al. Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. Nat Commun, 2015;6:7320-7320.

97. Peters U, Dixon A, Forno E. Obesity and asthma. J Allergy Clin Immunol. 2018;141(4):1169-1179.

98. Forno E, Young OM, Kumar R, Simhan HS, Celedón, JC. Maternal obesity in pregnancy, gestational weight gain, and risk of childhood asthma. Pediatrics 2014;134: e535-546.

99. Lodrup Carlsen KC, Carlsen KH, Nafstad P, Bakketeig L. Perinatal risk factors for recurrent wheeze in early life. Pediatr Allergy Immunol. 1999 May;10(2):89-95.

100. Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics 2012;129:735-44.

101. Wongtrakool C, Wang N, Hyde DM, Roman J, Spindel E. Prenatal nicotine exposure alters lung function and airway geometry through 7 nicotinic receptors. American Journal of Respiratory Cell & Molecular Biology 2012;46:695-702.

102. McEvoy C, Spindel E. Pulmonary effects on the fetus and child: Effects on lung development, respiratory morbidities, and long life lung health. Paediatr Respir Rev. 2017;21:27-33

103. Kulig M, Luck W, Lau S, Niggemann B, Bergmann R, Klettke U, et al. Effect of pre- and postnatal tobacco smoke exposure on specific sensitization to food and inhalant allergens during the first 3 years of life. Multicenter Allergy Study Group, Germany. Allergy. 1999;54(3):220-8

104. Murray CS, Woodcock A, Smillie FI, Cain G, Kissen P, Custovic A. Tobacco smoke exposure, wheeze, and atopy. Pediatric pulmonology. 2004;37(6):492-8.

105. Arshad SH, Kurukulaaratchy RJ, Fenn M, Matthews S. Early life risk factors for current wheeze, asthma, and bronchial hyperresponsiveness at 10 years of age. Chest. 2005 Feb;127(2):502-8

106. Lannero E, Wickman M, van Hage M, Bergstrom A, Pershagen G, Nordvall L. Exposure to environmental tobacco smoke and sensitisation in children. Thorax. 2008 Feb;63(2):172-6.

107. Joubert BR, Håberg S, Nilsen RM, Wang, X, Vollset S, Murphy S. 450K epigenome-wide scan identifies differential DNA methylation in

newborns related to maternal smoking during pregnancy. Environ Health Perspect. 2012 Oct;120(10):1425-31

108. Magnus M. Grandmother's smoking when pregnant with the mother and asthma in the grandchild: the Norwegian Mother and Child Cohort Study. Thorax. 2015 Mar;70(3):237-43.

109. Schultz ES, Gruzieva O, Bellander T, Bottai M, Hallberg J, Kull I, et al. Traffic-related air pollution and lung function in children at 8 years of age: a birth cohort study. American journal of respiratory and critical care medicine 2012;186(12):1286-1291.

110. Gehring U, Wijga AH, Hoek G, Bellander T, Berdel D, Brüske I. Exposure to air pollution and development of asthma and rhinoconjunctivitis throughout childhood and adolescence: a population-based birth cohort study. Lancet Respir Med. 2015;3(12):933-42.

111. Bowatte G, Lodge C, Lowe AJ, Erbas B, Perret J, Abramson MJ. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. Allergy 2015; 70: 245-256.

112. Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Niuwenhuijsen M. Exposure to traffic-related air pollution and risk of development of childhood asthma: A systematic review and meta-analysis. Environ Int 2017; 100: 1-31.

113. Wong GW, Lai CK. Outdoor air pollution and asthma. Curr Opin Pulm Med 2004;10:62-6.

114. Zheng XY, Ding H, Jiang LN, Chen SW, Zheng JP, Qiu M, Zhou YX, et al. Association between air pollutants and asthma emergency room visits and hospital admissions in time series studies: A systematic review and meta-analysis. PLoS One 2015;10:e0138146.

115. Lim H, Kwon HJ, Lim JA, Choi JH, Ha M, Hwang SS, et al. Short-term Effect of Fine Particulate Matter on Children's Hospital Admissions and Emergency Department Visits for Asthma: A Systematic Review and Meta-analysis. J Prev Med Public Health 2016;49:205-19

116. Achakulwisut P, Brauer M, Hystad P, Anenberg S. Global, national, and urban burdens of paediatric asthma incidence attributable

to ambient NO2 pollution: estimates from global datasets. Lancet Planet Health 2019; 3: e166-e178.

117. Hehua Z, Qing C, Shanyan G, Qijun W, Zohong Z. The impact of prenatal exposure to air pollution on childhood wheezing and asthma: A systematic review. Environ Res 2017;159:519-530.

118. Potaczek P, Harb H, Michel S, Alhamwe BA, Renz H, Tost J. Epigenetics and allergy: from basic mechanisms to clinical applications. Epigenomics 2017;9(4):539-572.

119. Breysse PN, Diette GB, Matsui EC, Butz AM, Hansel NN, McCormack MC. Indoor air pollution and asthma in children. Proc Am Thorac Soc 2010;7:102

120. Tischer CG, Hohmann C, Thiering E, Herbarth O, Muller A, Henderson J, et al. Meta-analysis of mould and dampness on asthma and allergy in eight European birth cohorts: an ENRIECO initiative. Allergy. 2011;66(12):1570-9.

121. Quansah R, Jaakkola MS, Hugg T, Heikkinen S, Jaakkola J, et al. Residential dampness and molds and the risk of developing asthma: a systematic review and meta-analysis. PLoS One. 2012;7(11): e47526.

122. Norbäck D, Zock JP, Plana E, Heinrich J, Svanes C, Sunyer J, et al. Mould and dampness in welling places, and onset of asthma: the population-based cohort ECRHS. Occup Environ Med. 2013;70(5):325-31.

123. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989 Nov18;299(6710):1259-60.

124. Haahtela T, Holgate S, Pawankar R, Akdi C, Benjaponpitak S, Caraballo L, et al. The biodiversity hypothesis and allergic disease: world allergy organization position statement. World Allergy Organization Journal 2013; 6: 3.

125. Riedler J, Braun-Fahrlander C, Eder W, Schreuer M, Waser M, Maisch S. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. Lancet 2001; 358: 1129-1133.

126. Braun-Fahrlander C, Riedler J, Herz U, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. New England Journal of Medicine 2002; 347: 869-877.

127. Eriksson J, Ekerljung L, Lötvall J, Pullerits T, Wennergren G, Rönmark E, et al. Growing up on a farm leads to lifelong protection against allergic rhinitis. Allergy. 2010;65(11):1397-403.

128. Karvonen AM, Hyvarinen A, Gehring U, Korppi M, Doekes G, Riedler J. Exposure to microbial agents in house dust and wheezing, atopic dermatitis and atopic sensitization in early childhood: a birth cohort study in rural areas. Clinical & Experimental Allergy 2012; 42: 1246-1256.

129. Azad MB, Konya T, Maughan H, Guttman D, Field, C, Radha S. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. CMAJ 2013; 185: 385-394.

130. Huang L, Chen Q, Zhao Y, Wang W, Fang F, Bao, Y. Is elective cesarean section associated with a higher risk of asthma? A meta-analysis. Journal of Asthma 2015; 52: 16-25.

131. Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 1999;354:541-5.

132. Matricardi PM, Rosmini F, Riondino S, Fortini M, Ferrigno L, Rapicetta M, et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. BMJ (Clinical research ed.) 2000 Feb12;320(7232):412-7.

133. von Mutius E. Infection: friend or foe in the development of atopy and asthma? The epidemiological evidence. Eur Respir J. 2001 Nov;18(5):872-81

134. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. American journal of respiratory and critical care medicine. 2005 Jan 15;171(2):137-41

135. Sigurs N, Aljassim F, Kjellman B, Robinson PD, Sigurbergsson F, Bjarnason R, et al. Asthma and allergy patterns over 18 years after severe RSV bronchiolitis in the first year of life. Thorax 2010;65:1045-52.

136. Sly PD, Kusel M, Holt PG. Do early-life viral infections cause asthma? J Allergy Clin Immunol 2010;125:1202-5.

137. Thomsen SF, van der Sluis S, Stensballe LG, Posthuma D, Skytthe A, Kyvik KO, et al. Exploring the association between severe respiratory syncytial virus infection and asthma: a registry-based twin study. American journal of respiratory and critical care medicine. 2009 Jun 15;179(12):1091-7.

138. Stensballe LG, Simonsen JB, Thomsen SF, Larsen AM, Lysdal SH, Aaby P, et al. The causal direction in the association between respiratory syncytial virus hospitalization and asthma. The Journal of allergy and clinical immunology. 2009 Jan;123(1):131-7 e1.

139. Goksör E, Åmark M, Alm B, Ekerljung L, Lundbäck B, Wennergren G. High risk of adult asthma following severe wheezing in early life. Pediatr Pulmonol 2015 Aug;50(8):789-97.

140. Marra F, Lynd L, Coombes M, Richardson K, Legal M, Fitzgerald JM, et al. Does antibiotic exposure during infancy lead to development of asthma?: a systematic review and metaanalysis. Chest. 2006 Mar;129(3):610-8.

141. Marra F, Marra CA, Richardson K, Lynd LD, Kozyrskyj A, Patrick DM, et al. Antibiotic use in children is associated with increased risk of asthma. Pediatrics. 2009 Mar;123(3):1003-10

142. Baron R, Taye M, der Vaart IB, Seidell J, Verhoeff A. The relationship of prenatal antibiotic exposure and infant antibiotic administration with childhood allergies: a systematic review. BMC Pediatr 2020; 20: 312

143. Kummeling I, Stelma FF, Dagnelie PC, Snijders BE, Penders J, Huber M, et al. Early life exposure to antibiotics and the subsequent development of eczema, wheeze, and allergic sensitization in the first 2 years of life: the KOALA Birth Cohort Study. Pediatrics. 2007 Jan;119(1):e225-31

144. Alm B, Erdes L, Mollborg P, Pettersson R, Norvenius SG, Aberg N, et al. Neonatal antibiotic treatment is a risk factor for early wheezing. Pediatrics. 2008;121(4):697-702.

145. Goksör E, Alm B, Thengilsdottir H, Pettersson R, Åberg N, Wennergren G. Preschool wheeze – impact of early fish introduction and neonatal antibiotics. Acta Paediatr 2011; 100 (12): 1561-6.

146. Goksör E, Alm B, Pettersson R, Möllborg P, Erdes L, Åberg N, et al. Early fish introduction and neonatal antibiotics affect the risk of asthma into school age. Pediatr Allergy Immunol 2013; 24 (4): 339-44.

147. Örtqvist AK, Lundholm C, Kieler H, Ludvigsson JF, Fall T, Ye W, et al. Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis. BMJ. 2014 Nov 28;349:g6979.

148. Beasley R, Clayton T, Crane J, von Mutius E, Lai CK, Montefort S, et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. Lancet. 2008 Sep20;372(9643):1039-48

149. Eyers S, Weatherall M, Jefferies S, Beasley R. Paracetamol in pregnancy and the risk of wheezing in offspring: a systematic review and meta-analysis. Clin Exp Allergy 2011;41:482-9

150. Goksör E, Thengilsdottir H, Alm B, Norvenius G, Wennergren G. Prenatal paracetamol exposure and risk of wheeze at preschool age. Acta Paediatr. 2011;100(12):1567-71

151. Cheelo M, Lodge CJ, Dharmage SC, Simpson JA, Matheson M, Heinrich J, et al. Paracetamol exposure in pregnancy and early childhood and development of childhood asthma: a systematic review and meta-analysis. Arch Dis Child 2015;100:81-9

152. Shaheen SO, Newson RB, Henderson AJ, Headley JE, Stratton FD, Jones RW, et al. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. Clin Exp Allergy. 2005 Jan;35(1):18-25.

153. Andersen AB, Farkas DK, Mehnert F, Ehrenstein V, Erichsen R. Use of prescription paracetamol during pregnancy and risk of asthma in children: a population-based Danish cohort study. Clin Epidemiol 2012;4:33-40.

154. Farquhar H, Stewart A, Mitchell E, Crane J, Eyers S, Weatherall M, Beasley R. The role of paracetamol in the pathogenesis of asthma. Clin Exp All 2010;40(1):32-41

155. Greer FR, Sicherer SH, Burks. AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics. 2008 Jan;121(1):183-91.

156. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD000133.

157. Fleischer DM, Spergel JM, Assaad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. J Allergy Clin Immunol Pract. 2013 Jan;1(1):29-36.

158. Romieu I, Torrent M, Garcia-Esteban R, Ferrer C, Ribas-Fito N, Anto JM, et al. Maternal fish intake during pregnancy and atopy and asthma in infancy. Clin Exp Allergy. 2007;37(4):518-25.

159. Maslova E, Granstrom C, Hansen S, Petersen S, Strøm M, Willett W, et al. Peanut and tree nut consumption during pregnancy and allergic disease in children-should mothers decrease their intake? Longitudinal evidence from the Danish National Birth Cohort. J Allergy Clin Immunol 2012; 130: 724-732.

160. Maslova E, Strom M, Oken E, Campos H, Lange, C, Gold D et al. Fish intake during pregnancy and the risk of child asthma and allergic rhinitis -longitudinal evidence from the Danish National Birth Cohort. British Journal of Nutrition 2013; 110: 1313-1325.

161. Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, Workman, L, Sordillo, J, Camargo C et al. Peanut, milk, and wheat intake during pregnancy is associated with reduced allergy and asthma in children. Journal of Allergy & Clinical Immunology 2014; 133: 1373-1382

162. Frazier AL, Camargo CA Jr, Malspeis S, Willett WC, Young MC. Prospective study of peripregnancy or tree nuts by mothers and the risk

of peanut or tree nut allergy in their offspring. JAMA Pediatr. 2014 Feb;168(2):156-62.

163. Kull I, Wickman M, Lilja G, Nordvall SL, Pershagen G. Breast feeding and allergic diseases in infants-a prospective birth cohort study. Archives of disease in childhood. 2002 Dec;87(6):478-81.

164. Elliott L, Henderson J, Northstone K, Chiu GY, Dunson D, London SJ. Prospective study of breast-feeding in relation to wheeze, atopy, and bronchial hyperresponsiveness in the Avon Longitudinal Study of Parents and Children (ALSPAC). The Journal of allergy and clinical immunology. 2008 Jul;122(1):49-54, e1-3.

165. Kramer MS, Kakuma R. Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD000133.

166. Fleischer DM, Spergel JM, Assa'ad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. J Allergy Clin Immunol Pract. 2013 Jan;1(1):29-36

167. Kull I, Melén E, Alm J, Hallberg J, Svartengren M, van Hage M, et al. Breast-feeding in relation to asthma, lung function and sensitization in young school children. J Allergy Clin Immunol. 2010 May;125(5):1013-9

168. Chan-Yeung M, Becker A. Primary prevention of childhood asthma and allergic disorders. Current Opinion in Allergy & Clinical Immunology 2006; 6: 146-151.

169. Brozek JL, Bousquet J, Baena-Cagnani CE, Bousquet PJ, Brozek GW, T Casale et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. Journal of Allergy & Clinical Immunology 2010; 126: 466-476.

170. Grimshaw KE, Allen K, Edwards CA, Beyer K, Boulay A, van der Aa LB, et al. Infant feeding and allergy prevention: a review of current knowledge and recommendations. A EuroPrevall state of the art paper. Allergy. 2009 Oct;64(10):1407-16.

171. Friedman NJ, Zeiger RS. The role of breast-feeding in the development of allergies and asthma. J Allergy Clin Immunol 2005;115:1238-48

172. Osborn DA, Sinn J. Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. Cochrane database of systematic reviews (Online). 2006(4):CD003664.

173. von Berg A, Koletzko S, Filipiak-Pittroff B, Laubereau B, Grubl A, Wichmann HE, et al. Certain hydrolyzed formulas reduce the incidence of atopic dermatitis but not that of asthma: three-year results of the German Infant Nutritional Intervention Study. The Journal of allergy and clinical immunology. 2007 Mar;119(3):718-25.

174. von Berg A, Filipiak-Pittroff B, Krämer U, Hoffmann B, Link E, Beckmann C, et al. GINIplus study group. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. J Allergy Clin Immunol. 2013 Jun;131(6):1565-73

175. Kull I, Bergstrom A, Lilja G, Pershagen G, Wickman M. Fish consumption during the first year of life and development of allergic diseases during childhood. Allergy. 2006 Aug;61(8):1009-15.

176. Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, Livne I, Lack GJ. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. Allergy Clin Immunol. 2008 Nov;122(5):984-91.

177. J Wei-Liang Tan, C Valerio, EH Barnes. A randomized trial of egg introduction from 4 months of age in infants at risk for egg allergy

J Allergy Clin Immunol, 139 (2017), pp. 1621-1628.e8

178. Nwaru BI, Takkinen HM, Niemelä O, Kaila M, Erkkola, M, Ahonen S et al. Timing of infant feeding in relation to childhood asthma and allergic diseases. J Allergy Clin Immunol. 2013;131(1):78-86.

179. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015 Feb 26;372(9):803-13.

180. Ierodiakonou D, Garcia-Larsen V, Logan A, Groome A, Cunha S, Chivinge J et al. Timing of allergenic food introduction to the Infant Diet and Risk of Allergenic or Autoimmune disease. A systematic review and Meta-analysis. JAMA 2016; 316 (11):1181-1192.

181. Greer FR, Sicherer SH, Burks AW. The effects of early nutritional interventions on the development of atopic disease in infants and children: The role of maternal dietary restriction, breastfeeding, hydrolyzed formulas, and timing of introduction of allergenic complementary foods. Pediatrics 2019; 143

182. Hicke-Roberts A, Wennergren G, Hesselmar B. Late introduction of solids into infants' diets may increase the risk of food allergy development. BMC Pediatr. 2020 Jun 3;20(1):273.

183. Skjerven HO, Lie A, Vettukattil R, Rehbinder EM, LeBlanc M, Asarnoj A, et al. Early food intervention and skin emollients to prevent food allergy in young children (PreventADALL): a factorial, multicentre, cluster-randomised trial. Lancet. 2022;399(10344):2398-2411

184. Wells HG. Studies on the chemistry of anaphylaxis. J Infect Dis. 1911;8:147-171.

185. Wawrzyniak M, O'Mahony L, Akdis M (2017) Role of regulatory cells in oral tolerance. Allergy Asthma Immunol Res 9:107–115

186. Klinberg S, Brekke H, Ludvigsson J. Oral tolerance, developed by ingestion of food allergens, could also be part of the explanation to why early fish introduction is associated to a decreased risk of especially atopic asthma in the all babies in southeast Sweden cohort study. European Journal of Pediatrics 2019; 178:395-402.

187. Du Toit G, Sayre PH, Roberts G, Sever M, Lawson K, Bahnson H, et al; Immune Tolerance Network LEAP-On Study Team. Effect of avoidance on peanut allergy after early peanut consumption. N Engl J Med. 2016;374(15):1435-1443

188. Klinnert MD, Nelson HS, Price MR, Adinoff AD, Leung DY, Mrazek DA. Onset and persistence of childhood asthma: predictors from infancy. Pediatrics 2001;108:E69.

189. Kozyrskyj AL, Mai XM, McGrath P, Hayglass KT, Becker AB, Macneil B. Continued exposure to maternal distress in early life is associated with an increased risk of childhood asthma. Am J Respir Crit Care Med 2008;177:142-7.)

190. Galil N. Depression and asthma in children. Curr Opin Pediatr. 2000 Aug;12(4):331-5.

191. Gao YH, Zhao HS, Zhang FR, Gao Y, Shen P, Chen RC et al. The relationship between depression and asthma: A meta-analysis of prospective studies. PLoS One 2015;10:e0132424.)

192. Dreger LC, Kozyrskyj AL, HayGlass KT, Becker AB, MacNeil BJ. Lower cortisol levels in children with asthma exposed to recurrent maternal distress from birth. J Allergy Clin Immunol 2010;125:116-22).

193. Chrousos P. The hypothalamic-pituitary-adrenal axis and immune mediated inflammation. N Engl J Med. 1995;323:1351-62.

194. Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. Ann N Y Acad Sci. 2004;1024:138-46.

195. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychological bulletin. 2004 Jul;130(4):601-30.

196. Fiscella K, Williams R. Health disparities based on socioeconomic inequities: implications for urban health care. Acad Med. 2004;79(12):1139-47

197. Poyser MA, Nelson H, Ehrlich RI, Bateman ED, Parnell S, Puterman A, et al. Socioeconomic deprivation and asthma prevalence and severity in young adolescents. Eur Respir J 2002;19:892-8.

198. Aligne CA, Auinger P, Byrd RS, Weitzman M. Risk factors for pediatric asthma. Contributions of poverty, race, and urban residence. Am J Respir Crit Care Med 2000;162:873-7.

199. Braback L, Hjern A, Rasmussen F. Social class in asthma and allergic rhinitis: a national cohort study over three decades. Eur Respir J 2005;26:1064-8.

200. Chrousos P. The hypothalamic-pituitary-adrenal axis and immune mediated inflammation. N Engl J Med. 1995;323:1351-62.

201. Elenkov IJ. Glucocorticoids and the Th1/Th2 balance. Ann N Y Acad Sci. 2004;1024:138-46.

202. Knackstedt MK, Hamelmann E, Arck PC. Mothers in stress: consequences for the offspring. Am J Reprod Immunol. 2005 Aug;54(2):63-9.

203. Charpin D, Birnbaum J, Haddi E, Genard G, Lanteaume A, Toumi M, et al. Altitude and allergy to house-dust mites. A paradigm of the influence of environmental exposure on allergic sensitization. Am Rev Respir Dis 1991;143:983-6.

204. Sporik R, Ingram JM, Price W, Sussman JH, Honsinger RW, Platts-Mills TA. Association of asthma with serum IgE and skin test reactivity to allergens among children living at high altitude. Tickling the dragon's breath. Am J Respir Crit Care Med 1995;151:1388-92.

205. Wahn U, Lau S, Bergmann R, Kulig M, Forster J, Bergmann K, et al. Indoor allergen exposure is a risk factor for sensitization during the first three years of life. J Allergy Clin Immunol 1997;99:763-9.

206. Huss K, Adkinson NF, Jr., Eggleston PA, Dawson C, Van Natta ML, Hamilton RG. House dust mite and cockroach exposure are strong risk factors for positive allergy skin test responses in the Childhood Asthma Management Program. J Allergy Clin Immunol 2001;107:48-54.

207. Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. N Engl J Med 2003;349:1414-22.

208. Palmqvist M, Pettersson K, Sjostrand M, Andersson B, Lowhagen O, Lotvall J. Mild experimental exacerbation of asthma induced by individualised low-dose repeated allergen exposure. A double-blind evaluation. Respiratory medicine. 1998 Oct;92(10):1223-30.

209. Almqvist C, Wickman M, Perfetti L, Berglind N, Renstrom A, Hedren M, et al. Worsening of asthma in children allergic to cats, after indirect exposure to cat at school. American journal of respiratory and critical care 2001;(163):694-8

210. Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. N Engl J Med 1990;323:502-7. medicine. 2001;163(3 Pt1):694-8.

211. Hogaboam CM, Carpenter KJ, Schuh JM, Buckland KF. Aspergillus and asthma--any link? Med Mycol 2005;43 Suppl 1:S197-202.

212. Quansah R, Jaakkola MS, Hugg TT, Heikkinen SA, Jaakkola JJ. Residential dampness and molds and the risk of developing asthma: a systematic review and meta-analysis. PLoS ONE [Electronic Resource] 2012;7:e47526.

213. Hesselmar B, Aberg N, Aberg B, Eriksson B, Björkstén B Does early exposure to cat or dog protect against later allergy development? Clin Exp Allergy. 1999 May;29(5):611-7.

214. Platts-Mills T, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. Lancet 2001;357:752-6.

215. Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. JAMA 2002;288:963-72.

216. Gern JE, Reardon CL, Hoffjan S, Nicolae D, Li Z, Roberg KA, Neaville WA, et al. Effects of dog ownership and genotype on immune development and atopy in infancy. J Allergy Clin Immunol 2004;113:307-14.

217. Lodge CJ, Lowe AJ, Gurrin LC, Matheson MC, Balloch A, Axelrad C, et al. Pets at birth do not increase allergic disease in at-risk children. Clinical and experimental allergy. 2012;42:1377–85. pmid:22925324

218. Hesselmar B, Hicke-Roberts A, Lundell AC, Adlerberth I, Rudin A, Saalman R, Wennergren G, Wold AE. Pet-keeping in early life reduces the risk of allergy in a dose-dependent fashion. PLoS One. 2018 Dec 19;13(12):e0208472. doi: 10.1371

219. Celedon JC, Litonjua AA, Ryan L, Platts-Mills T, Weiss ST, Gold DR. Exposure to cat allergen, maternal history of asthma, and wheezing in first 5 years of life. Lancet 2002;360:781-2.

220. Melén E, Wickman M, Nordvall SL, van Hage-Hamsten M, Lindfors A. Influence of early and current environmental exposure factors on sensitization and outcome of asthma in pre-school children. Allergy 2001;56:646-52.

221. Almqvist C, Egmar AC, van Hage-Hamsten M, Berglind N, Pershagen G, Nordvall SL, et al. Heredity, pet ownership, and confounding control in a population-based birth cohort. J Allergy Clin Immunol 2003;111:800-6.

222. Konradsen JR, Fujisawa T, van Hage M, Hedlin G, Hilger C, Kleine-Tebbe, J et al. Allergy to furry animals: New insights, diagnostic approaches, and challenges. J Allergy Clin Immunol. 2015 Mar;135(3):616-25.

223. Millqvist E, Johansson A, Mansson T, Bende M. A prospective study of allergy development in 158 children and 128 adults with new extensive exposure to furred animals. Clin Exp Allergy. 2007 Jun;37(6):948-53.

224. Erbas B, Lowe AJ, Lodge CJ, Matheson MC, Hosking CS, Hill DJ, Vicendese D, Allern, KJ, Abrahamson MJ, Dharmage SC. Persistent pollen exposure during infancy is associated with increased risk of subsequent childhood asthma and hayfever. Clin Exp Allergy 213; 43:337-343

225. World Health Organization. Epidemiology [Cited 2022, December 14]

226. Rothman KJ. Epidemiology – An introduction: Oxford University Press; 2002.

227. Andersson I. Epidemiologi för hälsovetare – En introduktion: Studentlitteratur; 2006.

228. Swedish Board of Health and Welfare [Socialstyrelsen]. National Medical Birth Register. [cited January 9, 2023].

229. Swedish Board of Health and Welfare [Socialstyrelsen]. National patient register. [cited January 9, 2023].

230. Swedish Board of Health and Welfare [Socialstyrelsen]. National Prescribed Drug Register. [cited January 9, 2023].

231. Landis JR, Koch GG. The measurement of observer agreement forcategorical data. Biometrics. 1977;33:159-174.

232. Akobeng AK. Understanding type I and type II errors, statistical power and sample size. Acta Paediatr. 2016;105(6):605-9.

233. Marra F, Lynd L, Coombes M, Richardson K, Legal M, Fitzgerald JM, et al. Does antibiotic exposure during infancy lead to development of asthma?: a systematic review and metaanalysis. Chest. 2006 Mar;129(3):610-8.

234. Baron R, Taye M, der Vaart IB, Ujčič-Voortman J, Szajewska H, Seidell JC, et al. The relationship of prenatal antibiotic exposure and infant antibiotic administration with childhood allergies: a systematic review. BMC Pediatr 2020; 20: 312

235. Örtqvist AK, Lundholm C, Kieler H, Ludvigsson JF, Fall T, Ye W, Almqvist C. Antibiotics in fetal and early life and subsequent childhood asthma: nationwide population based study with sibling analysis.. BMJ 2014 Nov;349():g6979

236. Schaub B, Liu J, Schleich I, Hoppler S, Sattler C, von Mutius E. Impairment of T helper and T regulatory cell responses at birth. Allergy 2008; 63: 1438–47.

237. Noverr MC, Huffnagle GB. The microflora hypothesis of allergic disease. Clin Exp Allergy 2005; 35: 1511–20.

238. Dekker HT, Sonnenschein-van der Voort AM, Jaddoe VW, Reiss IK, de Jongste JC, Duijts L. Breastfeeding and asthma outcomes at the age of 6 years: the Generation R Study. Pediatr Allergy Immunol 2016; 27: 486–92.

239. Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. Pediatr Clin N Am 2013; 60: 49–74.

240. G. Nagel, G. Buchele, G. Weinmayr, B. Bjorksten, Y.Z. Chen, H. Wang, et al. Effect of breastfeeding on asthma, lung function and bronchial hyperreactivity in ISAAC Phase II. Eur Respir J, 33 (2009), pp. 993-1002

241. Ronmark E, Jonsson E, Platts-Mills T, Lundback B. Different pattern of risk factors for atopic and nonatopic asthma among children – report from the Obstructive Lung Disease in Northern Sweden Study. Allergy 1999;54:926-935.

242. Konradsen JR, Nordlund B, Lidegran M, Pedroletti C, Grönlund H, van Hage M, et al. Problematic severe asthma: a proposed approach to identifying children who are severely resistant to therapy. Pediatr Allergy Immunol 2011; 22: 9–18.

243. Bloom B, Jones LI, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2012. Vital Health Stat 10 2013; (258): 1–81.

244. Morsbach S, Prinz R. Understanding and improving the validity of self-report of parenting. Clin Child Fam Psychol Revi. 2006;9(1):1-21.

245. Smeeton NC, Rona RJ, Oyarzun M, Diaz PV. Agreement between responses to a standardized asthma questionnaire and a questionnaire following a demonstration of asthma symptoms in adults. Am J Epidemiol. 2006;163(4):384-391.