From the Institute of Environmental Medicine
Karolinska Institutet, Stockholm, Sweden

OVERWEIGHT IN RELATION TO ALLERGIC DISEASE IN CHILDHOOD AND ADOLESCENCE

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Stockholm 2018

Published by Karolinska Institutet.
Printed by E-print AB 2018

ISBN 978-91-7676-950-8

Overweight in relation to allergic disease in childhood and adolescence

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

The prevalences of childhood overweight and allergic diseases have increased in parallel during the last decades. The overall aim of this thesis was to investigate the associations between overweight (maternal and childhood) and allergic diseases, as well as lung function, throughout childhood up to adolescence. In addition, we investigated the validity of self-reported height, weight and corresponding body mass index (BMI) among Swedish adolescents.

All studies were based on the BAMSE study, a population-based birth cohort of 4,089 children followed until age 16 years. Maternal BMI was obtained from the Swedish medical birth register, while childhood BMI was measured at clinical investigations, collected from child and school health care records and self-reported. Allergic diseases were assessed by repeated questionnaires regarding symptoms and medications, while allergic sensitization to inhalant allergens was defined by the presence of specific immunoglobulin E (IgE)-antibodies in blood. Lung function was measured by spirometry at 8 and 16 years and by impulse oscillometry (IOS) at 16 years.

The results of **Study I** showed that maternal BMI in early pregnancy was associated with asthma, but not rhinitis, eczema or allergic sensitization in the offspring up to 16 years. The association was strongest for persistent asthma, while no increased risk was observed for transient asthma. Categorization of maternal BMI showed that maternal obesity, but not overweight, was significantly associated with childhood asthma. However, the child's own weight status could partly explain the observed association between maternal BMI and asthma in the offspring.

In **Study II**, we found that girls with persistent asthma had a higher BMI and an increased risk of overweight throughout childhood, compared to girls without asthma. Girls with transient asthma had an increased risk of overweight at ages 4-7.9 years, whereas girls with late-onset asthma had a tendency towards an increased risk of overweight at age ≥15 years. In boys, the difference in BMI between children with and without asthma was smaller, and no consistent association was observed between asthma phenotypes and overweight.

In **Study III**, we observed that overweight and obesity at age 8 years were associated with increased forced vital capacity (FVC) and to some extent forced expiratory volume in one second (FEV_1), but reduced FEV_1/FVC ratios at 8 and 16 years. The strongest association with FEV_1/FVC was observed for persistent overweight at both 8 and 16 years, whereas no significant association was found for transient overweight. Cross-sectional analyses of IOS showed that overweight and obesity were associated with higher peripheral airway resistance and reactance at 16 years.

The result of **Study IV** showed that self-reported and measured height and weight were highly correlated at 16 years (r=0.98 for height, r=0.96 for weight). On average, self-reported weight was underreported by 1.1 kg and height was overreported by 0.5 cm, leading to an underestimation of BMI by 0.5 kg/m^2. The accuracy of self-reported BMI was somewhat lower among girls and among overweight and obese participants, compared to normal weight participants.

Our results suggest that maternal and childhood overweight and obesity are associated with asthma and evidence of airway obstruction in children and adolescents. The association between maternal BMI and asthma may, to some extent, be mediated through childhood overweight and seems to be explained by non-allergic mechanisms. In addition, we conclude that web-based self-reported BMI can be used as a valid, quick and cost-effective alternative to measured BMI among Swedish adolescents. The accuracy however declines with increasing BMI, and is somewhat lower among girls compared to boys.

LIST OF SCIENTIFIC PAPERS

The thesis is based on the following four publications, which will be referred to by their Roman numbers. The papers are reproduced at the end of the thesis.

I. **Ekström S,** Magnusson J, Kull I, Lind T, Almqvist C, Melén E, Bergström A. Maternal body mass index in early pregnancy and offspring asthma, rhinitis and eczema up to 16 years of age. *Clin Exp Allergy* 2015;45(1):283-91.

II. **Ekström S,** Magnusson J, Kull I, Andersson N, Bottai M, Besharat Pour M, Melén E, Bergström A. Body mass index development and asthma throughout childhood. *Am J Epidemiol* 2017;186(2):255-63.

III. **Ekström S,** Hallberg J, Kull I, Protudjer JLP, Thunqvist P, Bottai M, Gustafsson PM, Bergström A, Melén E. Body mass index status and peripheral airway obstruction in school-age children: a population based cohort study. *Thorax* 2018 Jan 29 [Epub ahead of print].

IV. **Ekström S**, Kull I, Nilsson S, Bergström A**.** Web-based self-reported height, weight, and body mass index among Swedish adolescents: a validation study. *J Med Internet Res* 2015;17(3):e73.

CONTENTS

LIST OF ABBREVIATIONS

AX	Area of reactance
ATS	American Thoracic Society
BAMSE	Children (Barn), Allergy, Milieu, Stockholm, Epidemiology
BMI	Body mass index
CI	Confidence interval
CDC	Centers for Disease Control and Prevention
CS	Caesarian section
DAG	Directed acyclic graph
ERS	European Respiratory Society
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
FFQ	Food frequency questionnaire
GEE	Generalized estimating equations
IgE	Immunoglobulin E
IOTF	International Obesity Task Force
IOS	Impulse oscillometry
ISAAC	the International Study of Asthma and Allergies in Childhood
kU_A/L	Kilounits per liter
MBR	Medical birth register
MeDALL	Mechanisms of the Development of Allergies
OR	Odds ratio
PIAMA	the Prevention and Incidence of Asthma and Mite Allergy
R	Reactance
R_{5-20}	Frequency dependence of resistance
SD	Standard deviation
US	United States
WHO	World Health Organization
X	Reactance

1 BACKGROUND

1.1 CHILDHOOD ALLERGIC DISEASE

1.1.1 Introduction to childhood allergic disease

The prevalence of allergic disease (here referred to as asthma, rhinitis, eczema and food allergy) increased rapidly during the second half of the 20th century, and currently affects 30-40% of the population.[1] The concept of the "allergic march" is sometimes used to describe the typical sequence of allergic disease progression throughout childhood, from food allergy and eczema in infancy and early childhood to asthma and rhinitis in later childhood.[2] However, new onset and remission of allergic disease also occur continuously throughout childhood, and disease development in individuals does not always follow the "allergic march".[3] Although a large proportion of children with early allergic disease grow out of their symptoms, some persist into more severe disease. In children, the prevalence of asthma is estimated at around 7-9%, rhinitis around 9-15% and eczema around 15-20%, although large variations are seen across populations, ages and definitions.[1, 4-7] In a Swedish population-based study, around 30% of the children suffered from any allergic disease (asthma, rhinitis or eczema) at 12 years of age, and a large proportion had more than one of these diseases.[6]

Allergic disease is associated with sleep disturbances, missed school-days, lower school performance and reduced quality of life.[1, 8-11] On a societal level, these diseases give rise to extensive health care costs and lost productivity.[9] To effectively prevent and reduce the burden of allergic disease, it is important to identify modifiable risk factors. The main focus of the present thesis is to examine the role of maternal and childhood overweight for the development of allergic disease (in particular asthma) from birth to adolescence.

1.1.2 Development of allergic sensitization

Allergic disease can be classified as immunoglobulin E (IgE)-mediated and non-IgE-mediated disease. The former is characterized by hyperreactivity of the immune system to otherwise harmless substances (allergens) in environment. The sensitization process (i.e. initiating the production of IgE antibodies) starts when an allergen enters the epithelial barrier of the skin, airway or gut for the first time. This process may be facilitated by a dysfunctional epithelial barrier, which is typically caused by genetic or environmental factors.[12, 13] The allergen is taken up by the dendritic cell (antigen presenting cell) and is presented to the naïve T-cell at the lymph node.[13] Through communication with cytokines, the naïve T-cell develops into a Th_2 cell, which stimulates B-cells to produce allergen-specific IgE-antibodies. The specific IgE-antibodies are distributed systemically and bind to the surface of mast cells in the airway or nasal mucosa. The next time an individual is exposed to the allergen, it binds to the specific antibody on the mast cell. This leads to mast cell activation and degranulation characterized by the release of histamine and other inflammatory substances. The inflammatory substances cause smooth muscle contraction, mucous secretion and vasodilation, which gives rise to the typical allergic symptoms that may be specific to the tissue where the allergic reaction occur (e.g. runny nose or bronchoconstriction).[12] For non-IgE mediated disease, other pathophysiological

mechanisms related to genetics, viral infections or environmental factors are of importance.[14, 15]

1.1.3 Definitions and diagnosis

1.1.3.1 Asthma

Asthma is characterized by airway inflammation, resulting in narrowing of the airways with reoccurring symptoms such as coughing, wheeze, dyspnea and shortness of breath. Asthmatic airways are hyperreactive and may be triggered by inhaled substances such as allergens or irritants (e.g. tobacco smoke or cold air), physical activity or infections. Asthma is a heterogeneous disease, which may be classified into various phenotypes.[16] In accordance with the reasoning above, asthma can be divided into allergic (IgE-mediated) and non-allergic (non-IgE-mediated) disease. Allergic asthma is most common and is (typically) defined by the presence of specific IgE-antibodies to allergens such as pets or pollen.[17] Allergic asthma is often characterized by airway and systemic eosinophilic inflammation.

Asthma is diagnosed by symptom history, sometimes in combination with lung function and/or hyperreactivity tests. In epidemiological studies, asthma is commonly defined by questionnaire-reported symptoms, medication or doctor's diagnosis. In small children, asthma is difficult to diagnose, as similar symptoms often present during respiratory tract infections in early life. A large proportion of young children who show asthma symptoms during infection will outgrow their symptoms by school-age.[18]

Asthma treatment often includes short- and long-acting beta$_2$ agonists and inhaled corticosteroids to counteract airway inflammation. Additional treatment with antileukotriens or other asthma drugs may be needed for more difficult-to-treat asthma. Long-term asthma with chronic inflammation can cause airway remodeling with permanent airflow limitations and optimal treatment is therefore important to reduce the risk of irreversible impairment.[18]

1.1.3.2 Rhinitis

Rhinitis is characterized by inflammation in the nasal epithelium causing rhinorrhea, sneezing, and blocked or itchy nose. Allergic rhinitis is defined by the presence of IgE-antibodies against allergens in blood, whereas patients with non-allergic rhinitis may react to irritants or other non-allergic triggers.[4] Clinically, rhinitis is diagnosed by symptom history, nasal examination and IgE-sensitization tests.[4] In epidemiological studies, rhinitis is commonly defined by symptoms in the absence of an upper respiratory tract infection, sometimes in combination with exposure to allergens such as pollen or pets.

1.1.3.3 Eczema

Eczema is an inflammatory disease of the skin characterized by dry skin and itchy rash, caused by skin barrier dysfunction and/or a hyper-reactive immune response.[19] Eczema symptoms are relapsing and often present at age-specific locations. Clinically, eczema is diagnosed through visual inspection and defined according to certain diagnostic criteria.[20] In epidemiological studies, eczema is usually defined based on questions regarding symptoms, doctor's diagnosis and specific treatment.

1.1.3.4 Allergic sensitization

Allergic sensitization is determined by the ability to develop IgE-antibodies to specific allergens. Among Swedish children, pollen, furred animals and certain foods are examples of common allergens to be sensitized against. During childhood, the prevalence of sensitization to foods such as milk and egg have been shown to decrease from pre-school age up to adolescence, whereas the prevalence of sensitization to inhalant allergens have been shown to increase.[21] Allergic sensitization is measured by the presence of IgE-antibodies in blood or by a skin prick test. High levels of IgE-antibodies increase the likelihood of symptoms upon allergen exposure, but many individuals are sensitized without showing any allergic symptoms.[13]

1.1.4 Risk factors

Allergic diseases are multifactorial and appear to be caused by a combination of genetic and environmental factors. Heritability of allergic disease is estimated to around 60-80%, and a number of specific gene variants have been found to increase the risk of disease.[22, 23] One such example is the filaggrin gene, in which loss-of-function mutations have been associated with skin barrier dysfunction and increased the risk of eczema.[24] Parental allergy is a strong risk factor for allergic disease. However, the associations have been reported to be somewhat more pronounced for maternal, compared to paternal allergy, indicating that non-genetic factors such as *in-utero* programming are also important.[25, 26]

Second hand tobacco smoke exposure is one of the most established environmental risk factors for asthma, and may also increase the risk for other allergic diseases.[27] Both maternal smoking during pregnancy and second hand smoke exposure during childhood have been associated with wheeze and asthma in children.[27, 28] Air pollution and indoor mold and dampness are other environmental risk factors that have been linked to asthma and allergic disease in children.[29, 30]

The prevalence of allergic disease, including asthma, rhinitis and allergic sensitization are lower among children raised on a farm and in rural, compared to urban areas.[31-33] In addition, large family size and early day-care attendance have been shown to reduce the risk of asthma and allergic sensitization, although the risk of transient wheeze in early life may be increased.[34-36] These observations have been proposed to be explained by the hygiene hypothesis, which suggests that a diverse exposure to bacteria and parasites in infancy is important for immune function development.[37, 38] In contrast, some viral infections in infancy such as the respiratory syncytial virus and rhinovirus have been shown to increase the risk of asthma.[39] However, it is unknown whether these associations are causal or explained by increased susceptibility in these children.

Maternal factors during pregnancy such as obesity (described under section **1.4**), diet, certain medication and stress have also been suggested to contribute to the risk of asthma.[40] Although evidence is conflicting for many of the dietary factors, a meta-analysis of 32 studies observed that higher maternal intake of vitamin D, vitamin E and zinc during pregnancy were associated with reduced risk of wheeze in childhood.[41] In contrast, no association was found with asthma or for intake of other nutritional factors.

Birth weight and gestational age have also been shown to influence the risk of asthma, which may be explained by suboptimal airway and lung development in children born prematurely or with low birth weight. A meta-analysis of almost 150,000 children observed that preterm birth was associated with an increased risk of asthma independent of birth weight, while the association for birth weight was explained by gestational age at birth [42]. In addition, caesarian section (CS) has been suggested as a potential risk factor for asthma due to lack of exposure to certain microbes that are normally transferred during vaginal delivery. However, a register based cohort of 87,500 Swedish sibling pairs showed that emergency, but not elective CS, increased the risk of asthma medication in the child. These results suggest that indications for emergency CS (such as fetal respiratory stress or maternal complications), rather than the lack of microbe exposure, may explain the association between CS and asthma.[43] Both preterm birth[44, 45] and CS[46] are more common among obese mothers, compared to normal weight mothers, and these factors may also act as potential mediators in the observed association between maternal obesity and childhood asthma.

Factors in early childhood may also contribute to the risk of allergic disease. Breastfeeding has been shown to reduce the risk of asthma symptoms in early childhood, but the protective effect seems to diminish over time.[47, 48] Early introduction of allergenic foods, such as peanut and egg, was previously thought to increase the risk of allergic disease, but today is suggested to be important for inducing oral tolerance in high risk children.[49] Rapid growth in infancy and early childhood have also been found to increase the risk of asthma, in particular catch-up growth among low birth weight children.[42]

Since allergic disease continues to develop throughout childhood, lifestyle and environmental factors beyond infancy or early childhood may also influence the risk of disease. For example, childhood overweight and obesity have been associated with asthma (described more under section **1.5)**, while there is less evidence for other allergic diseases. Furthermore, certain dietary factors such as intake of oily fish and antioxidants have been shown to reduce the risk of asthma and rhinitis up to adolescence.[50, 51]

1.2 LUNG FUNCTION

The lungs continue to develop until early adulthood[52] and childhood is an important period for lung function development and future respiratory health. Asthma is associated with reduced lung function, mainly airway obstruction due to narrowing of the airways. Airway obstruction in children is usually reversed by bronchodilators, but may, for some individuals proceed into irreversible fixed airflow limitation characterized by airway remodeling.[53] Lung function can be measured by various techniques, each providing somewhat different information that can complement each other.

1.2.1 Dynamic spirometry

Dynamic spirometry is the most widely used method to measure lung function in clinical and research settings. By using a spirometer, air flow and volume during a forced expiration following a maximal inhalation is measured. The amount of air that can be exhaled in the first second is referred to as the forced expiratory volume in one second (FEV_1), which is a measure of flow and airway size. The total amount of air that can be exhaled during the full expiration is referred to as the forced vital capacity (FVC), and is

representative of lung size. The ratio between FEV_1/FVC is a measure of relative airway size, where low values indicate airway obstruction. In both children and adults, reference equations have been developed to compare lung function values with regards to age, sex, height and ethnicity.[54]

1.2.2 Impulse oscillometry

Impulse oscillometry (IOS) is an effort-independent method that measures airway resistance (R) and reactance (X), and provides information about airway obstruction in the central and peripheral airways.[55, 56] Measurements are performed during tidal breathing where external pressure impulses with frequencies between 5 and 35 Hz are forced upon the respiratory system. Higher frequencies (>20 Hz) reach the large and intermediate airways, whereas lower frequencies (around 5 Hz) travel deeper into the lung. For this reason, resistance at low frequencies reflects total airway resistance and resistance at high frequencies reflects large and intermediate airway resistance. The difference between these values (R_{5-20}) represents peripheral airway function. Airway reactance can be viewed as the rebound resistance of the lung, where the area under the reactance curve (AX) represent the total reactance at all frequencies.[56] R_{5-20} and AX are usually correlated in individuals.

1.3 OVERWEIGHT AND OBESITY

Overweight/obesity has emerged as one of the most serious public health challenges during the last decades and is a strong risk factor for several adverse health effects and chronic diseases.[57] According to the World Health Organization (WHO), overweight and obesity are defined as "abnormal or excessive fat accumulation that may impair health".[58] The underlying cause of obesity is an imbalance between energy intake and expenditure, which may be achieved by a combination of various dietary factors, physical inactivity and genetic factors.[59]

Body mass index (BMI), calculated as weight/height^2, is the most widely used measure of overweight and obesity. Although BMI cannot differentiate between adipose and lean tissue in individuals, it correlates well with body fat percentage and is linked to morbidity and mortality on a population level.[60, 61] In adults, BMI $\geq$ 25 kg/m^2 and $\geq$ 30 kg/m^2 are generally accepted cut-offs to define overweight and obesity, respectively.[58]

1.3.1 Maternal overweight and obesity

Maternal obesity is the most common complicating factor of pregnancy. According to the US National Health and Nutrition Examination Survey 2011-2012, 32% of all women aged 20-39 years were obese.[62] In Sweden, 12.4% of pregnant women were classified as obese at the first visit to the antenatal care unit around week 9-10 of pregnancy in 2014.[63]

Maternal obesity is associated with a number of birth-related complications and health consequences for the mother and child. These includes maternal hypertension, gestational diabetes, preterm birth, infants born large for gestational age and an increased risk of obesity in the offspring.[64]

1.3.2 Childhood overweight and obesity

1.3.2.1 Definition

In children, BMI varies naturally with age and differs slightly between girls and boys. Therefore, sex- and age-specific reference values are used to define childhood overweight and obesity. Different reference values are proposed by organizations such as the WHO 2007 BMI-for-age[65], for ages 5-19 years and the Center for Disease Control and Prevention (CDC) 2000 BMI-for-age[66], for ages 2-20 years. In addition, national reference values are frequently used to define overweight and obesity in children. In general, overweight and obesity are defined as the 85th and the 95th percentile and above, respectively (e.g. CDC 2000), or by +1 and +2 standard deviation scores (e.g. WHO 2007).

In order to provide a standard international definition of childhood overweight and obesity, the International Obesity Task Force (IOTF) constructed centile curves based on nationally representative surveys from Brazil, Great Britain, Hong Kong, the Netherlands, Singapore and the United States (US).[67, 68] The curves were calculated to pass through BMI 25 kg/m^2 and 30 kg/m^2 at 18 years; therefore corresponding to the adult cut-offs for overweight and obesity. Some years later, cut-offs for thinness corresponding to BMI 18.5 kg/m^2, 17 kg/m^2 and 16 kg/m^2 at age 18 years (thinness grade 1, 2 and 3) were also published.[69] The IOTF reference values were argued to be more internationally representative and less arbitrary compared to previous reference values.

The prevalence of overweight and obesity in children is dependent on reference method, where higher prevalences are obtained by the WHO, compared to the IOTF classification.[70] A comparison of the performance between the WHO 2007 and the IOTF 2012 classification system to predict overweight and obesity at 18 years based on BMI at 10 years showed that the WHO classification system had a higher sensitivity (captured more cases), while specificity was somewhat higher for IOTF (included less non-cases).[71]

1.3.2.2 Measurements (self-reported vs measured)

The prevalence of childhood overweight and obesity may also depend on whether weight and height are directly measured or reported by the parent or the child. In large epidemiological studies, self-reported or parental-reported weight and height are often used due to cost-efficiency. However, accuracy of exposure measurements is crucial in epidemiological studies, and the validity of self-reported weight and height should be considered before it is used. In general, self-reported weight is somewhat underreported, while self-reported height is slightly overreported, leading to an underestimation of BMI.[72] Overweight and obese individual tend to underreport weight to a higher extent than normal weight individuals, and females tend to underreport weight more than males.[72]

The validity of self-reported weight and height may depend on factors such as age, gender, geographical region and ethnicity, and it is important to assess validity within the specific population where the use is intended. Validity may also vary over time and by methods of data collection. Questionnaires can be distributed through the web or by paper, and may be answered in school or in the home environment. This may impact on participation rate, but also the perception of anonymity, parental involvement and the possibility to check weight and height before answering the questionnaire.

During adolescence, the accuracy of self-reported BMI may be particularly low because of rapid changes in body size and composition. Also, adolescents may be more concerned over body ideals, which could influence their willingness to report according to what is more socially accepted.

1.3.2.3 Occurrence

A recent pooled analysis of 2,416 studies of 31.5 million children aged 5-19 years examined global trends in childhood underweight, overweight and obesity, based on measured weight and height using the WHO 2007 reference.[57] The results showed that the global age-standardized prevalence of overweight (including obesity) increased between 1975 and 2016, from 4.0% to 17.5% in girls and from 4.6% to 19.2% in boys. For obesity, the corresponding prevalence increased from 0.7% to 5.6% in girls and from 0.9% to 7.8% in boys. Large regional differences were observed where the prevalence of obesity ranged from around 1-3% in many African and some Asian countries to >20% in the US, New Zealand and some Middle East countries in 2016. The highest prevalence was reported in some small South Pacific and Indian Ocean islands, for example the Cook Islands and Nauru, with >30% childhood obesity.

In Europe, the prevalence of childhood obesity varied and was the lowest in some parts of the northern and eastern Europe (around 5% in girls and 8-10% in boys in for example Sweden, Denmark, and Estonia) and highest in southern Europe (around 10% in girls and 15% in boys in for example Italy, Greece and Portugal) in 2016. In Sweden, the prevalence of overweight (including obesity) was 22.1% in girls and 25.1% in boys in 2016, and the prevalence of obesity was 4.7% in girls and 8.5% in boys.[57] In many high income countries, the rising trend in BMI among children and adolescents has plateaued since around the year 2000, whereas it has increased rapidly in some parts of Asia.[57] However, it has been debated whether the reported stabilization in the obesity epidemic is real or explained by bias or misinterpretation of the data.[73] This was further highlighted in a recent investigation based on the US National Health and Nutrition Examination Survey, which observed an increase in the overall prevalence of childhood overweight and obesity, with a sharp increase in obesity from 2015-2016 in the age group 2-5 years.[74]

In high income countries, an inverse gradient between socioeconomic status and childhood obesity has been observed.[75] For example, a study on 3,492 7-9 year old children from western Sweden, found large differences in obesity prevalence (IOTF reference) with 0% in girls and 1.6% in boys in high education areas, compared to 6.8% in girls and 3.9% in boys in low education areas.[76]

1.4 ASSOCIATION BETWEEN MATERNAL OVERWEIGHT AND CHILDHOOD ALLERGIC DISEASE

Maternal BMI may influence the risk of childhood allergic disease through several potential mechanisms. Maternal obesity is associated with fetal inflammation, epigenetic modifications and altered gut colonization, which may influence fetal immune system and lung development.[77-79] An association between maternal obesity and childhood allergic disease may also be explained by birth- or pregnancy-related complications (e.g. gestational diabetes, hypertension or preterm birth) or by shared genetics or lifestyle factors such as diet or physical activity.[64, 79]

A growing body of epidemiological evidence suggests that pre- or early pregnancy BMI is associated with wheeze and asthma in the offspring,[80] while very limited evidence exists on the potential association with other allergic diseases. Moreover, the majority of previous studies on wheeze or asthma followed children up to preschool age[81-87] or early school age[88-91] and there is less knowledge on whether these associations persist into adolescence. Due to the short follow-up and lack of longitudinal outcome assessments, there is limited evidence regarding the timing and onset of asthma in relation to maternal BMI. In one study, maternal BMI and adiposity was associated with transient, but not persistent wheeze up to age 6 years,[90] whereas another study reported strongest association with late-onset wheeze up to age 7 years.[88]

At the time **Study I** was published, two previous studies had examined the association between maternal BMI and wheeze or asthma in the offspring up to adolescence.[92, 93] In a Finnish cohort of almost 7,000 adolescents, maternal pre-pregnancy BMI was associated with asthma and wheeze at age 15-16 years, but only among children without parental history of atopy.[93] In the second study, Lowe and colleagues investigated the association between maternal obesity in early pregnancy and dispensed inhaled corticosteroids (as a proxy for asthma) in a register-based study of more than 400,000 Swedish children up to age 16 years.[92] The overall results showed that maternal obesity was associated with dispensed corticosteroids, whereas the association was only significant among girls in the age-group 13-16 years. In sibling-pair analyses, no association was observed between maternal obesity and corticosteroids, indicating that shared genetic or environmental risk factors may explain the observed association. For instance, overweight in the offspring, which may be caused by shared dietary and other lifestyle factors, could be a mediator in the association between maternal obesity and childhood asthma, but was not available for analysis in this register-based study.

1.5 ASSOCIATIONS BETWEEN CHILDHOOD OVERWEIGHT AND ASTHMA AND LUNG FUNCTION

In 1999, Camargo and colleagues published the first prospective study on BMI and asthma where they showed that obesity was associated with an increased risk of incident asthma among adult women in the Nurses' Health Study.[94] Shortly after, this association was also confirmed in longitudinal studies in children,[95-98] although some of these studies observed an association only in boys[98], and others only in girls[95]. For example, among 600 children from the Tucson Children's Respiratory Study, Castro-Rodriguez and colleagues observed that girls, but not boys, who became overweight or obese between 6-11 years had an increased risk of developing asthma symptoms at age 11 or 13 years.[95]

Ever since these initial longitudinal studies, an increasing number of studies have reported similar associations between obesity and asthma in children.[99-102] Two meta-analyses, each including six prospective child cohorts, found that overweight was associated with a 19% and 35% higher risk of asthma, respectively, while corresponding numbers for obesity were 102% and 50%.[103, 104] One of these meta-analyses found stronger associations in boys, whereas the other observed inconsistent results regarding gender differences.

Despite the large amount of studies on childhood obesity and asthma, there are still inconsistencies regarding the temporal association and the timing and onset of obesity or

weight gain. Some studies indicate that rapid weight gain in infancy is most important for asthma,[105-107] whereas others have shown that high BMI in early life does not increase the risk of asthma in school-aged children that develop normal weight.[108, 109] Only a few prospective cohorts have followed children with repeated BMI measurements throughout childhood, and BMI development in relation to asthma onset and persistence up to adolescence have not been previously investigated.

The association between obesity and asthma may be explained by several potential biological mechanisms, many of them which are similar to the suggested mechanisms behind the association between maternal BMI and childhood asthma. For example, chronic airway and systemic inflammation, epigenetic modifications or altered gut microbiota have been proposed as possible explanatory factors.[110, 111] Most studies on obesity and asthma have found stronger associations with non-IgE-mediated, compared to IgE-mediated asthma,[112, 113] and no or inverse associations with airway eosinophilic inflammation,[114, 115] suggesting that the mechanisms are not mediated through allergic pathways. The possibility that the association between obesity and asthma may be explained by over diagnosis or confounded by shared genetics, prenatal- or birth-related factors (e.g. maternal BMI, maternal dietary factors, breastfeeding, preterm birth or mode-of delivery) or by lifestyle factors in childhood have also been discussed.[110] In addition to obesity being a risk factor for asthma, the reverse has also been observed, in that asthma increase the risk for obesity.[116]

Another potential mechanism by which obesity may influence asthma is through effects on lung function. Most studies in children[117-120] have shown that overweight and obesity are associated with airway obstruction (decreased FEV_1/FVC), while FEV_1 and FVC are unaffected or increased (also referred to as dysanaptic growth[121]). However, it is unknown whether the dysanaptic pattern observed among overweight and obese children is of clinical importance or part of normal physiology. Studies combining spirometry with other lung function measures could provide more insight into the physiological mechanisms behind the obesity and lung function association in children.

From a public health perspective, it is important to investigate whether any influence of overweight on lung function is reversible. However, the majority of studies on overweight and lung function in children are cross-sectional, and have not been able to analyze temporal changes in BMI in relation to lung function. Therefore, large prospective studies with repeated exposure assessments are needed to fully explore these associations in childhood.

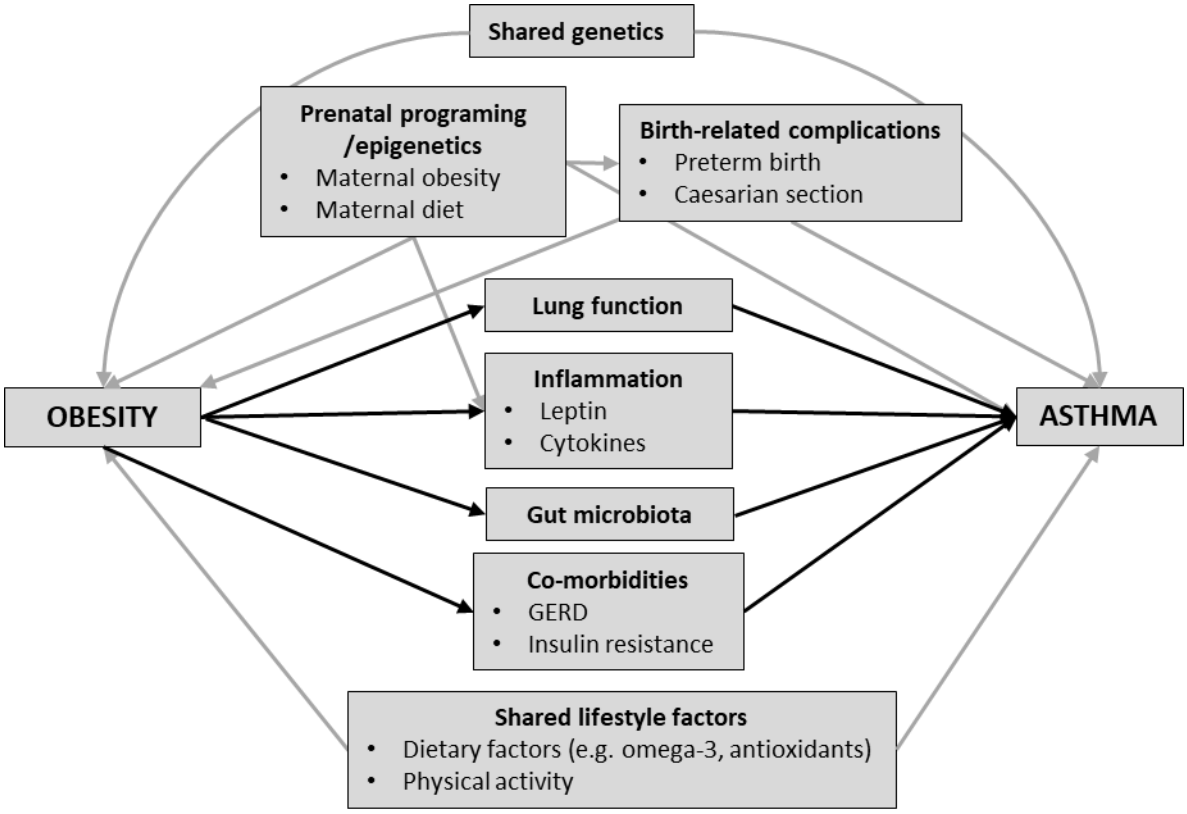

Figure 1.1. Illustration of some of the proposed mechanisms and explanatory factors for an association between obesity and asthma in children.[110, 122, 123] However, there are many other possible pathways. GERD: gastroesophageal reflux disease.

2 AIMS

The overall objective of this thesis was to study the associations between overweight and allergic diseases, in particular asthma, throughout childhood up to adolescence, including the role of maternal BMI, and the influence on lung function.

In addition, we aimed to investigate the accuracy of self-reported weight and height among Swedish adolescents, in order to evaluate whether this information can be used to define BMI status among adolescents.

The specific aims were:

I. To examine the association between maternal BMI in early pregnancy and asthma, rhinitis, eczema and allergic sensitization in the offspring up to 16 years of age.

II. To investigate BMI development and the risk of overweight from birth to adolescence in relation to asthma phenotypes.

III. To study the association between overweight and lung function, including peripheral airway function from school-age to adolescence.

IV. To validate self-reported height, weight and corresponding BMI among Swedish adolescents at age 16 years.

3 MATERIAL AND METHODS

3.1 THE BAMSE BIRTH COHORT

All studies within the thesis are based on the BAMSE (Swedish acronym for Children, [Barn], Allergy, Milieu, Stockholm, Epidemiology) study. The BAMSE study is an ongoing population-based prospective birth cohort with the primary aim to study risk factors for development of allergic disease in children.

3.1.1 Recruitment

Newborn children were recruited from child health care centers in four areas of Stockholm: the municipalities Järfälla, Solna, Sundbyberg and northwest parts of the inner city (Norrmalm and Vasastaden) (**Figure 3.1**) between February 1994 and November 1996. The specific areas were chosen in order to represent a varied distribution of socioeconomic factors and housing conditions. Out of 7,221 children born in the study area during the recruitment period, 5,488 were eligible according to the inclusion criteria (**Figure 3.2**). The final cohort consisted of 4,089 children (50.5% boys), i.e., 75% of eligible, whose parents answered a baseline questionnaire when the children were on average two months old.

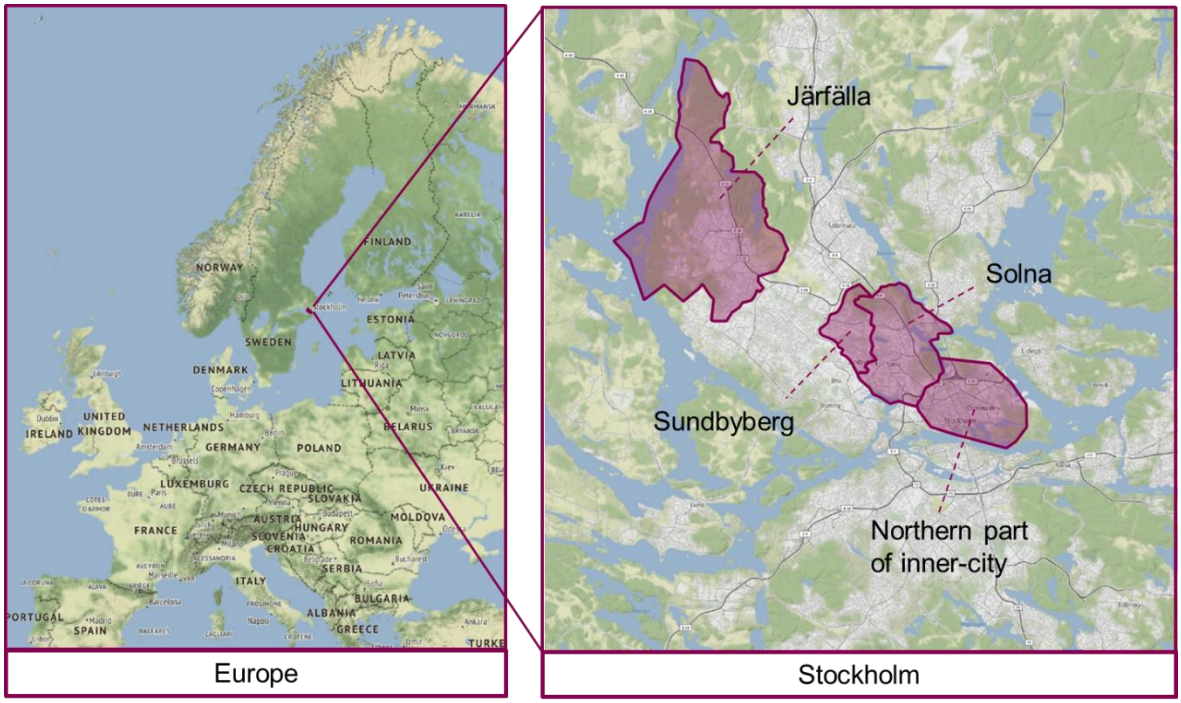

Figure 3.1. Map of the BAMSE study area. Maps adapted from ©OpenStreetMap contributors, created by Erica Schultz.

In order to evaluate the representativeness of the study population, non-responders of the initial survey and actively excluded families were sent a short questionnaire on selected exposures and parental allergic disease in 1996. The response-rate of the questionnaire was 83% for actively excluded families and 58% for non-responders. The results showed that the study population was comparable to non-responders and excluded children in terms of allergic heredity and pet ownership, however the prevalence of parental smoking was somewhat higher in the non-participants.[124]

3.1.2 Follow-up

Follow-up questionnaires focusing on symptoms of the child's health, especially allergic disease in the child, were sent out to the parents when the children were approximately 1, 2, 4, 8, 12 and 16 years. The response rates were 96%, 94% 91%, 84%, 82% and 78%, respectively. At 12 and 16 years, the adolescents themselves were also sent a questionnaire, which were answered by 68% and 76%, respectively. At 4, 8 and 16 years, children were invited to a clinical examination including blood sampling and measurement of height, weight and lung function.

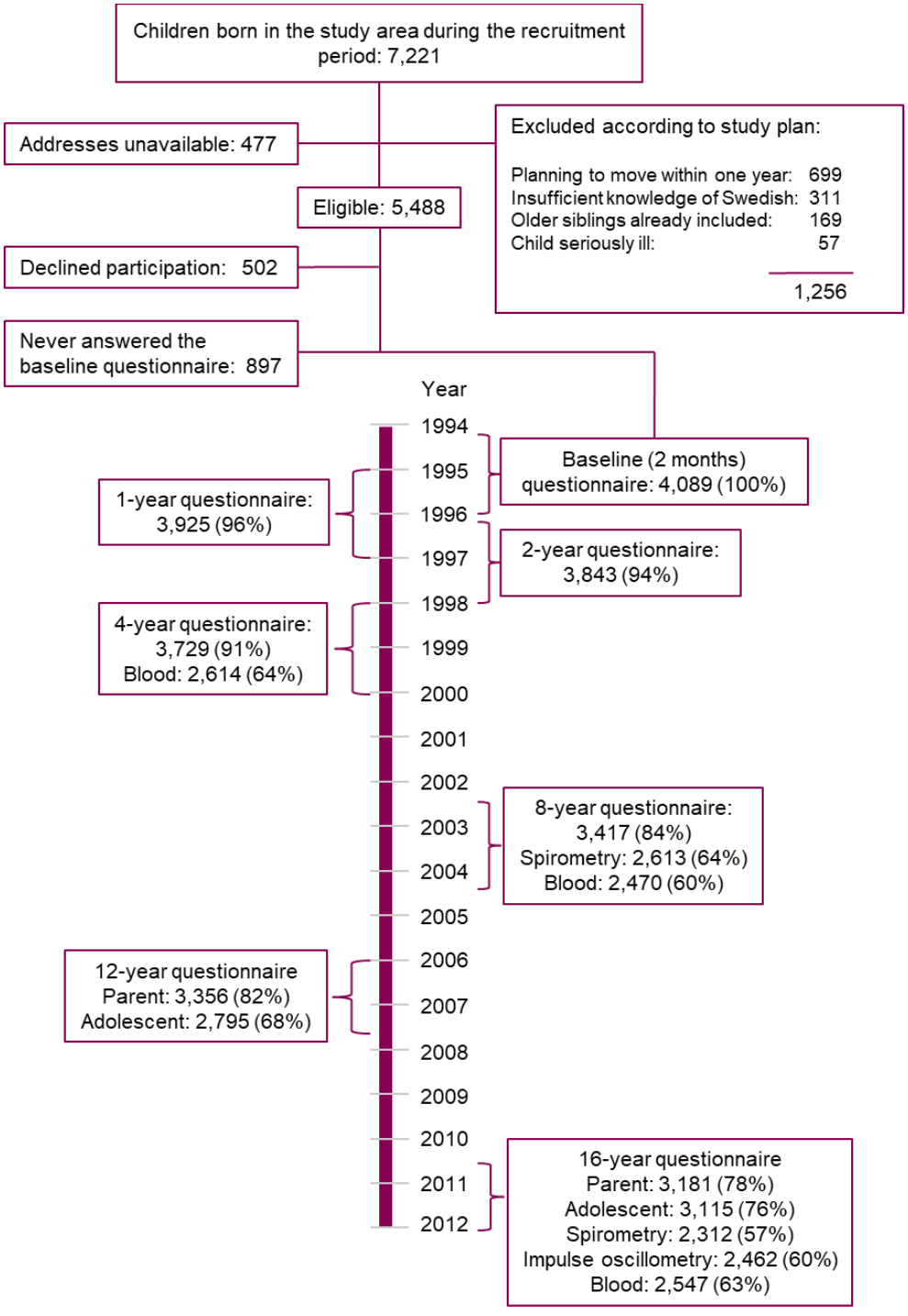

Figure 3.2. Flow chart of recruitment and follow-up of the BAMSE cohort

3.1.3 Questionnaires and clinical examinations

The baseline questionnaire covered lifestyle, socioeconomic and environmental exposures in the parents such as tobacco smoke and pet ownership, the child's health and detailed questions regarding allergic heredity. The majority of questionnaires (84%) were answered by both the mother and the father together, whereas 14% were answered by the mother only and 2% by the father only.

Follow-up questionnaires were focused on allergic disease in the child, including symptoms, medications and doctor's diagnosis of asthma, rhinitis and eczema. At 8 years of age, information on dietary intake was assessed through a food frequency questionnaire (FFQ), filled out by the parent or the parent together with the child at the clinical investigation. At 8 years, information regarding participation in organized physical activity and parental ethnicity were also collected. Additional questions regarding physical activity and sedentary behavior were included in the adolescent's questionnaire at 12 and 16 years, as well self-reported weight and height, pubertal status, tobacco use and self-perceived health. The question on self-reported height and weight was an open ended question formulated as "How tall are you (cm) and what do you weight (kg)?". At 16 years, an additional FFQ, adapted to and validated on teenagers (TeenMeal-Q), was included in the adolescent questionnaire.

All questionnaires were sent out continuously in relation to the child's date of birth, except the 12-year questionnaire which was sent out at one point in time when the children were between 11-14 years old (mean age 12.9 years). Up to 8 years of age, paper-based questionnaires were used, whereas web-based questionnaires were answered by the majority of parents and adolescents at 12 and 16 years. As far as possible, validated questions that were harmonized according to the International Study of Asthma and Allergies in Childhood (ISAAC),[125] and to the Mechanisms of the Development of Allergy (MeDALL)[126] project (for the questionnaires at age 16 years) were used.

Families were invited to the clinical investigation at 4, 8 and 16 years after answering the respective questionnaires. The median time between filling out the questionnaire and attending the clinical examination was 12.4 weeks at 4 years, 7.7 weeks at 8 years and 5.6 weeks at 16 years. The examinations were performed by trained nurses and included among others blood sampling and measurements of height, weight and lung function (described under **3.2** and **3.3**) at all ages. Blood samples were analyzed for allergic sensitization and remaining blood was stored at -80°C for subsequent analyses.

3.2 EXPOSURE AND COVARIATE ASSESSMENT

3.2.1 Maternal body mass index

Maternal body mass index (kg/m^2) was calculated from weight and height obtained through linkage to the Swedish medical birth register (MBR). The Swedish MBR was established in 1973 and covers more than 98% of all newborn children in Sweden.[127] Maternal height has been included in the register since 1983, and maternal weight in early pregnancy has been included since 1992.

The information on maternal height and weight in early pregnancy are recorded at the first visit to the antenatal care center. Between 1995-1998, most women attended their first

antenatal visit in week 9-10 of pregnancy, and 88% were registered before 13 completed weeks (i.e. first trimester).[128] The completeness of these variables varies across the years and during 1994-1996, they are available for 81-85% of the women. Evaluation of the MBR shows high validity of maternal height and weight in early pregnancy compared to medical records.[128] In addition, information on weight at admission to the delivery unit is included in the MBR, which enables calculation of gestational weight gain. However, after 1993, information on weight at delivery is only available for around 33-43% of the women[128] and was therefore not used in the current project.

Based on BMI in early pregnancy, mothers were categorized into underweight, normal weight, overweight and obesity, according to the WHO definition (**Table 3.1**).

Table 3.1. Definition of underweight, normal weight, overweight and obesity in adults

BMI category	Definition, BMI (kg/m^2)
Underweight	<18.5
Normal weight	18.5-24.9
Overweight	25-29.9
Obesity	≥30
Obesity class I	30-34.9
Obesity class II	35.39.9
Obesity class III	≥40

3.2.2 Childhood body mass index

Childhood BMI (kg/m^2) was calculated from weight and height obtained through measurements, records, registers and self-reports.

3.2.2.1 Measurements and questionnaire data in BAMSE

At 4, 8 and 16 years, weight and height were measured in the clinical examination. Weight was measured with light indoor clothes to the nearest 0.1 kg and height was measured without shoes to the nearest 0.1 cm. Height was measured twice and the mean value was used for analyses. Self-reported information on weight and height was collected at 12 years and 16 years in the adolescent questionnaire.

3.2.2.2 Record- and register-data

Information on weight and length at birth were obtained from the Swedish MBR. After birth, Swedish children's weight and height are monitored regularly at pre-defined ages in child health care and school health centers according to standard national protocols. Almost all children attend the child health care centers between the ages 0-5 years (99.5% of all registered children in Stockholm county in the year 2013).[129] In the 12-year questionnaire, parents were asked for permission to collect information on measured weight and height from the child health care and school health care records. In total, 3,151 parents provided consent and data was received from 2,597 children for up to 10 pre-defined ages from 6 months to 12 years of age. An overview of the available BMI data among children in the BAMSE cohort is presented in **Table 3.2**.

Table 3.2. Overview of the available data on body mass index among participants in the BAMSE cohort (N=4,089)

	Medical birth register	Health- and school records[1]	Clinical investigation	Self-reported	Total
Age (y)	n (%)	n (%)	n (%)	n (%)	n (%)
0	3,960 (97)				3,960 (97)
0,5		2,290 (56)			2,290 (56)
1		2,264 (55)			2,264 (55)
1,5		2,188 (54)			2,188 (54)
2		1,526 (37)			1,526 (37)
3		1,262 (31)			1,262 (31)
4		2,261 (55)	2,932 (72)		3,274 (80)
5		2,204 (54)			2,204 (54)
7		2,471 (60)			2,471 (60)
8			2,620 (64)		2,620 (64)
10		2,239 (55)			2,239 (55)
12		2,253 (55)		2,708 (66)	2,928 (72)
16			2,599 (64)	3,057 (75)	3,107 (76)

[1]Exact age at measurement was not available. Age varied with ± 2 w at 0,5 years, ± 4 w at 1 and 1.5 years, ± 6 months at 2-5 years and 6 m to + 11 m at 7, 10 and 12 years

3.2.2.3 Definitions of BMI categories

Reference values from the International Obesity Task Force[67-69] were used to categorize children into underweight/thinness, normal weight, overweight and obesity (**Studies I, III and IV**). Before 2 years of age, the gender-specific 85th percentile in the BAMSE cohort was used to define high BMI. In **Study II**, overweight was defined as the gender specific 85th percentile of BMI for pre-defined age-groups within the cohort.

3.2.3 Definitions of covariates

A description of the covariates in the individual studies together with their definitions are found in **Table 11.1** in the appendix.

3.3 DEFINITIONS OF HEALTH OUTCOMES

3.3.1 Allergic disease

Allergic disease (asthma, rhinitis and eczema) were defined based on parental questionnaire reports, except in **Study III** where we used adolescents reports at 16 years to define asthma symptoms and medication. A combination of a number of symptoms as well as medication or reported doctor's diagnosis were generally used to define allergic disease. The definition of asthma in BAMSE is somewhat more stringent compared to the definition used by the Swedish pediatric allergy section, which require three episodes of wheeze before the age of two years (one episode if IgE-mediated or in combination with eczema, food allergy or allergic heredity) and one episode at age two years and older.[130] For example, in BAMSE, asthma at one and two years was defined as at least three episodes of wheeze in the last 12 months in combination with signs of bronchial hyperreactivity without concurrent upper respiratory infection and/or treatment with inhaled corticosteroids (**Table 3.3**).

Phenotypes of asthma were defined based on onset and remission of disease (**Table 3.3**). Prevalent disease was defined as fulfilling the definition of the specific outcome at each age, and incident disease was defined as fulfilling the definition of the specific outcome at

each age, without fulfilling it at any previous age. Age-specific definitions of all allergic diseases are described in **Table 3.3**.

Table 3.3. Definitions of allergic outcomes

Variable	Definition	Study
ASTHMA		
1 year	At least 3 episodes of wheeze after 3 months of age in combination with treatment with inhaled glucocorticosteroids and/or signs of bronchial hyperreactivity without concurrent upper respiratory infection	I
2 years	At least 3 episodes of wheeze after 1 year of age in combination with treatment with inhaled glucocorticosteroids and/or signs of bronchial hyperreactivity without concurrent upper respiratory infections	I
4, 8, 12 and 16 years	At least 4 episodes of wheeze in the last 12 months or at least 1 episode of wheeze during the same time period in combination with occasional or regular treatment with inhaled glucocorticosteroids.	I
Transient asthma	Fulfilling the definition of asthma at 1, 2 and/or 4 years, but not at 8, 12 or 16 years	I, II
Late-onset asthma	Fulfilling the definition of asthma at 8, 12 and/or 16 years, but not at 1, 2 or 4 years	I[1], II
Persistent asthma	Fulfilling the definition of asthma at 1, 2 and/or 4 years as well as at 8, 12 and/or 16 years	I, II
RHINITIS		
1 year	Symptoms from eyes or nose after exposure to furred pets or pollen or a doctor's diagnosis of allergic rhinitis after 3 months of age	I
2, 4 and 8 years	Symptoms from eyes or nose (sneezing, a runny or blocked nose or itchy, red and watery eyes) after exposure to furred pets or pollen or a doctor's diagnosis of allergic rhinitis after the previous questionnaire	I
12 years	Symptoms from eyes or nose (sneezing, a runny or blocked nose or itchy, red and watery eyes) after exposure to furred pets or pollen in the last 12 months or a doctor's diagnosis of allergic rhinitis after 10 years of age	I
16 years	Symptoms from eyes or nose (sneezing, a runny or blocked nose or itchy, red and watery eyes) after exposure to furred pets or pollen in the last 12 months or a doctor's diagnosis of allergic rhinitis after 12 years of age	I
ECZEMA		
1 and 2 years	Dry skin in combination with itchy rash for at least 2 weeks at typical location (face or arm or leg extension surfaces, or arm or leg flexures, or wrist or ankle flexures) or doctor's diagnosis of eczema in the last 12 months.	I
4 years	Dry skin in combination with itchy rash for at least 2 weeks during the last 12 months at typical location (face or arm or leg extension surfaces, or arm or leg flexures, or wrist or ankle flexures) or doctor's diagnosis of eczema after 2 years of age.	I
8 years	Dry skin in combination with itchy rash for at least 2 weeks during the last 12 months at typical location (face or arm or leg flexures, or wrists or ankles, or neck) or doctor's diagnosis of eczema after 7 years of age.	I

12 years	Dry skin in combination with itchy rash for at least 2 weeks during the last 12 months at typical location (arm or leg flexures, or wrists or ankles, or neck) or doctor's diagnosis of eczema after 10 years of age.	I
16 years	Dry skin in combination with itchy rash for at least 2 weeks during the last 12 months at typical location (arm or leg flexures, or wrists or ankles, or neck) or doctor's diagnosis of eczema after 12 years of age.	I

[1]Termed school-age onset asthma in Study I

3.3.2 IgE-Sensitization

IgE antibodies in blood were analyzed with ImmunoCAP (Thermo Fisher Specific, Uppsala, Sweden) at 4, 8 and 16 years. Sensitization to inhalant allergen was defined as a specific IgE ≥0.35 kU/L (technical cut-off) against cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus* (house dust mite) or *Cladosporium* (mold).

3.3.3 Lung function

Lung function was measured by spirometry at 8 and 16 years and by IOS at 16 years.[131] Spirometry was measured using a 2200 Pulmonary Function Laboratory (Sensormedics, Anaheim, CA) in 2,613 participants 8 years and a Jaeger MasterScreen-IOS system (Carefusion Technologies, San Diego, CA) in 2,312 participants at 16 years. Participants performed repeated maximal expiratory flow volume (MEFV) measurements. The curves were manually inspected and evaluated according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) criteria.[132] MEFV curves were considered acceptable if they passed visual inspection, were coded as maximal effort by the test leader, and the two highest FEV_1 and FVC readings were reproducible according to the ATS/ERS criteria. FEV_1 and FVC were analyzed using Global Lung function Initiative z-scores which accounts for sex and height.[54] FEV_1/FVC ratios were calculated and expressed as percentages.

The IOS measurements were performed using a Jaeger MasterScreen-IOS system (Carefusion Technologies, San Diego, CA) in 2462 participants at 16 years. Participants were instructed to tightly seal their lips around the mouthpiece while performing tidal breathing. Each participant performed at least two measurements, and after visual quality inspection, the mean value of resistance between 5 Hz and 20 Hz (R_{5-20}) and the square root of the area under the reactance curve ($AX^{0.5}$) were used for analyses.

3.3.4 Fractional exhaled nitric oxide

Fractional exhaled nitric oxide (FeNO) was analyzed as a measure of eosinophilic airway inflammation. FeNO (expressed as parts per billion [ppb]) was measured at 16 years using an online chemiluminescent (CLD88) analyzer (ECO Medics AG, Duernten, Switzerland) at an expiratory flow of 50 mL/s (FeNO50) according to ATS/ERS guidelines.[133]

3.3.5 Biomarkers of inflammation

Peripheral blood samples were analyzed for eosinophil and neutrophil cell count at 16 years (10^9 cells/L) as biomarkers for systemic inflammation. These analyses were performed at the Department of Clinical Chemistry, Karolinska University Hospital, Stockholm, Sweden.

3.4 STUDY POPULATIONS AND STUDY DESIGN

All studies in this thesis have an observational study design (i.e. the exposure status is outside the control of the researcher). **Studies I-III** are longitudinal (i.e. the outcomes and/or the exposures are assessed repeatedly over time). **Study IV** is a validation study, evaluating self-reported height, weight and BMI in relation to measured values at one point in time. Depending on the specific study aim and inclusion criteria, each study consist of different study populations.

In **Study I**, children with available information on maternal BMI in early pregnancy and information on an outcome from at least three follow-up questionnaires were included. In total, 3,294 children were included in the analyses on allergic disease outcomes and 2,850 children were included in the analyses on sensitization to inhalant allergens. When analyzing maternal BMI as a continuous variable, underweight children (n=117) were excluded, since there were indications of a U-shaped association between maternal BMI and asthma.

In **Study II**, children with available information on asthma phenotypes and at least one BMI measurement from birth to 16 years were included, in total 2,818 children.

In **Study III**, children with information on BMI and spirometry at 8 or 16 years or on IOS and BMI status at 16 years were included. In total, 2,889 children were included in the study population, however the number with available data varied for the different outcomes. Most children were included in the longitudinal analyses (n=2,293), where information on lung function was required from one time point only. Fewer children were included in analyses on change in overweight status between 8 and 16 years (n=1,560), since this analyses required information on BMI status at both 8 and 16 years.

In **Study IV**, children with information on measured and web-based self-reported weight and height at 16 years with no more than 8 weeks between the reported and measured values were included. This resulted in a study population of 1,698 adolescents. In the analysis of potential prediction factors for differences between self-reported and measured BMI, complete information on all tested variables were required, and resulted in a subpopulation of 1,337 adolescents.

3.5 STATISTICAL ANALYSES

3.5.1 Main statistical methods

The main statistical methods for association analyses in the thesis were logistic regression for dichotomous outcomes and linear regression for continuous outcomes. The results are presented as odds ratios (ORs) for logistic regression and as β-coefficients for linear regression, together with the 95% confidence intervals (CIs).

For longitudinal outcomes, generalized estimating equations (GEE) were applied to the logistic regression analyses (association between maternal BMI and allergic disease in **Study I** and the risk of overweight in relation to asthma phenotypes in **Study II**) and mixed effect models were applied to the linear regression analyses (association between BMI status at 8 years and lung function up to 16 years in **Study III**). GEE and mixed effect models take into account that repeated measurements on the same individual are correlated.

Interaction terms between the exposures and the time variables were incorporated into the models to estimate age-specific associations and changes in the outcome over time. Multinomial logistic regression was used when the outcomes consisted of more than two categories (e.g. asthma phenotypes in **Study I**).

Quantile regression was used to investigate associations at different percentiles of the outcome. Quantile regression can be used to analyze associations at any percentile of the dependent variable, thus allowing for varying effects over the distribution of the outcome. In **Study II**, quantile regression was used to analyze BMI at the 85^{th} percentile as the main analysis (considered as high BMI/overweight) and at the median as a sensitivity analysis. To capture the characteristic shape of the BMI growth curve, restricted cubic splines with five knots were applied. Quantile regression was also used in **Study III** to analyze associations between BMI status and IOS and inflammatory markers on the median due to non-normally distributed data.

In **Study IV** we used one-sample t-tests to compare self-reported and measured height weight and BMI at 16 years. Agreement was evaluated by Pearson correlation coefficients, and a Bland-Altman plot was used to visually investigate absolute agreement between self-reported and measured BMI. Prediction factors for validity of self-reported BMI were identified through backward selection, using a p-value of <0.2 from the log-likelihood test to determine the model.

3.5.2 Covariate selection

Potential confounding factors were identified from *a priori* knowledge/previous literature (**Study I** and **II**), as well on their association with asthma phenotypes (**Study II**). Factors considered as potential mediators were additionally identified and evaluated by their impact on the observed associations. Specifically, overweight in the offspring was considered as a potential mediator between maternal BMI and offspring asthma in **Study I**, since maternal BMI is a risk factor for offspring overweight (observed OR in **Study I**: 2.42, 95% CI: 2.04-2.86 at 16 years) and childhood overweight previously have been associated with asthma (discussed in section **1.5**). In order to investigate the impact of overweight in the offspring on the observed associations between maternal BMI and asthma, we performed separate analyses adjusted for childhood overweight. Moreover, we performed a causal inference test at 16 years to investigate whether the association between maternal BMI and asthma in the offspring was explained by overweight in the offspring.

In **Study III**, the final covariate model was selected based on testing whether each potential confounder affected the observed estimates by ≥ 10% in the main analyses. The exception was the adjustment for adolescent smoking when analyzing FeNO, which is known to affect FeNO levels.

Effect modification was evaluated by the Wald test using an interaction term between the exposure and the potential effect modifier. Analyses were stratified by gender in **Studies II-IV** and by BMI status in **Study IV**.

All analyzes were performed using the statistical software Stata (StataCorp, College Station LP, TX, USA). A p-value of <0.05 was considered statistical significant.

3.6 ETHICAL CONSIDERATIONS

The BAMSE study (and each follow-up) was approved by the Ethics committee of Karolinska Institutet, Stockholm, Sweden. The parents of all participants provided informed consent and were informed that they were free to withdraw from the study at any stage.

4 RESULTS

4.1 MATERNAL BMI AND ALLERGIC DISEASE IN THE OFFSPRING

4.1.1 Descriptive results on allergic disease and maternal BMI

The prevalences of asthma, rhinitis and eczema from ages 1-16 years (**Study I)** are presented in **Figure 4.1**. The prevalence of asthma averaged at around 6-7% throughout the follow-ups, whereas the prevalence of rhinitis increased with age to around 25% at 16 years. Eczema was most prevalent in early childhood, but decreased from 20% at 4 years to around 9% at 16 years.

Among children with available information on asthma phenotypes (n=2,436), 143 (5.9%) were classified as having early transient asthma, 225 (9.2%) as having school-age onset asthma and 155 (6.4%) as having persistent asthma. Sensitization to inhalant allergens was present among 356 (15.7%) of the children at 4 years, 554 (26.3%) at 8 years and 939 (42.9%) at 16 years.

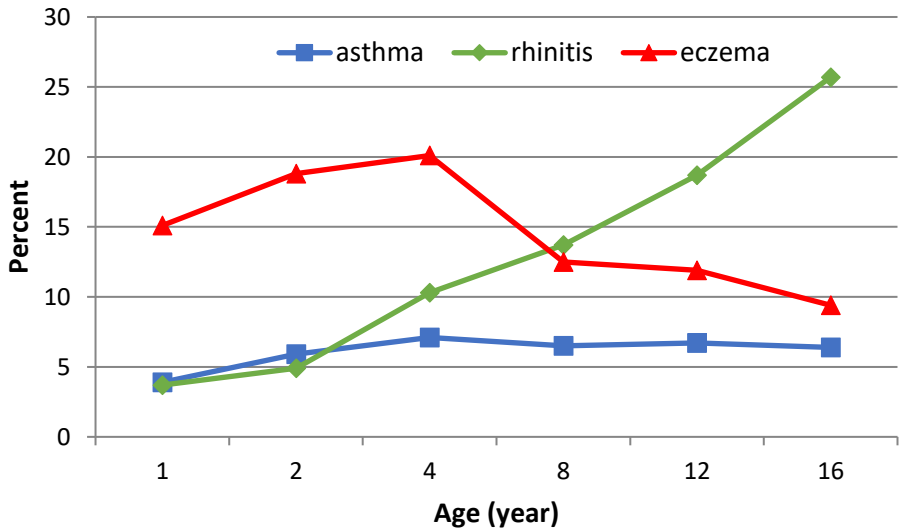

Figure 4.1 Prevalence of allergic disease among children included in **Study I** (n=3,294)

The mean maternal BMI in **Study I** was 22.9 kg/m^2 (range 14.7-44.4 kg/m^2 median 22.3 kg/m^2). Maternal overweight and obesity was present in 535 (16.2%) and 126 (3.8%) of the participants, respectively, whereas 117 (3.6%) of the mothers were underweight (**Figure 4.2**).

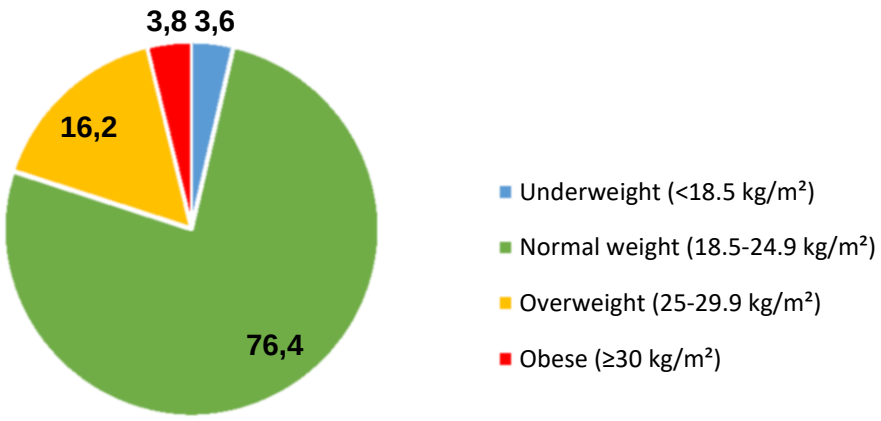

Figure 4.2 Categories of maternal BMI in early pregnancy (%) in **Study I** (n=3,294)

4.1.2 Associations between maternal BMI and allergic disease

In analyses of BMI as a continuous variable, increasing maternal BMI in early pregnancy was associated with asthma in the offspring among mothers with a BMI ≥ 18.5 kg/m^2 (overall OR up to 16 years per 5 kg/m^2: 1.23, 95% CI: 1.07-1.40 for prevalent asthma and 1.17, 95% CI: 1.03-1.32 for incident asthma). The association was not statistically different between girls and boys, or between children with and without sensitization to inhalant allergens or allergic heredity. Age-specific analyses of prevalent asthma showed that the association reached statistical significance only at 2 years of age (OR per 5 kg/m^2: 1.42, 95% CI: 1.17-1.73), although increased ORs were observed also at the other ages (**Figure 4.3**). No association was observed between maternal BMI in early pregnancy and rhinitis (overall OR per 5 kg/m^2: 1.07, 95% CI: 0.96-1.19), eczema (overall OR per 5 kg/m^2: 1.03, 95% CI: 0.93-1.14) or allergic sensitization (overall OR per 5 kg/m^2: 1.05, 95% CI: 0.93-1.19) in the offspring up to 16 years.

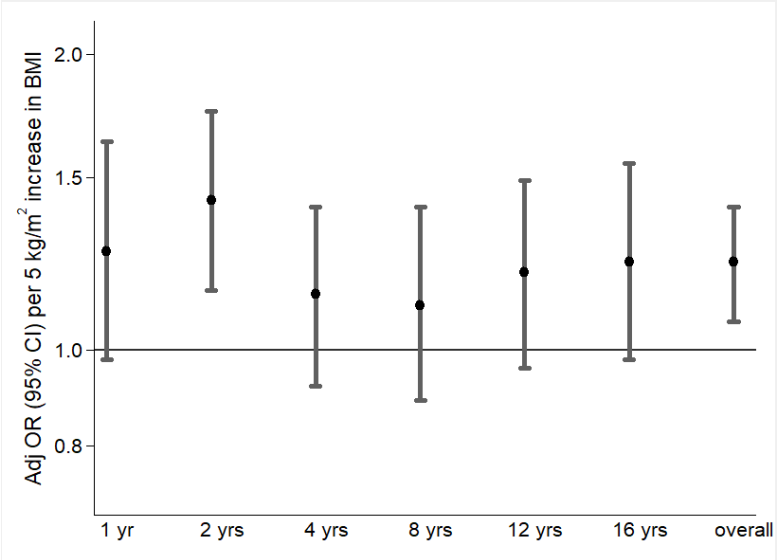

Figure 4.3. Associations between maternal BMI in early pregnancy and prevalent asthma in the offspring at 1-16 years among children with maternal BMI ≥ 18.5 kg/m^2 (n=3,177).

Analyses of asthma phenotypes showed that maternal BMI was most strongly associated with persistent asthma (OR per 5 kg/m^2: 1.31, 95% CI: 1.03-1.67). The corresponding OR for school-age onset asthma was 1.22, 95% CI: 0.98-1.52, whereas no association was observed with early transient asthma (OR per 5 kg/m^2: 1.02, 95% CI: 0.77-1.36).

Maternal BMI in early pregnancy was subsequently categorized into underweight, normal weight (referent), overweight and obesity and analyzed in relation to overall risk of prevalent asthma in the offspring up to 16 years. The results showed that maternal obesity was associated with asthma (OR: 1.53, 95% CI: 1.04-2.26), whereas there was no significant association among overweight (corresponding OR: 1.14, 95% CI: 0.90-1.45) or underweight (corresponding OR: 1.29: 0.83-2.01) mothers.

The overall association between maternal BMI and asthma up to 16 years was somewhat attenuated and became non-significant when adjusting for overweight in the child at each age (OR: 1.15, 95% CI: 0.99-1.33, compared to 1.23, 95% CI: 1.07-1.40). The associations were mainly attenuated at ages 8 and 12 years, whereas the estimates were essentially unaffected at the early ages. The association between maternal obesity and asthma up to 16 years was further attenuated and became non-significant when adjusting for overweight in the offspring at each age (OR: 1.24, 95% CI: 0.80-1.94, compared to 1.53, 95% CI: 1.04-2.26), whereas the association between maternal BMI and persistent asthma was only slightly changed when adjusting for overweight at 16 years (OR 1.29, 95% CI: 0.98-1.70, compared to 1.31, 1.03-1.67). A causal inference test additionally suggested that childhood overweight may partly mediate the observed association between maternal BMI and childhood asthma at 16 years.

4.2 CHILDHOOD OVERWEIGHT AND ASTHMA

4.2.1 BMI development throughout childhood

The available BMI data and estimated percentiles of BMI development for girls and boys included in **Study II** are shown in **Figure 4.4**. The observed BMI development followed the same pattern as international surveys[67], with a rapid increase in BMI during the first year of life. After around one year of age, BMI subsequently decreased until around six years of age at the median (commonly referred to as the adiposity rebound). After approximately six years, BMI increased with increasing age throughout the rest of childhood.

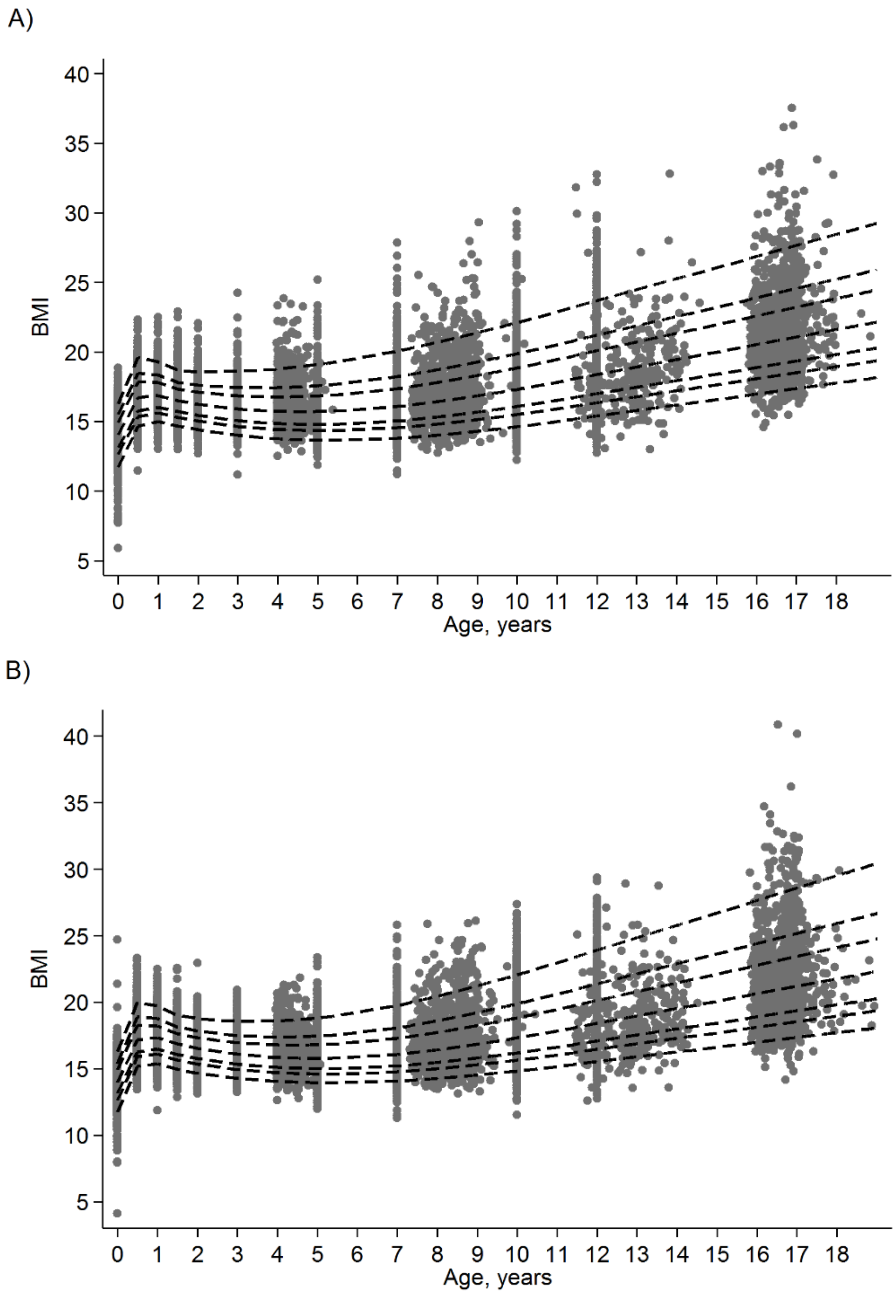

Figure 4.4. Body mass index (BMI, kg/m^2) measurments and estimated percentiles (5th, 15th, 25th, 50th, 75th, 85th and 95th) throughout childhood among A) girls and B) boys. BMI development was modeled through quantile regression using splines with 5 knots. At ages 4, 8, 12 and 16 years, BMI from clinical investigations and questionnaires was used. At the other ages, register and health record data without exact age at each measurement was used.

4.2.2 Childhood overweight in relation to asthma

The 85th percentile BMI in relation to asthma phenotypes are shown in **Figure 4.5**. Among girls, BMI was highest among children with persistent asthma throughout childhood, whereas children without asthma had the lowest BMI. Girls with transient and late-onset asthma had relatively similar BMI development; in general slightly higher compared to girls without asthma, although lower compared to girls with persistent asthma. The difference in BMI between girls with persistent asthma and the other asthma phenotypes increased with age. At 16 years, the 85th percentile BMI was 23.6 kg/m^2 among girls without asthma, compared to 27.4 kg/m^2 among girls with persistent asthma (corresponding to a 10.6 kg difference in weight for a female who is 167 cm tall). In boys, there were only small differences in BMI between children with or without asthma.

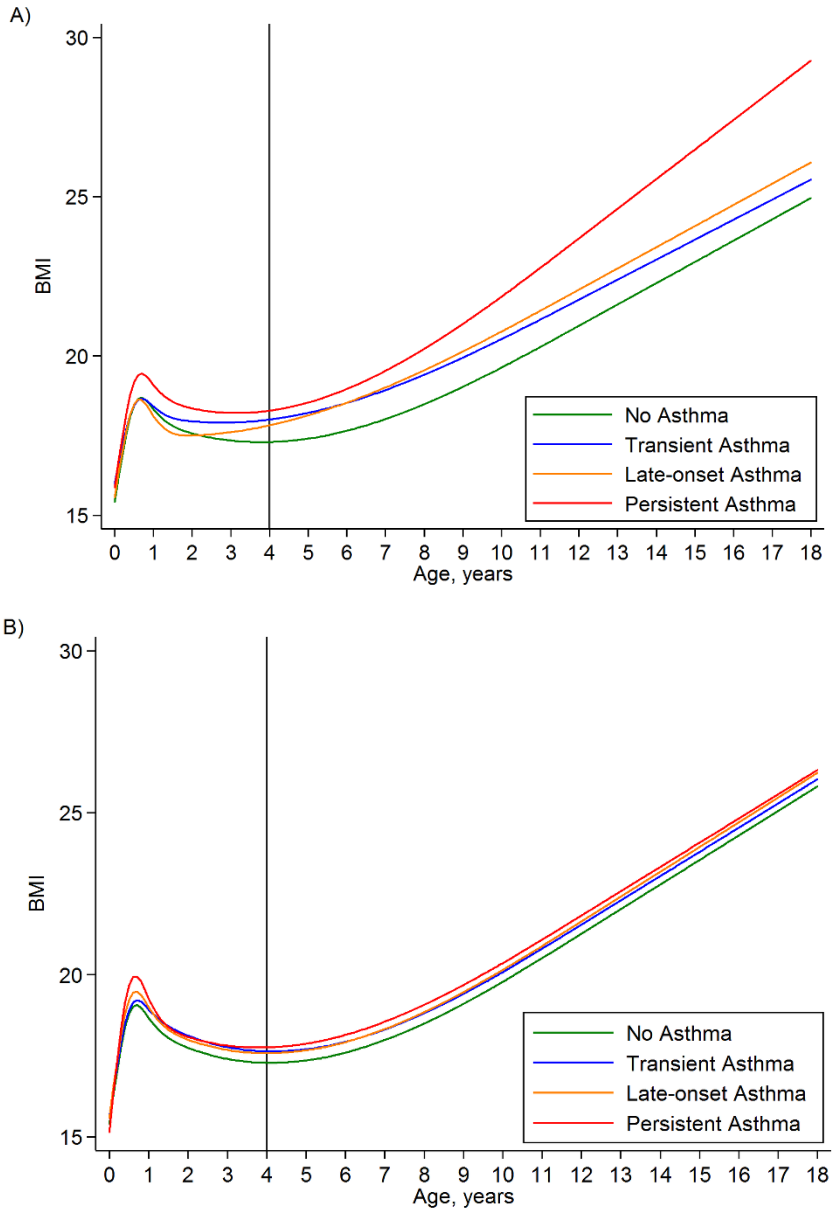

Figure 4.5. The 85th percentile body mass index (BMI, kg/m^2) throughout childhood in relation to asthma phenotype among A) girls and B) boys. BMI development was modeled through quantile regression using splines with 5 knots.

The associations between asthma phenotypes and overweight are shown in **Figure 4.6**. Among girls, transient asthma was associated with overweight in the age group 4-7.9 years, although non-significant increased odds ratios were also seen in some of the other age groups (**Figure 4.6 A**). Late-onset asthma was associated with a trend towards overweight in adolescence, whereas no association was observed in early childhood (**Figure 4.6 B**). Persistent asthma was significantly associated with overweight at all age groups from two years and onwards (**Figure 4.6 C**). All asthma phenotypes were associated with a tendency towards increased risk of overweight at birth.

Among boys (**Figure 4.6 D-F**), the associations between asthma phenotypes and overweight were less consistent. A statistically significant association was observed between persistent asthma and overweight in the age-group 6 months-1.9 years, however increased but non-significant ORs were observed also at other ages for all three asthma phenotypes.

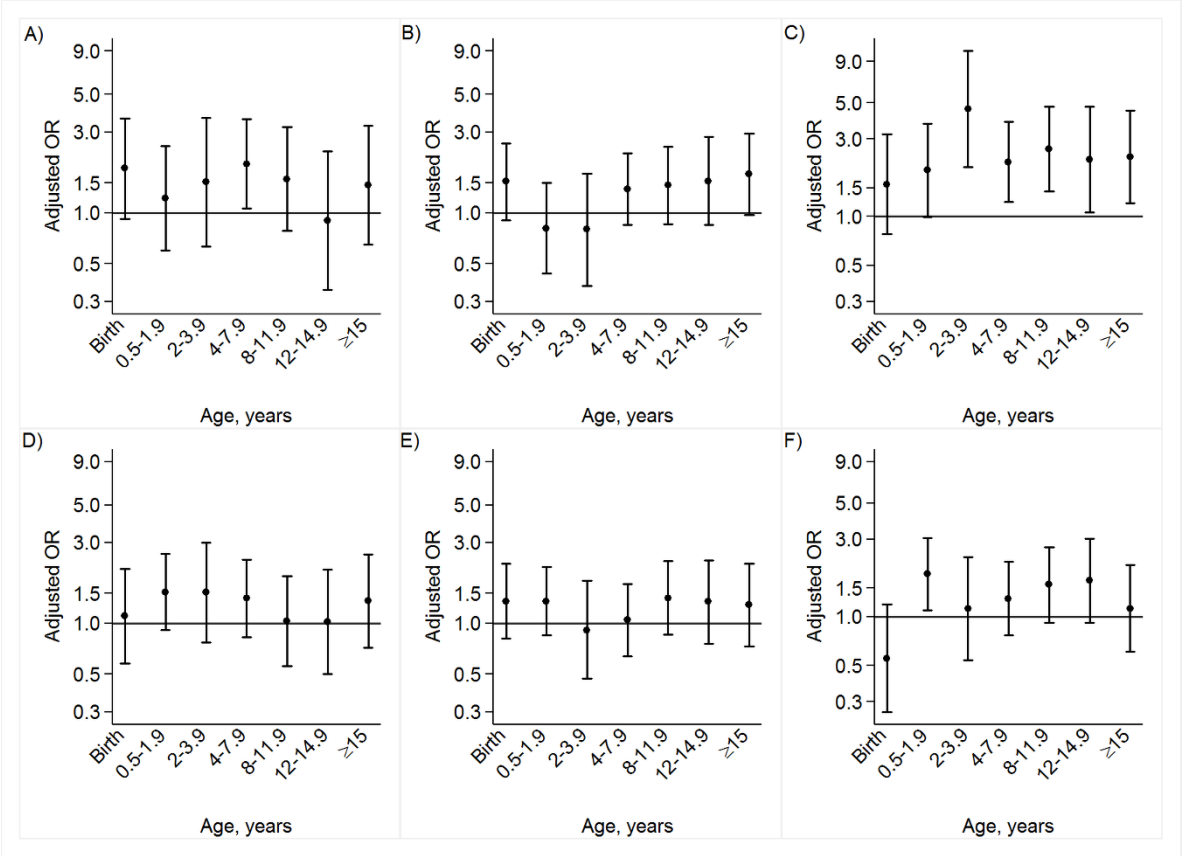

Figure 4.6. Adjusted odds ratio of overweight (body mass index [BMI, kg/m^2] above the 85th percentile [as calculated in the non-asthmatics]) for A) Transient asthma in girls, B) Late-onset asthma in girls, C) Persistent asthma in girls, D) Transient asthma in boys, E) Late-onset asthma in boys, F) Persistent asthma in boys. Analyzes were performed using generalized estimating equation models adjusted for allergic heredity, maternal smoking during pregnancy and/or in infancy, parental occupation, maternal BMI in early pregnancy, gestational age and breastfeeding.

4.3 CHILDHOOD OVERWEIGHT AND LUNG FUNCTION

4.3.1 Descriptive results on lung function at ages 8 and 16 years

Summary statistics of lung function at 8 and 16 years, as well as inflammatory markers at 16 years are shown in **Table 4.1**. Between 8 and 16 years, FEV_1 increased from 1,732 ml to 2,481 ml in girls and from 1,821 ml to 4,491 ml in boys. In contrast, z-scores of FEV_1 decreased from 0.47 to -0.04 in girls and from 0.36 to -0.04 in boys, indicating an overall reduction in FEV_1 trajectory in this dataset compared to the reference values. A similar pattern was observed for FVC with increased absolute values (ml) but decreased values relative to the reference (z-scores).

Table 4.1. Descriptive statistics of lung function and inflammatory markers among 2,889 children in the 8 and 16-year examination

	8 years				16 years			
	Girls		Boys		Girls		Boys	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
FEV_1 (ml)	920	1732.1 (256.6)	912	1820.5 (279.9)	1121	3480.5 (445.6)	933	4491.4 (650.2)
FVC (ml)	920	1987.7 (294.1)	912	2144.5 (339.7)	1121	4033.2 (522.8)	933	5380.4 (777.1)
FEV_1/FVC (%)	920	87.3 (5.3)	912	85.2 (5.9)	1121	86.5 (6.1)	933	83.8 (6.6)
FEV_1 (z-score)	919	0.47 (0.94)	912	0.36 (0.93)	1119	-0.04 (0.91)	933	-0.04 (0.97)
FVC (z-score)	920	0.62 (0.90)	912	0.56 (0.91)	1119	0.15 (0.91)	933	0.15 (0.96)
					N	Median (IQR)	N	Median
R_5-R_{20} ($Pa \cdot L^{-1} \cdot s$)					1260	20.0 (55.0)	1191	15.0 (45.0)
$AX^{0.5}$ $(Pa \cdot L^{-1})^{0.5}$					1260	16.4 (5.8)	1190	12.6 (5.0)
FeNO (ppb)					1044	14.0 (10.1)	1015	17.5 (13.8)
Blood eosinophils (10^9 cells/L)					1225	0.1 (0.1)	1168	0.2 (0.1)
Blood neutrophils (10^9 cells/L)					1225	3.5 (1.6)	1168	3.0 (1.4)

4.3.2 Association between BMI status and lung function

BMI status (underweight, normal weight [referent], overweight and obesity) were analyzed in relation to lung function at 8 and 16 years. Overweight and obesity at 8 years were both associated with higher FVC at 8 and 16 years in girls and boys (**Figure 4.7**). Overweight was further associated with higher FEV_1 in boys at both ages and in girls at 16 years, and obesity was associated with higher FEV_1 in girls at both ages and in boys at 8 years. However, overweight and obesity were associated with lower FEV_1/FVC in girls (-2.0%, 95% CI: -4.0;-0.0 for obesity) and boys (-3.8%, 95% CI: -6.3;-1.2 for obesity) at 16 years, whereas the association did not reach statistical significance for obesity at 8 years. Thinness was associated with lower FVC and FEV_1, but there were no clear association between thinness and FEV_1/FVC (**Figure 4.7**). Cross-sectional analyses at 16 years showed that there was no statistically significant difference in the association between overweight (including obesity) and FEV_1/FVC among children with or without wheeze.

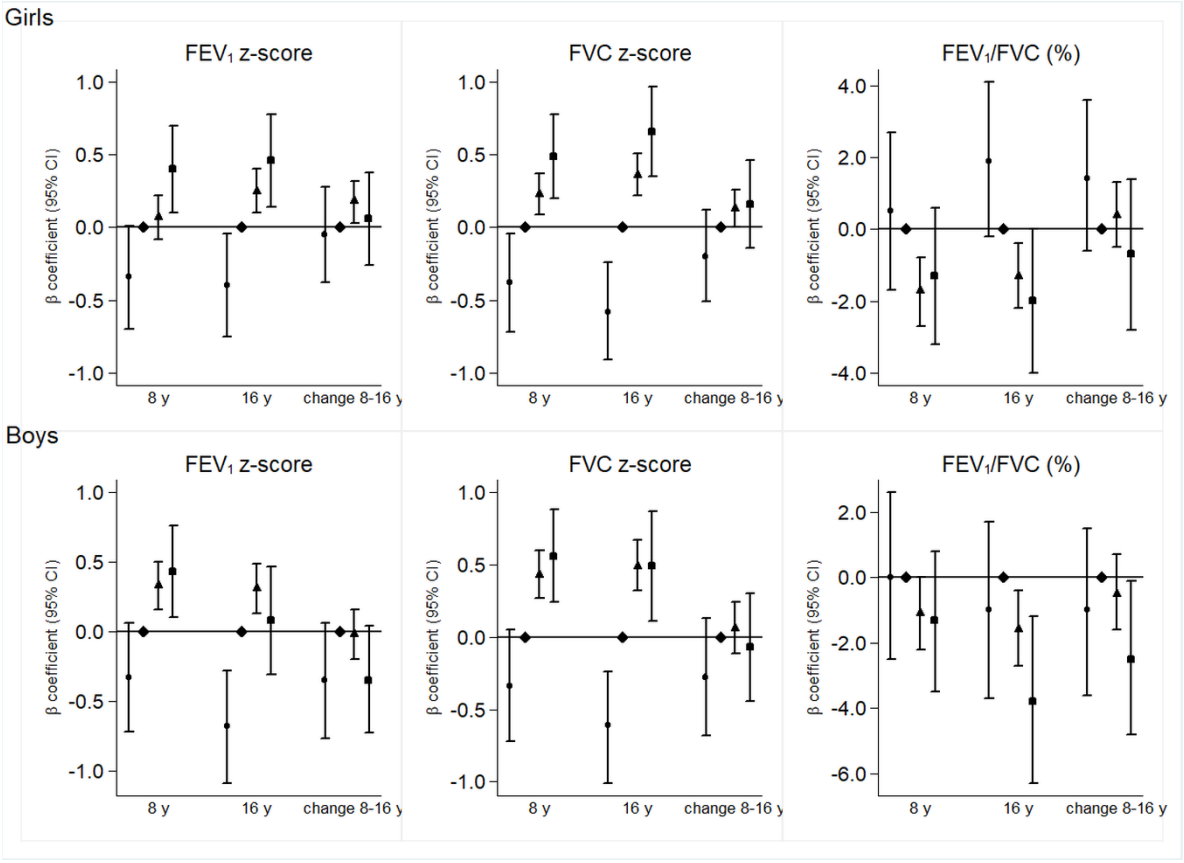

Figure 4.7. Association between BMI status (thinness [●], normal weight [♦, referent], overweight [▲] and obesity [■]) at 8 years and lung function (FEV_1, [z-scores] FVC [z-scores] and FEV_1/FVC [%]) up to 16 years. β-coefficients and 95% confidence intervals (CI) are estimated using mixed effect models (n=1,158 girls with 1,827 observations and n=1,135 boys with 1,689 observations).

In particular, persistent overweight at both 8 and 16 years was associated with reduced FEV_1/FVC at 16 years (-2.8%, 95% CI: -4.1;-1.2 in boys and -2.7%, 95% CI: -4.4;-1.1 in girls). Overweight at 8 years only (transient overweight) or at 16 years only (late-onset overweight) was associated with a tendency towards lower FEV_1/FVC at 16 years, although the estimates did not reach statistical significance (**Figure 4.8).** Analyses of change in lung function between 8 and 16 years in relation to BMI status at 8 years showed that overweight, but not obesity, was associated with somewhat increased FEV_1 and FVC in girls, but not boys. Obesity, but not overweight was associated with decreased FEV_1/FVC between 8 and 16 years in boys, but not in girls.

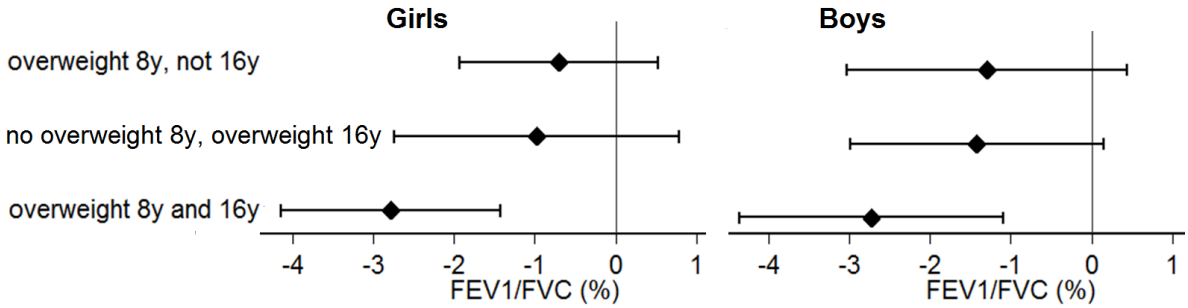

Figure 4.8. Association between overweight (includes overweight and obesity) status between 8 and 16 years and FEV_1/FVC at 16 years (n=840 girls and 720 boys). The point estimates represent mean difference in FEV_1/FVC compared to the reference group (children with normal weight at 8 and 16 years) calculated by linear regression adjusted for age and height. Children with thinness are excluded.

Analyses of peripheral airway function at 16 years using the IOS technique (**Table 4.2**) showed that overweight and obesity at 16 years were both associated with higher frequency dependence of resistance (R_{5-20}) and larger area under the reactance curve ($AX^{0.5}$). In contrast, thinness was associated with lower R_{5-20}. Analyses of BMI status at 8 years in relation to peripheral airway function at 16 years resulted in somewhat weaker associations, although the trend was similar as compared to BMI status at 16 years.

Table 4.2. Cross-sectional associations between body mass index (BMI) status and impulse oscillometry at 16 years (n= 1,258 girls and 1,191 boys)

	R_{5-20} ($Pa \cdot L^{-1} \cdot s$)					
	Girls			**Boys**		
BMI category	β^1	95% CI	p-value	β^1	95% CI	p-value
Thinness	-15.9	-25.8;-6.0	0.002	-12.9	-21.9;-3.9	0.005
Normal weight	Referent			Referent		
Overweight	32.7	24.5;40.9	<0.001	22.3	16.1;28.5	<0.001
Obesity	56.8	38.3;75.4	<0.001	47.8	34.9;60.7	<0.001
	$AX^{0.5}$ $(Pa \cdot L^{-1})^{0.5}$					
	Girls			**Boys**		
	β^1	95% CI	p-value	β^1	95% CI	p-value
Thinness	-0.4	-1.4;0.6	0.42	-0.3	-1.2;0.7	0.58
Normal weight	Referent			Referent		
Overweight	3.1	2.3;3.9	<0.001	1.6	0.9;2.2	<0.001
Obesity	3.1	1.3;4.9	0.001	3.5	2.2;4.8	<0.001

[1]Represent median difference in outcome compared to the reference group, calculated by linear regression on the median adjusted for age and height

Cross-sectional analyses on biomarkers of local and systemic inflammation at 16 years showed no association between BMI status and FeNO. In contrast, increased blood neutrophil cell count were observed in overweight ($0.3*10^9$ cells/L, 95% CI: 0.03;0.57) and obese ($0.9*10^9$ cells/L, 95% CI: 0.24;1.56) girls, whereas no significant association was found in boys. In addition, blood eosinophil cell count were somewhat elevated in obese, but not in overweight girls, while there were no association between BMI status and eosinophils in boys.

4.4 VALIDITY OF SELF-REPORTED HEIGHT, WEIGHT AND BMI

A summary of mean self-reported and measured height, weight and corresponding BMI among adolescents included in **Study IV** are shown in **Table 4.3**. Overall, height was overreported by on average 0.5 cm and weight was underreported by on average 1.1 kg, leading to an underestimation of BMI by 0.5 kg/m^2. Boys overreported height somewhat more than girls (0.6 cm vs 0.4 cm) and girls underreported weight somewhat more than boys (-1.5 kg vs -0.7 kg). The Pearson correlation coefficients comparing self-reported and measured values were 0.98 for height, 0.96 for weight and 0.94 for BMI. Similar coefficients were observed among boys and girls.

Table 4.3. Summary of self-reported and measured height, weight and BMI by gender

Anthropometrics	Self-reported, mean (SD)	Measured, mean (SD)	Difference, mean (SD)	p-value
Total (N=1,698)				
Height (cm)	173.6 (9.0)	173.1 (9.0)	0.5 (1.8)	<0.001
Weight (kg)	63.9 (11.0)	65.0 (11.5)	–1.1 (2.9)	<0.001
BMI (kg/m^2)	21.1 (2.8)	21.6 (3.1)	–0.5 (1.1)	<0.001
Girls (n=889)				
Height (cm)	167.9 (6.1)	167.4 (6.2)	0.4[a] (1.5)	<0.001
Weight (kg)	59.0 (8.7)	60.5 (9.2)	–1.5[b] (2.5)	<0.001
BMI (kg/m^2)	20.9 (2.8)	21.6 (3.0)	–0.6[b] (1.0)	<0.001
Boys (n=809)				
Height (cm)	179.9 (7.2)	179.3 (7.2)	0.6 (2.1)	<0.001
Weight (kg)	69.2 (10.7)	69.9 (11.7)	–0.7 (3.2)	<0.001
BMI (kg/m^2)	21.3 (2.8)	21.7 (3.2)	–0.4 (1.1)	<0.001

[a] Significantly different from boys (p=.02)

[b] Significantly different from boys (p <.001)

BMI was underreported to a higher extent among overweight (1.2 kg/m^2) and obese (2.0 kg/m^2), compared to normal weight adolescents (0.4 kg/m^2). In contrast, underweight adolescents overreported BMI by 0.3 kg/m^2. In total 86.4% of adolescents were classified into the correct BMI category (underweight, normal weight, overweight or obese) using self-reported information on weight and height. The proportion of correctly classified were highest among normal weight adolescents (93.7%), followed by underweight (71.1%), overweight (60.2%) and obese (45.5%) adolescents. **Figure 4.9** shows a Bland-Altman plot illustrating differences between self-reported and measured BMI in relation to measured BMI. Higher measured BMI was associated with increasing differences between self-reported and measured BMI (more underreporting).

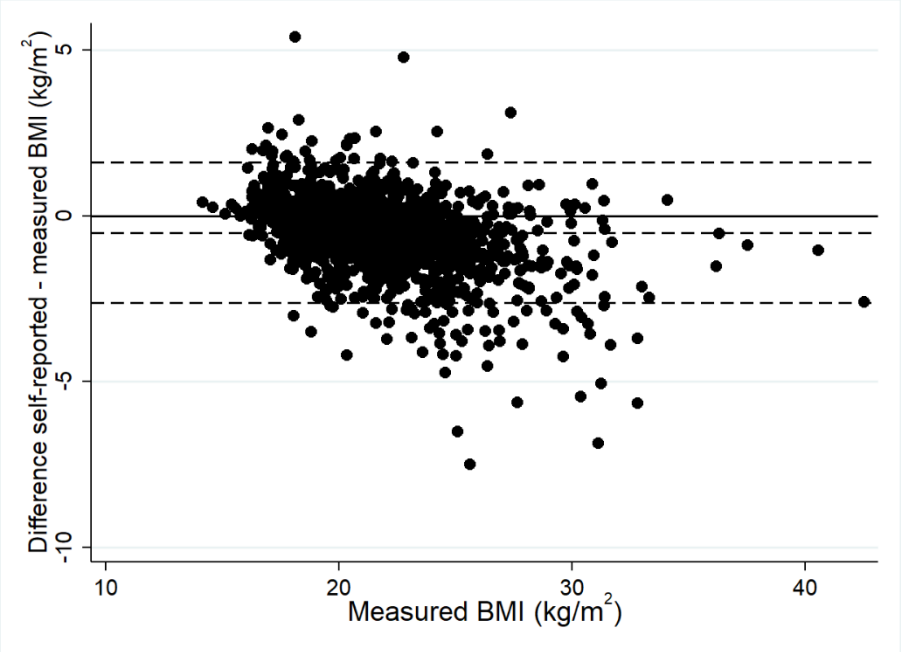

Figure 4.9. Difference between self-reported and measured BMI in relation to measured BMI. The solid line represent no difference between self-reported and measured BMI. The dashed lines represents mean difference and ± 2 SD

There was no significant association between age, parental ethnicity, parental socioeconomic status, physical activity, sedentary time, pubertal status, sleep duration, fruit and vegetable intake, tobacco use or self-perceived health and differences between self-reported and measured BMI. Only gender (girls underreported 0.4 kg/m^2 more than boys in the in the mutual adjusted analysis) and BMI status (overweight underreported 0.8 kg/m^2 more and obese underreported 1.5 kg/m^2 more, compared to normal weight adolescents in the mutual adjusted analysis) were significantly associated with accuracy of self-reported BMI.

5 DISCUSSION

5.1 MAIN FINDINGS AND INTERPRETATIONS

5.1.1 Maternal BMI and allergic disease in the offspring

In **Study I**, we observed that maternal BMI in early pregnancy increased the risk of asthma, but not rhinitis, eczema or allergic sensitization in the offspring up to age 16 years. The risk was strongest for persistent asthma, whereas no association was found for transient asthma. Categorization of maternal BMI showed that maternal obesity, but not overweight, significantly increased the risk of asthma in the offspring. Overweight in the offspring was found to, at least partly, mediate the association between maternal BMI and childhood asthma.

At the time **Study I** was initiated, a limited number of studies had investigated the potential role of maternal BMI before pregnancy or in early pregnancy in relation to risk of allergic disease in the offspring. Overall, an association between maternal BMI and asthma symptoms, diagnosis and medication up to preschool age or early school age had been observed[86-88, 90, 91], however, few studies had followed children up to adolescence[92, 93]. In contrast to asthma, the risk of other allergic diseases such as eczema or rhinitis were largely unknown, and not all study designs permitted consideration of childhood BMI. Therefore, our study could contribute with new information regarding the risk of allergic outcomes in relation to maternal BMI.

The results of **Study I** suggested that maternal BMI in early pregnancy was a risk factor for asthma in the offspring up to age 16 years, thereby extending the knowledge from previous studies. The longitudinal design and repeatedly collected information on symptoms and medication further gave us the possibility to investigate timing of onset and remission of asthma throughout childhood. Although maternal BMI was significantly associated with asthma at age two years only, the association was strongest for persistent asthma, while no increased risk was observed for transient asthma. These results highlight the clinical importance and indicate that maternal BMI may be associated with a more severe disease phenotype. Since our results were published, a meta-analysis[80] and a pooled analysis of 14 European birth cohorts up to age two years (not including our **Study I**)[134] have confirmed the association between maternal BMI and childhood wheeze/asthma, whereas more studies are still needed to confirm our results up to adolescence.

Regarding allergic outcomes other than asthma, the results of **Study I** are in line with the few reports of no associations with eczema, hay fever[88] or allergic sensitization[90, 91]. Taken together, these results indicate that maternal BMI may impact childhood asthma by other mechanisms than through allergic pathways.

Childhood obesity has been suggested to be a potential mediator in the association between maternal BMI and childhood asthma. Most,[87, 90, 91, 93] but not all[135], previous studies however found no or limited impact of adjustment for childhood BMI, indicating that independent effects (e.g. through prenatal programming) are also plausible. In contrast, significant mediation of childhood BMI was found in a formal mediation analysis of the association between maternal obesity and wheeze, but not asthma, up to age 7-8 years in

3,185 mother-child dyads from a Dutch birth cohort.[136] The conflicting results between studies may be explained by age differences or that self-reported information on childhood BMI was sometimes used. It is possible that any potential mediating effect of offspring BMI differ with age since our results in **Study I** showed that childhood overweight primarily influenced the observed association at later ages.

The association between maternal BMI and offspring asthma may be explained by several potential biological mechanisms, albeit most of these are speculative and more studies are needed to fully understand the underlying factors. Obesity is associated with low-grade systemic inflammation with elevated levels of pro-inflammatory cytokines, adipokines and hormones such as tumor necrosis factor-α, C-reactive protein, interleukin-6, leptin and cortisol.[77, 82, 137] The increased inflammatory environment of maternal obesity has been suggested to cause fetal inflammation and immune dysregulation through an enhanced inflammatory response of the placenta.[77, 138] Furthermore, both maternal BMI and dietary factors have been associated with epigenetic modifications in the offspring; therefore fetal programing may play an important role.[77, 139] Maternal dietary factors such as fish intake, antioxidants or Vitamin D may also influence the risk of asthma through other pathways, although epidemiological studies have reported inconclusive results between these factors and childhood asthma.[41] In addition, pregnancy and birth-related complications, such as gestational hypertension and preterm birth, have been suggested as explanatory factors, but did not influence the results in our study. Gestational weight gain during pregnancy has also been associated with wheeze and asthma in the offspring, although the results are less consistent compared to maternal obesity.[80]

Moreover, the association between maternal BMI and asthma in the offspring may be explained by neonatal lung function development. A study of 2,606 children from a Dutch prospective birth cohort found that the association between maternal BMI and early wheeze was partially explained by impaired infant lung function, whereas infant lung function was of minor importance for the association with wheeze at later age.[135] Finally, the association between maternal BMI and offspring asthma may be explained by the gut microbiota. The gut microbiota is involved in energy regulation, and altered microbiota has been observed in obesity.[78] The microbiota is also important for immune function development and both maternal and fetal microbiota have been linked to wheeze and atopic outcomes in childhood.[78, 140] Maternal flora influences fetal gut colonization through birth, where CS has been suggested to increase the risk of asthma, due to fetal colonization of different bacterial species. However, a sibling study suggested that indications for CS (such as fetal respiratory stress or maternal complications), rather than the lack of microbe exposure, are more likely to explain the association between CS and asthma.[43]

5.1.2 Childhood overweight and asthma

In **Study II**, we found that girls with persistent asthma had higher BMI and an increased risk of overweight throughout childhood, compared to girls without asthma. Girls with transient asthma had an increased risk of overweight in early and middle childhood, whereas girls with late-onset asthma had a tendency towards increased risk of overweight in late childhood. In contrast, no consistent associations between asthma phenotypes and overweight were observed among boys.

Extensive previous literature reviews including large prospective cohorts[103, 104] and a Mendelian randomization study[141] have linked BMI or overweight/obesity and asthma in childhood. A unique feature of **Study II** was the large number of BMI measurements from birth to age 16 years, which permitted us to investigate BMI development throughout the entire childhood in relation to asthma onset and remission. Only a few previous birth cohorts have followed children up to adolescence using repeated measurements of BMI. In the Isle of Wight cohort the risk of asthma was analyzed in relation to BMI trajectories up to age 18 years based on information on BMI at ages 1, 4, 10 and 18 years.[142] Comparable to our findings, the risk of asthma at 18 years was strongest among children categorized into the 'early persistent overweight' trajectory, but was also increased among the 'delayed overweight' trajectory.[142] No association between 'early transient overweight' and asthma at age 18 years was present, which is in line with a previous study from the BAMSE cohort, showing that current, but not early-transient overweight up to age 7 years was associated with an increased risk of asthma at age 8 years.[108]

Some studies have suggested that rapid infant or early childhood weight gain may be most important for the risk of asthma development, speculating that early abnormal growth may impact lung or immune function during critical development periods.[105, 106, 143] In **Study II**, we observed that children with persistent asthma had an increased BMI already in early childhood (before age two years), suggesting that early rapid weight gain and/or common risk factors in early life may be of importance. However, girls with late-onset asthma did not have an elevated BMI in infancy and later BMI may also be of importance, at least for late-onset asthma. The difference in BMI among girls with persistent asthma, compared to no asthma was present throughout childhood and seemed to increase with age, indicating that asthma may also influence later BMI development in girls.

The potential bidirectional association between BMI and asthma has garnered more attention recently. Asthma may impact on the risk of obesity through reduced levels of physical activity due to symptoms during exercise. In a study of 2,171 US children, having an asthma diagnosis at age 5-8 years increased the risk of developing obesity during childhood and adolescence.[116] Among Norwegian adolescents followed up to young adulthood, a bidirectional association between obesity and asthma was also found in males, but not females.[144] Taken together, it may be possible that infancy and childhood weight gain contribute to the risk of asthma development, while asthma itself contributes to weight gain later in childhood.

Among children, conflicting results have been observed regarding gender differences in the obesity-asthma association.[103] In adults, the association between obesity and asthma seems to be more pronounced in women, and obesity have been associated with a specific non-allergic, female, late-onset phenotype of asthma.[145] The stronger association among adult women may be related to female sex hormones, although we found stronger associations among females also in younger children.

The mechanisms behind the association between obesity and asthma are likely multifactorial and several review studies have discussed these in detail.[110, 111] Obesity, particularly abdominal fat mass, has been shown to directly affect lung function mechanics and compliance of the chest wall resulting in lower expiratory reserve volume and

functional residual capacity.[146, 147] The association between obesity and lung function was investigated in **Study III** and is discussed more under Section **5.1.3**.

Low-grade inflammation with elevated levels of cytokines and other pro-inflammatory factors may also play a role in the obesity-asthma association. The pro-inflammatory hormone leptin is positively correlated with obesity and has been found to increase airway hyperresponsiveness in mice.[111, 148] Elevated serum levels of leptin have also been found in asthmatics compared to healthy controls.[111, 148] In addition, a metabolic link with asthma may be present through insulin resistance, which has been associated with airway hyperresponsiveness and airway obstruction in obese children.[146, 149]

The obesity-asthma link could also be explained through shared risk factors and comorbidity such as gastro-esophageal reflux and sleep-disordered breathing.[150] Dietary components including antioxidants[51], oily fish intake[151] and Vitamin D[152] have been shown to influence the risk of childhood asthma, possibly through anti-inflammatory or immunomodulatory mechanisms. Shared genetics and epigenetics could also play a role as gene variants in, for example, the adrenoceptor beta 2, tumor necrosis factor and DENN Domain containing 1B genes have been associated with both obesity and asthma.[146, 153] Furthermore, specific DNA methylation related to inflammation and metabolic dysregulation have been observed in obese asthmatics[154]. Finally, the gut microbiota may also be involved due to its role in immune function.[140]

5.1.3 Childhood overweight and lung function

In **Study III**, we observed that overweight and obesity in school-age was associated with airway obstruction and reduced peripheral airway function up to adolescence. The association between overweight and airway obstruction was present both among children with and without wheeze at age 16 years, indicating that asthma symptoms may not fully explain the observed association. Analyses on change in overweight status between 8 and 16 years showed that persistent overweight at both 8 and 16 years was associated with airway obstruction and increased peripheral airway resistance at age 16 years, whereas no association was found for transient overweight.

Several previous studies[118-120], including one recent meta-analysis[117], observed an association between overweight/obesity and reduced FEV_1/FVC, but increased or normal FEV_1 and FVC in children and adolescents. This had led to the hypothesis that childhood obesity may cause airway dysanapsis (asymmetry between airway and lung size). In a recent study including six US child cohorts, obesity was found to increase the risk of airway dysanapsis in both asthmatics and non-asthmatics, and the association was suggested to be, at least partly, unrelated to bronchospasm or airway inflammation.[121]

Although dysanapsis was shown to be associated with an increased risk of severe exacerbation and corticosteroid use in asthmatics,[121] it is debated whether reduced FEV_1/FVC despite normal FEV_1 in obese non-asthmatic children is of clinical relevance or part of the normal continuum. The inclusion of IOS as an alternative measure of lung function at 16 years in **Study III** provided additional insight into the physiological mechanisms and gave us the possibility to discriminate between the peripheral and central airways. We observed strong cross-sectional associations between overweight and obesity

and increased peripheral airway resistance and reactance at age 16 years, while results were weaker for BMI status at 8 years. This may be explained by the fact that some of the overweight and obese children at 8 years had normalized their BMI by 16 years, and changes in peripheral airway may have reversed in these subjects.

Previous evidence regarding the impact of overweight and obesity on peripheral airway function is limited. In adults, associations between high BMI and increased IOS parameters have been observed in a few small cross-sectional studies.[155-157] Two studies on bariatric surgery patient[158, 159] observed improved small airway resistance in relation to weight loss, indicating that the physiological impact of obesity is reversible. In children, conflicting results have been reported in the few previous studies on BMI and peripheral airway function. In a study of 99 Finish children hospitalized for bronchiolitis in infancy[160], current BMI at age 5-7 years was associated with increased airway resistance and impedance, whereas no association was observed among 518 German 6-year-old children[161] or among 188 Brazilian school-children aged 8-16 years[162]. The authors of the latter study concluded that overweight may be associated with a disproportional lung growth that is independent of respiratory disease.[162]

The observed inconsistencies between our results and some of the previous studies regarding peripheral airway function may be explained by power issues due to small sample sizes. In addition, timing and duration of overweight/obesity may be important, which is not possible to consider in cross-sectional studies. In the present study, persistent overweight at both 8 and 16 years was associated with airway obstruction and reduced peripheral airway function at 16 years, while no association was observed for transient overweight. Similar results were observed for spirometry outcomes in the Dutch PIAMA birth cohort, where persistent high BMI and waist circumference between 8 and 12 years were associated with reduced FEV_1/FVC at age 12 years.[118] However, no previous longitudinal studies have investigated the association between timing and duration of overweight in relation to peripheral airway function in children and adolescents.

Regarding airway inflammation, we found no association between obesity and FeNO in **Study III**. These results are in line with some previous studies in children, which observed null or inverse associations between BMI or adiposity and FeNO.[114, 115] In addition, we analyzed eosinophil and neutrophil cell counts in blood as a measure of systemic inflammation, and found that overweight and obesity were associated with increased neutrophils, especially in girls. Although we also found slightly higher eosinophils among obese girls, the weighted evidence suggest that overweight and obesity primarily are related to non-allergic inflammation.

Obesity seems to impact lung function differently in adults and children. In adults, obesity is associated with reduced functional residual capacity and reserve volume, while this has not been consistently shown in children.[163] Moreover, obesity in adults is associated with a restrictive lung function (reduced FEV_1 and FVC), while FEV_1/FVC is usually not influenced.[117] Large prospective studies following children from childhood to adulthood with detailed assessment of lung function including peripheral airway function are needed to further explore the obesity-lung function association during the transition from childhood to adulthood.

5.1.4 Validity of self-reported height, weight and BMI

In **Study IV**, only small differences between web-based self-reported and measured height, weight and corresponding BMI were observed. Overall, weight was underreported by 1.1 kg and height was overreported by 0.5 cm, leading to an underestimation of BMI by 0.5 kg/m^2. The accuracy of self-reported BMI was somewhat lower among girls compared to boys, and lower among overweight and obese participants, compared to normal weight participants. In contrast, underweight adolescents slightly overreported BMI.

The results of **Study IV** are comparable to other validation studies on self-reported height, weight and BMI among adolescents. A recent study of 3,379 Estonian school-children aged 11-15 years[164] observed decreasing bias in self-reported values with increasing age. Compared to our study, slightly lower underestimation of weight was observed in the 15-year old age group (0.6 kg in boys and 0.9 kg in girls), while in contrast to our study, boys slightly underreported height (0.4 cm). On the other hand, a review including 11 studies of US adolescents aged 12-17 years, found slightly larger discrepancies and lower correlations between self-reported and measured height and weight in most of the included studies.[72] One recent meta-analysis of 23 studies (including **Study IV**) assessed the accuracy of self-reported BMI to detect overweight and obesity in children and adolescents and found a pooled sensitivity of 0.76 and a pooled specificity of 0.96.[165] The authors concluded that self-reported BMI has a high specificity and moderate sensitivity and is a viable alternative when measured BMI is not available. However, the validity depended on which reference values were used (e.g. IOTF, or national-specific percentiles) as well as study region.[165]

In **Study IV**, we observed decreasing accuracy of self-reported BMI with increasing BMI. Only 60% of overweight and 46% of obese were correctly classified, which was somewhat lower compared to the above mentioned meta-analysis.[165] The trend of decreasing validity with increasing BMI is widely observed in the literature,[166-168] and may be explained by a general tendency of answering questions according to what is socially accepted (i.e. social desirability bias). Some suggest that self-reported BMI should be corrected before it is used, and have provided equations to do so.[167, 169]

Regarding gender differences, our results are in line with several other studies in adolescents[164, 167, 170] showing slightly higher underreporting of weight and BMI in girls, while some found no difference[168] or larger underreporting in boys.[171] Gender differences may be explained by different social norms and ideals in females and males. On the other hand, adolescent boys generally grow faster and may be less aware of current weight and height, compared to girls. However, we found no differences in the accuracy in relation to pubertal status, indicating that growth rate may not be of major importance.

Except for gender and BMI, no other lifestyle or socioeconomic factor was found to influence the validity of self-reported BMI. Previous studies have found conflicting results regarding determinant factors for accuracy of self-reported weight and height. In a national representative sample of 7,160 US students, screen time and high consumption of fast food was associated with overreporting of BMI.[166] However, a study in 137 middle school and 242 high school students observed larger underreporting of weight among participants with a high amount of moderate physical activity.[168] Additional studies regarding potential

prediction factors could be utilized to develop population-specific formulas to correct self-reported BMI.

One of the aims of **Study IV** was to evaluate whether self-reported weight and height could be used in future studies in BASME. Based on the results from **Study IV**, we decided to include information on self-reported BMI among adolescents with missing information on measured BMI in **Study II**.

5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 Strengths

The studies included in the present thesis have several strengths. Using the large population-based prospective BAMSE cohort with a high response rate and repeatedly collected high-quality data from birth to 16 years is a major strength. Weight and height were objectively measured for the majority of participants and objective outcome information for lung function and allergic sensitization were analyzed in addition to questionnaire-based information on allergic disease.

5.2.2 Random errors

The reliability of an epidemiological study depends on the amount of systematic (described in **5.2.3**) and random error. Random error arises from sampling variability related to the study size as well as the prevalence of exposure and outcome (if categorical). Low amount of random error (i.e. high precision) means that the results would be reproduced if the study was repeated under the exact same conditions. The amount of statistical variability is indicated by the width of the confidence intervals. In a small study with a rare exposure or outcome, random error is higher (wider confidence intervals) compared to a large study with a more common exposure or outcome (more narrow confidence intervals).

Considering the relatively common outcomes, the sample sizes in the present studies were comparatively large (n >2,800 in **Studies I-III** and n=1,698 in **Study IV**), with rather narrow confidence intervals. Lower precision was present in stratified and sub-analyses, such as the analysis on overweight in combination with wheeze in **Study III**. Likewise, for some exposure categories such as underweight (mothers in **Study I** and children in **Study III**), there were few subjects, resulting in lower precision.

Another concept related to random error is multiple testing. In the present studies, a substantial number of analyses were performed with several outcomes and different exposure models being evaluated. A large number of analyses increases the risk of chance findings, which is incorrect rejection of the null hypothesis (type I error). However, specific pre-defined hypotheses were tested and the analyses were not independent. Adjusting for multiple comparisons may in this case be too conservative and increases the risk of type II error (the incorrect decision to not reject the null hypothesis). In epidemiological studies, there is always a trade-off between the risk of chance findings, which is set by the significance level, and the ability to detect a true association.[172] However, the significance level is an arbitrary value which one may use as a guide rather than a definite cut-off to interpret the results. In the present thesis, the main findings are, in addition to their

statistical significance, in line with previous research and therefore unlikely to solely be explained by chance.

5.2.3 Systematic errors

The amount of systematic error reflect to what extent the study measure what it is supposed to measure. In contrast to random errors, systematic errors are not related to study size or prevalence of exposure or outcome. Systematic errors can be divided into selection bias, misclassification and confounding.

5.2.3.1 Selection bias

Selection bias occurs when study participants are not representative of the target population. Selection bias may affect the prevalence, or more seriously, the observed association between exposure and outcome. The short questionnaire that was sent out to non-participants and excluded children in BAMSE showed that there were no major differences between the final cohort and non-participants or excluded children regarding known risk factors for allergic disease, except for parental smoking which was less common in the study population. Parental BMI was not assessed at this time point, but maternal BMI in our study population was similar to the average BMI in early pregnancy among all women in Stockholm during the study period (22.9 kg/m^2 compared to 23.3 kg/m^2). Selection bias will only influence the estimated association between exposure and outcome if the association differs between included and non-included subjects. Such a bias is generally less likely to be present at baseline in a cohort study as participants are included before disease onset.

During follow-up, participation rate might differ in relation to exposure or outcome, which may introduce more serious selection bias. Fortunately, the BAMSE cohort has a low drop-out rate (78% of the original cohort answered the 16-year questionnaire), which reduces the risk of selection bias. For example, maternal BMI in early pregnancy was 22.9 kg/m^2 among those answering the 16-year questionnaire, compared to 23.1 kg/m^2 among those that did not answer this questionnaire. In addition, only small differences were observed between each study population and the original cohort, suggesting that no major selection bias was introduced when defining the study populations. Despite this, selection bias cannot be completely ruled out. For example, children who develop extreme obesity may drop-out to a higher extent or do not give permission to collect data from the school health care records compared to moderately obese children. If these children also have a higher risk of asthma or reduced lung function, the association between obesity and asthma/lung function will be underestimated.

5.2.3.2 Misclassification

Misclassification (also referred to as information bias) occurs when exposure or outcome are measured or classified incorrectly. Non-differential misclassification refers to misclassification that is equally distributed in relation to exposure or outcome. Under most circumstances, non-differential misclassification leads to a dilution of the association, whereas differential misclassification can cause an overestimation or underestimation of the association.

In the present studies, maternal and childhood BMI were measured for the majority of participants, which limits misclassification compared to self-reports. Small measurement errors, for example measuring weight with clothes on, are however relevant for the validation study (**Study IV**) and may have explained some of the observed differences between reported and measured weight. In **Study I**, maternal BMI was collected during pregnancy, i.e. before children were born and any allergic symptoms appeared. Any misclassification of maternal BMI should therefore be non-differential in relation to allergic outcomes in the offspring and may only have led to a dilution of the association. For the majority of participants, maternal BMI was assessed in the first trimester of pregnancy where median weight gain has been shown to be minimal in normal weight, overweight and obese women.[173]

BMI is a quick and simple measure of overweight/obesity that has been shown to be highly specific and moderately sensitive to identify children[174] and adults[175] with excessive fat mass. However, BMI cannot differentiate between lean and adipose tissue on an individual level, and if we believe that adiposity and not BMI per se is the important risk factor, some participants (children or mothers) may have been misclassified with regards to BMI status. Participants with low proportion of adiposity but high BMI (e.g. very athletic) may have been misclassified as overweight (less likely due to the high specificity), whereas the opposite may have occurred among participants with high proportion of adiposity but normal BMI (more likely due to the moderate sensitivity). Although asthma has been found to be somewhat more common among athletes, this is mainly seen among endurance athletes for example skiers where BMI generally is not elevated.[176] Any misclassification of overweight is therefore probably non-differential in relation to outcome and may only lead to a dilution of the observed associations.

The outcomes asthma, rhinitis and eczema were mostly based on parental questionnaire reports of validated and widely used questions. However, some misclassification of self-reported allergic outcomes is difficult to avoid as parents may interpret questions differently or may not accurately remember their children's symptoms or medications. For example, parents with allergic disease themselves may be more aware of allergic symptoms in their child, compared to non-allergic parents. Therefore, in **Study I**, parental allergic disease was evaluated as a potential effect modifier, but no significant differences in the results were observed among children with or without parental allergic disease.

Another potential source of misclassification is over-reporting of respiratory symptoms among overweight/obese, as breathing difficulties during exercise may be misinterpreted as asthmatic symptoms.[150] Such a bias would lead to an overestimation of the association between asthma and BMI in children, but is difficult to estimate in the present study. In order to minimize the risk of misclassification of non-asthmatic symptoms as asthma, rather strict definitions of asthma with a combination of repeated symptoms and/or single symptoms and medications were used in the present studies. However, defining asthma in children is challenging as no gold standard exists and there is a trade-off between missing cases using a too strict definition (high specificity, but lower sensitivity) and the risk of classifying non-cases as cases using a too inclusive definition (high sensitivity but lower specificity).

The risk of misclassification is lower for the objectively measured outcomes lung function, allergic sensitization and inflammation. Lung function was measured by trained nurses and checked for quality control using ATS/ERS guidelines. Although different spirometers were used at 8 and 16 years, any systematic differences should not be related to BMI status and may only lead to a dilution of the observed association. The cut-off 0.35 kU_A/L for sensitization is a technical cut-off that is widely used in the literature.

Finally, the time between the questionnaire and the clinical investigation may have introduced bias. Especially in the validation study (**Study IV)**, the time period between the questionnaire and the measurements may have led to some small but actual changes in height and weight. In order to avoid bias, we restricted the study population to adolescents with up to 8 weeks between self-reported and measured values.

5.2.3.3 Confounding

Confounding occurs when there is a factor outside the studied exposure that affects the outcome (increase or decrease the risk) and is associated with the exposure, but not an effect of the outcome or exposure.[172] Confounding is sometimes referred to as a mixing of effects,[172] meaning that the observed association is due to another factor than the investigated exposure. Methods such as restriction, stratification or regression modelling can be used to control for confounding. Given no other errors, perfect confounding control will give the causal effect of the exposure on the outcome. Uncontrolled confounding will result in an overestimate, underestimate or even a reverse of the true association under extreme conditions.

In the BAMSE study, extensive exposure information have been collected, which allowed for evaluation of many potentially important confounding factors, including parental smoking, socioeconomic status and allergic heredity. Confounders were selected based on a-priori knowledge or testing and controlled for by regression modelling. Potential mediators were handled separately, and included in separate models only to investigate whether there were any direct associations that were independent of the mediators. Another increasingly used method to select covariates is to use a directed acyclic graph (DAG). A DAG is a visual presentation of causal associations between variables that can be used to determine which factors to control for in order to estimate the causal association between a specific exposure and outcome. Within the present project, DAGs were explored but not used as we encountered challenges with drawing the complex associations between all factors related to BMI and allergic disease. However with more training and experience, I believe that the DAGs could be a useful method to consider in future projects.

Although a large number of variables were considered as potential confounders in the present studies, unmeasured or residual confounding may still be present. Socioeconomic status may be an important confounder in the association between BMI status and allergic disease as it has previously been associated with both allergic disease[177] and BMI status.[76] Socioeconomic status is a complex variable that can be defined by occupation, income or education. In the present study, socioeconomic status was defined based on parental occupation which may not represent all aspects of this concept. However, other variables such as parental age, smoking, maternal BMI and breastfeeding are associated with

socioeconomic status and may together capture a large part of what is represented by this variable.

Moreover, dietary factors and physical activity could potentially confound the associations in the present studies, as certain dietary factors including fruit, vegetables and fish have been associated with lower risk of asthma symptoms,[178] while sedentary behavior may increase the risk.[179] In the present project, we lacked information on maternal diet and physical activity, which may be important for the association between maternal BMI and asthma in **Study I**. However, adjusting for oily fish intake and physical activity at 16 years did not influence the association between asthma phenotypes and BMI in **Study II**. In addition, physical activity at age 16 years did not influence the results between BMI and lung function in **Study III,** and was not found to be a predictor of validity of self-reported BMI in **Study IV**.

5.2.4 Generalizability

The population-based design of the BAMSE study increase generalizability. The BAMSE study included 75% of all eligible subjects and participants did not differ from non-participants and excluded children, except for the prevalence of parental smoking which was somewhat lower in the included cohort. However, one of the exclusion criteria of the BAMSE study was insufficient knowledge of the Swedish language which likely led to fewer parents of non-Swedish origin. At the same time, we have no reason to assume that the underlying biological mechanisms would differ across ethnicity, and therefore we still think that the results could be generalizable to other populations.

For the validity of self-reported weight, height and BMI, we do belive that the results could differ between populations as validity may depend on specific characteristics such as age, ethnicity and sociodemographic factors.

6 CONCLUSIONS

Based on the results from this thesis and the current scientific literature, it may be concluded that overweight and obesity are associated with asthma and evidence of airway obstruction in children and adolescents. From **Studies I-IV**, the following specific conclusions can be drawn:

I. Maternal BMI may increase the risk of asthma in the offspring up to adolescence, however, the association may partly be explained by overweight in the offspring. Maternal BMI does not seem to be associated with rhinitis, eczema or allergic sensitization in the offspring, indicating that non-allergic mechanisms are predominating.

II. Asthma, in particular persistent asthma throughout childhood, is associated with high BMI development and increased risk of overweight among girls, whereas the potential association between asthma and BMI is more uncertain among boys. Altogether, the current evidence indicates that the temporal direction of the association between overweight and asthma may be bidirectional.

III. Overweight and obesity in school-age and adolescence appear to be associated with airway obstruction up to adolescence, and also involving the peripheral airways.

IV. Web-based self-reported BMI can be used as a valid, quick and cost-effective alternative to measured BMI among Swedish adolescents. However, the accuracy declines with increasing BMI.

7 FUTURE PERSPECTIVES

Allergic diseases affect a large proportion of the population and contribute to a substantial burden for the affected individuals, families and society. Identifying modifiable risk factors, such as overweight and obesity, are necessary for successful prevention of allergic diseases. The studies in this thesis add to the body of evidence suggesting that maternal and childhood overweight is associated with asthma and signs of airway obstruction in childhood and adolescence. The validation study may be helpful for future research with self-reported weight and height, however, validation studies need to be continuously performed on the specific populations where they are intended for use.

To date, few intervention studies on weight-loss in relation to asthma and lung function have been performed[180-182], and there is a need for large randomized trials to be able to provide evidence-based advice and treatments. These studies could investigate 1) whether weight-loss improves asthma symptoms/severity and lung function and 2) which type of weight-loss intervention is most effective for asthma control and lung function. Preferable, detailed assessment of body composition should be performed to provide more insight into the underlying factors and to avoid misclassification (in particular during physical activity interventions, where adiposity may decrease although BMI remains unchanged).

In addition, only a few studies have analyzed the risk of incident obesity in asthmatics and future studies should focus more on the potential bidirectional association between obesity and asthma across the life course. These studies could also investigate whether there are particular groups of asthmatics (e.g. regarding gender, allergic status or activity level) who have an increased risk of obesity, and should be targeted for prevention.

Finally, the underlying factors for an association between maternal obesity and asthma in the offspring need to be better understood. More research on the role of lifestyle factors during pregnancy such as diet and physical activity, as well as gestational weight gain, would provide evidence to strengthen the advice given to pregnant women.

8 POPULÄRVETENSKAPLIG SAMMANFATTNING

Allergiska sjukdomar såsom astma, hösnuva och eksem debuterar ofta i barndomen och förekommer hos ca 30-40% av befolkningen. Förekomsten av övervikt och allergiska sjukdomar har ökat parallellt under de senaste decennierna, och flera studier har indikerat att barn med övervikt och fetma har en ökad risk att utveckla astma. Det övergripande syftet med denna avhandling var att undersöka sambanden mellan övervikt (hos modern och barnet) och allergiska sjukdomar samt lungfunktion under barndomen upp till tonåren. Dessutom undersökte vi tillförlitligheten av självrapporterad längd, vikt och motsvarande body mass index (BMI) vid 16 års ålder. Avhandlingen innefattar fyra delarbeten vilka alla baseras på den svenska BAMSE-studien där drygt 4000 barn följts från födseln upp till 16 års ålder.

I det **första delarbetet** undersökte vi sambandet mellan moderns BMI i tidig graviditet och allergiska sjukdomar samt allergisk sensibilisering hos barnet upp till 16 års ålder. Information om moderns BMI erhölls från det medicinska födelseregistret där vikt och längd registrerats vid första besöket hos mödrahälsovården runt graviditetsvecka 10. Allergisk sjukdom hos barnet samlades in via upprepade frågeformulär med fokus på symptom och medicinering, medan sensibilisering definierades utifrån uppmätta allergiantikroppar mot luftburna allergen i blod. Resultaten visade att mammans BMI i tidig graviditet var kopplat till en ökad risk för astma, men inte hösnuva, eksem eller allergisk sensibilisering hos barnet upp till 16 års ålder. Starkast samband sågs för bestående astma, s.k. persistent astma, medan ingen ökad risk observerades för tidig övergående astma. Fortsatta analyser visade att det framförallt var fetma hos modern som bidrog till en ökad risk för astma, medan inget signifikant samband sågs för övervikt. Dock fann vi att barnets egen viktstatus delvis kunde förklara sambandet mellan moderns BMI och astma hos barnet.

I **delarbete två** analyserade vi BMI-utveckling under barndomen samt risken för övervikt i förhållande till astma. Barnets BMI mättes vid kliniska undersökningar och samlades in från skol- och barnhälsovårdsjournaler. Vi de senare åldrarna kompletterades dessa data med självrapporterad vikt och längd för de ungdomar som saknade uppmätta värden. Resultaten visade att flickor med bestående astma hade högre BMI och en ökad risk för övervikt under barndomen jämfört med flickor utan astma. Flickor med tidig övergående astma hade en ökad risk för övervikt mellan 4-8 års ålder, medan flickor med senare debuterande astma hade en tendens till ökad risk för övervikt under tonåren. Hos pojkar sågs betydligt mindre skillnader i BMI mellan barn med och utan astma och inget tydligt samband mellan astma och övervikt observerades.

I det **tredje delarbetet** undersökte vi sambandet mellan övervikt och lungfunktion från skolåldern till tonåren. Lungfunktion mättes med två olika metoder vilket gav möjlighet att analysera både de centrala och de små luftvägarna. Resultaten visade att övervikt och fetma vid 8 års ålder var kopplat till större lungvolymer men en relativ lungfunktionsnedsättning (uppmätt som lägre FEV_1/FVC kvot) samt ett ökat luftvägsmotstånd i de små luftvägarna. Lägst FEV_1/FVC sågs hos dem med övervikt vid både 8 och 16 år, medan inget signifikant samband sågs hos dem som utvecklat normalvikt vid 16 års ålder.

I **delarbete fyra** jämförde vi självrapporterad och uppmätt vikt, längd och motsvarande BMI vid 16 års ålder. Resultaten visade att självrapporterad vikt och längd överlag var starkt korrelerade. I genomsnitt var självrapporterad vikt 1,1 kg lägre än uppmätt, medan självrapporterad längd var 0,5 cm högre än uppmätt, vilket ledde till en underskattning av BMI med i genomsnitt 0,5 kg/m^2. Tillförlitligheten av självrapporterad BMI var något lägre bland flickor jämfört med pojkar, samt bland ungdomar med övervikt och fetma jämfört med normalvikt.

Sammanfattningsvis tyder våra resultat på att moderns och barnets viktstatus är kopplade till astma och nedsatt lungfunktion under barndomen och tonåren. Sambandet mellan moderns BMI och astma hos barnet verkar till viss del kunna förklaras av barnets egen viktstatus. Att vi inte ser någon koppling till eksem och hösnuva tyder på att de bakomliggande mekanismerna främst innefattar icke-allergiska faktorer, till exempel påverkad lungfunktion.

Slutligen kan vi konstatera att självrapporterat BMI kan användas som ett snabbt och kostnadseffektivt alternativ till uppmätt BMI hos svenska ungdomar. Dock är tillförlitligheten lägre hos ungdomar med övervikt och fetma, jämfört med normalviktiga ungdomar.

9 ACKNOWLEDGEMENTS

Many people have contributed to this thesis and I would like to thank all of you for your help and support.

Firstly, I would like to express my gratitude to all the participating families in the BAMSE study for your time and effort throughout the years.

My main supervisor, **Anna Bergström**. You have always taken time for me and given me concrete, thorough, and relevant feedback. Your skilled guidance in epidemiology have helped me to develop on so many levels. Thank you also for your encouragement, kindness and the way you care for your employees. I feel fortunate to have been part of your research group!

My co-supervisor, **Erik Melén**. Your rapid answers and feedback were always spot on. Thank you for your inspiring and including attitude that always made me feel welcome in your lung function group. I have learnt a lot from your expertise in pediatric and clinical epidemiology.

Head of the unit, **Göran Pershagen** for excellent leadership. Thank you also for contributing to the KID application for this project and for providing supervision at the beginning of the project.

Former and present head of the department, **Anders Ahlbom** and **Ulla Stenius** for providing the possibility to perform PhD-studies in such a great research environment. My mentor, **Johanna Zilliacus** for sharing scientific advice.

I would also like to thank my co-authors for invaluable contributions to our papers. I have been really lucky to have had such a broad range of experts around me: **Inger Kull**, for your epidemiological and clinical expertise and for your supportive and warm personality, **Tomas Lind** and **Matteo Bottai** for statistical support, **Per Gustafsson, Per Thunqvist** and **Jenny Hallberg** for sharing your expertise in lung function, **Jennifer Protudjer** and **Catarina Almqvist** for your expertise in epidemiology and early risk factors for asthma.

Past and present colleagues in BAMSE and at the Unit of Environmental Epidemiology for creating such a great and stimulating work environment: **Jessica Magnusson**, for all our everyday discussions about everything from work (also for excellent contributions as a co-author) to private life. I really enjoyed sharing office with you and hope I did not disturb you too much with all my questions. **Erica Schultz** and **Anna Gref**, for your positive spirit and all our fika conversations. **Alva Wallas**, for providing me with chocolate (and oranges!) and for fun training sessions, **Jesse Thacher**, for always answering my question and for invaluable help with language corrections, **Simon Kebede Merid** for being such a nice roomie, **Niklas Andersson** for statistical support and travel adventures, **Olena Gruzieva** for being a terrific person and for always organizing celebrations, **Andrei Pyko, Auriba Raza, Åsa Persson, Maria Ödling, Marina Jonsson, Markus Dahlquist, Michal Korek, Charlotta Eriksson, Tom Bellander, Antonis Georgellis, Ann-Sophie Merritt, Mare Löhmus Sundström, Petra Um Bergström, Emma Johansson, Natalia Ballardini, Elin Dahlén, Susanne Lundin, Åsa Neuman,** and **Mohsen Besharat Pour**, it has been a privilege to work with you all.

The BAMSE secretariat: **Eva Hallner, Sara Nilsson** (also for contributions as a co-author) and **André Lauber**. It has been a fortune to have access to such a structured and well-organized material as BAMSE. All the work you do is fantastic!

The BAMSE clinic staff: **Ulrika Hellberg, Eva Petersson, Barbara Ekman, Marie Carp** and **Carina Wallén,** for welcoming me at my short stay in the BAMSE clinic. You made my visits there truly enjoyable.

Members of Journal Clubs throughout the years, especially **German Carrasquilla, Florencia Harari, Cecilia Orellana, Josefin Edwall Löfvenborg, Rebecka Hjort**, **Andreas Eklund** and **Sara Fagerstedt Nilsson,** for challenging and fruitful discussions.

The "lunch group" from the Unit of Metals and Health for entertaining breaks.

My supervisor at the bachelor and master's degree project **Katarina Bälter** for welcoming me in your group and for excellent supervision. Former PhD-students at MEB **Stephanie Bonn, Sara Christensen** and **Lisa Möller,** for making my two stays at MEB great, and for teaching me Stata.

Some special teachers I have had throughout the years: **Per Rönnkvist, Henrik Forselius, Ann-Marie Wahlberg Andersson** and **Anders Palm**. You have been true role models and you made me think that learning is fun.

Sist vill jag tacka vänner och familj som fyller på min energi mellan varven, speciellt:

Joanna och **Malin**, ni är bäst! Tack för alla middagar, resor och umgänge med er och era fina familjer - och för att jag kan prata med er om allt. **Elinor**, för att du trots avståndet alltid finns där och för din (och din familjs) gästvänlighet. **Majken**, för lekplatshäng tidiga helgmorgnar. **Christina** och **Sofie**, för alla träningspass som blev så mycket roligare. **Marie**, för alla skratt och pluggdagar under nutritionistlinjen.

Mamma och pappa, för allt stöd och för all hjälp med Nellie. **Katarina och Helena,** för härligt umgänge med era underbara familjer. **Kristina**, för din generositet och för alla förishämtningar. **Nillan**, för att du är ett proffs och dyrkad av N. **Arne**, för att du är världens bästa extramorfar.

Jocke och **Nellie**, ni betyder allt för mig. Jag älskar er över allt annat. ♥

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11 APPENDIX

Table 11.1. Definition of covariates

Variable	Source of data	Definition	Study
Sex	Q0	Biological sex of participant (female or male)	I, II[1], III, IV[1,2]
Birth weight	MBR	Birth weight of the child (grams)	I[3] , III[3]
Gestational age	MBR	Gestational age of the child at birth (weeks)	II, III[3]
Mode of delivery	MBR	Birth mode of delivery (vaginal or caesarian section)	I[3]
Newborn respiratory diagnosis	MBR	Hypoxia, asphyxia, respiratory distress syndrome and other respiratory conditions of the fetus or newborn (ICD 9: 768-770)	I[3]
Maternal age	Q0	Maternal age at the child's birth (years)	I
Maternal BMI	MBR	Maternal body mass index in early pregnancy	II, III[3]
Older siblings	MBR	Maternal parity ≥1 at the time of birth	I
Parental ethnicity	Q8	Any parent born outside of Scandinavia	IV[2]
Parental allergic disease	Q0	Mother or father reporting doctor's diagnosis of asthma in combination with asthma medication or doctor's diagnosis of hay fever in combination with allergy to furred pets- or pollen	I, II, III[3]
Maternal smoking	Q0	The mother smoked at least one cigarette per day at any time during pregnancy or during the child's infancy	I, II, III[3]
Socioeconomic status	Q0	Parental occupation categorized into three (blue collar worker, white collar worker or other) or six groups (unskilled blue-collar workers, skilled blue collar workers, low level white collar workers, intermediate level white collar workers, high level white collar workers and other (student) according to Statistics Sweden "Socioeconomic division (SEI); Reports on Statistical Coordination 1982:4") with dominance order	I, II, III[3], IV[2]
Breastfeeding	Q1	Exclusive breastfeeding (≥4 months or <4 months)	I[3], II, III[3]
Pubertal status	cQ12, cQ16	Pubertal status categorized into five categories: pre-pubertal, early pubertal, mid-pubertal, late pubertal or post-pubertal according to a pubertal development scale based on questions on body hair development, linear growth spurt, and pubic hair growth (both boys and girls); voice change and beard growth (boys only); and breast development and menarche (girls only)[183]	II[3], III[3], IV[2]
Physical activity	cQ12, cQ16	Self-reported amount of vigorous physical activity (hours/week) such as lifting heavy weights, aerobics, or high speed bicycling in the last 12 months. Mean of summer and winter season was calculated	II[3], III[3] IV[2]
Fatty fish intake	cQ16	Intake of salmon, herring or mackerel (<1/week or ≥1/week)	II[3]
Sedentary time	cQ16	Time (hours/day) outside of school spent on watching TV, computer use, video games or reading.	IV[2]
Sleep	cQ16	Average sleep per night (<8 hours or ≥8 hours)	IV[2]
Fruit and vegetable consumption	cQ16	Intake of fruit and vegetables (every day or less than every day)	IV[2]
Tobacco use	cQ16	Regular or irregular use of cigarettes or snuff	IV[2]
Smoking	cQ16	Regular or irregular smoking at 16 years	III[3]

Self-perceived health	cQ16	Self-rated health (completely healthy or fairly healthy/not very healthy)	IV[2]

[1]used for stratification only
[2]evaluated in prediction models only
[3]evaluated as a potential mediator or confounder in sensitivity analyses only
MBR: medical birth register, Q: questionnaire, cQ: child's questionnaire