# Epidemiological studies of sociodemographic factors, early life factors, health, and medical care consumption among small children

Mangrio, Elisabeth

2011

*Document Version:*
Publisher's PDF, also known as Version of record

Link to publication

*Citation for published version (APA):*
Mangrio, E. (2011). *Epidemiological studies of sociodemographic factors, early life factors, health, and medical care consumption among small children*. [Doctoral Thesis (compilation), Social Medicine and Health Policy]. Department of Clinical Sciences, Lund University.

*Total number of authors:*
1

# Epidemiological studies of sociodemographic factors, early life factors, health, and medical care consumption among small children

Elisabeth Mangrio

LUND UNIVERSITY

Faculty of Medicine

Malmö 2011

# Abstract

By international standards, children in Sweden experience good health. Sweden has low infant mortality rates, low accident mortality rates, a high number of breastfed children and a high proportion of vaccinated children. However, during the past twenty years the prevalence of overweight children has doubled in Sweden, while that of obese children has increased 4-5 times. Furthermore, there has been an increase in self-reported problems such as anxiety and sleeping disturbances among adolescents. Asthma and other types of allergic diseases are the most common chronic diseases during childhood, while infectious diseases are the most common causes of short-term morbidity. It is well-known that the social position of the family, living conditions, and parental health-related behaviors are closely connected with health in childhood. The socioeconomic position (SEP) of the family affects the child's health from the very beginning of life through the mother's health-related behaviors during pregnancy. Even though the prevailing etiological model for adult chronic disease emphasizes adult risk factors, the importance of earlier life circumstances has recently attracted considerable attention. A life course perspective seems to increase our understanding of health in childhood as well as later on, in adulthood. In this thesis, the associations between sociodemographic factors and early life factors (e.g., maternal smoking during pregnancy, exposure to secondhand tobacco smoke, breastfeeding, and high birth weight) on the one hand and health and medical care consumption on the other hand, were investigated among small children in Malmö. The studies in the thesis were population-based and cross-sectional, and the study populations comprised children who visited the Child health care (CHC) centers for their 8-month or 4-year check-up during 2003-2008 and whose parents answered a self-administered questionnaire. The self-administered questionnaire was handed out to the parents of 8-month-old and 4-year-old children in conjunction with their check-up at the CHC centers aiming to reach all children in Malmö in these two age groups. The questionnaire was distributed by the pediatric nurses at the centers. The results showed that antibiotic consumption at an early age was influenced by several factors including parental sociodemographic factors, lifestyle factors, psychosocial support, as well as child-related factors. The results further showed associations between exposure to unfavorable early life factors and the development of childhood allergy and overweight or obesity. Such effects were enhanced when there were presence of parental allergy or parental overweight, respectively. Children with less-educated mothers were exposed to more health risks, fewer health promoting factors, worse social support and had a higher medical care consumption than children with mothers with higher levels of education. In conclusion, the results show that that children's health seems to be highly influenced by the characteristics of the families into which they are born. The results also put focus on the importance of early targeted interventions.

ISBN 978-91-86871-52-9
ISSN 1652-8220

Social Medicine and Health Policy
Faculty of Medicine, Lund University, 2011:102
Printed by Media-Tryck, Lund

*To my dear husband Wilfred and our children*
*Rachel, Isabella and Gabriel.*

*“Children are a bridge to heaven”*

*Persian Proverb*

# Contents

**Material and methods**



**Statistics**



**Results and conclusions**



**General discussion**

# List of papers

This thesis is based on the following publications which will be referred to by their Roman numerals:

I. Mangrio E, Wremp A, Moghaddassi M, Merlo J, Bramhagen AC, Rosvall M. Antibiotic use among 8-month-old children in Malmö, Sweden--in relation to child characteristics and parental sociodemographic, psychosocial and lifestyle factors. *BMC Pediatr.* 2009;9:31.

II. Hansen K, Mangrio E, Lindström M, Rosvall M. Early exposure to secondhand tobacco smoke and the development of allergic diseases in 4 year old children in Malmö, Sweden. *BMC Pediatr.* 2010;10:61

III. Mangrio E, Lindström M, Rosvall M. Early life factors and being overweight at 4 years of age among children in Malmö, Sweden. *BMC Public Health* 2010;10:764

IV. Mangrio E, Hansen K, Lindström M, Köhler M, Rosvall M. Maternal educational level, parental preventive behaviour, risk behaviour, social support and medical care consumption in 8-month-old children in Malmö, Sweden. *Manuscript submitted for publication.*

# Abbreviations

| | |
|---|---|
| BFHI | Baby Friendly Hospitals Initiative |
| BMI | Body mass index |
| CHC | Child Health Care |
| CI | Confidence interval |
| CVD | Cardiovascular disease |
| LGA | Large for gestational age |
| OR | Odds ratio |
| SEP | Socioeconomic position |
| SES | Socioeconomic status |
| SGA | Small for gestational age |
| SI | Synergy index |
| SIDS | Sudden Infant Death Syndrome |
| UNICEF | United Nations Children's fund |
| WHO | World Health Organization |

# Introduction

One fifth of the Swedish population consists of children under the age of 18 years [1], though this proportion has reduced over the past four decades as the population gets older and fertility rates decline. By international standards, children in Sweden experience good health. Sweden has low infant mortality rates, low accident mortality rates, a high number of breastfed children and a high proportion of vaccinated children [1]. Furthermore, in comparison to other countries in Europe and the United States, Swedish children are among the best regarding tooth hygiene and have a relatively low use of nicotine, alcohol and narcotics [2,3]. However, during the past twenty years the prevalence of overweight children has doubled in Sweden, while that of obese children has increased 4-5 times, though the increase has started to level out in recent years. During the last twenty years, there has also been an increase in self-reported problems such as anxiety and sleeping disturbances, and also an increase in hospitalizations due to self-inflicted injuries and depression among adolescents [3]. Asthma and other types of allergic diseases are the most common chronic diseases during childhood, while infectious diseases are the most common causes of short-term morbidity [3]. Asthma, hay fever, and eczema have rapidly increased in prevalence since the 1950s, but have leveled out in recent years [1,3].

It is well-known that the social position of the family, living conditions, and parental health-related behaviors are closely connected with health in childhood [1,3]. In Sweden, the number of low-income households has gradually increased during the last thirty years, with single-parent families seeing a particularly unfavorable economic development. The number of children living with both of their parents has decreased since the 1970s, and today only 90 % of 1-year-old children and 60 % of 17-year-old children live with both their parents [1]. In recent years, there has been an increased recognition of the effects of exposure to health risks during fetal life and early childhood on health later in life [4]. The socioeconomic position (SEP) of the family affects the child's health from the very beginning of life through the mother's health-related behaviors during pregnancy [5]. Even though the prevailing etiological model for adult chronic disease emphasizes adult risk factors, the importance of earlier life circumstances has recently attracted considerable attention [4,6]. An unfavorable environment in early life is thought to elicit a range of physiological and cellular adaptive responses in key organ systems. These adaptive changes result in permanent alterations and might lead to pathology later in life [4]. A life course perspective seems to increase our understanding of health in childhood as well as later on, in adulthood. In this thesis, the associations between sociodemographic factors and early life factors on

the one hand and health and medical care consumption on the other hand, were investigated in a population of small children.

# *Childhood health*

## a) Epidemiology of allergic diseases

### Definition

Allergic diseases are characterized by symptoms from the respiratory airways, the gastrointestinal system, or the skin, when in contact with substances that people in general tolerate without discomfort. These diseases are based on immunological mechanisms. Sometimes the concept of atopic disease is used instead, which concerns a more specific tendency to form IgE-antibodies in contact with certain substances, that is, allergens [5].

### Time trends

Allergic diseases among children in Sweden have become more prevalent during the last fifty years, though this upward trend seems to have leveled out in recent years. For example, data from the ULF-investigations (Undersökning av levnadsförhållande) based on national samples and performed by Statistics Sweden show that there was no increase in asthma due to contact with pollen or fur from animals during the period 1996/1997 to 2004/2005 among those aged less than 25 years [3]. Similar results were reported in a recent population-based study from northern Sweden, which found no significant changes in the prevalence of current wheeze, allergic rhinitis or eczema in 7-8-year-old children during the period 1996-2006 [7].

### Geographical and social differences

The large international studies ISAAC (The International Study of Asthma and Allergies in Childhood) [8] and ECRHS (European Community Respiratory Health Survey) [9] showed a higher risk of asthma and hay fever in northwestern Europe and the lowest risk in southern and eastern Europe. The highest risk was seen in Great Britain and Ireland, and the lowest risk in Greece and Albania, with Scandinavia in an intermediate position. There are also differences within Sweden in the prevalences of allergic diseases, with the highest levels in the north of Sweden and the lowest in the south [5].

During the last century, allergic diseases were more prevalent among more affluent groups [3,10]. However, these differences have been reduced over time [3]. Recent studies have shown that asthma among children in a low social position often causes more severe symptoms and more hospitalizations [5]. Data from the Swedish BAMSE-study further showed that asthma and food allergies at 4 years of age were more common among children whose parents belonged to low SEP groups [11].

## Determinants

Most children with allergic diseases fall ill during the first 4-5 years of life [12]. The organ systems that are affected and the allergens that children react against tend to change with increasing age. For example, allergic nose and eye symptoms are most common among school children and are often connected to contacts with pollen and fur from animals [3], while eczema is more common among smaller children. National data from "Barnens miljöhälsoenkät 2003" showed that about a quarter of 4-year-old children in Sweden have some kind of ongoing allergic disease (i.e., hay fever, asthma, food allergy, eczema or other symptoms from allergy) [12].

It has long been recognized that there are hereditary components involved in the functioning of the immune system, making some families more prone to develop allergic diseases compared to others [5]. Many studies have shown an increased risk of developing an allergy if one's parents have an allergy [13-16]. In recent years, the roles of many environmental factors in the development of allergic diseases have been evaluated including maternal smoking during pregnancy, secondhand tobacco smoke, breastfeeding, early contact with animals with fur, and air pollution. Smoking during pregnancy affects fetal growth and maturity, lung development and lung function, which in turn might affect lung function later in life [3,17]. Early exposure to secondhand smoking has been shown to be associated with the development of wheezing episodes [18], allergic sensitization and sensitization to food allergens [17,19], and the development of atopic eczema [14]. If established asthma is present, secondhand tobacco smoke is associated with a more severe course [18]. A recent review showed that secondhand tobacco smoke was associated with both the onset and severity of asthma [20]. However, there are also studies showing no associations between exposure to secondhand tobacco smoke and allergic sensitization [18] and a larger effect of prenatal than postnatal exposure of tobacco on sensitization in children [5,15]. Breastfeeding decreases the risk for infectious asthma, while the protective effect on atopic diseases is less evident [5]. However, there are studies that have shown a protective effect of breast milk given to the offspring of allergic mothers with regard to allergic airway inflammation [21] and also with regard to asthma, atopic dermatitis and allergic

rhinitis [22]. Early contact with fur has in some studies been shown to be associated with wheeze and asthma [23]. Several studies have shown associations between exposure to air pollution caused by car exhaust and the development of allergies and asthma [24-26]. Small children seem more vulnerable to the effects from air pollution due to their immature immune system and the fact that their lungs are not yet properly developed [3].

## b) Epidemiology of overweight/obesity

### Definition

For children, overweight and obesity are defined using age and sex specific normograms for body mass index (BMI). In this thesis, overweight and obesity were assessed via BMI according to the classification by Cole et al. with cut-offs of 17.55 (boys) and 17.28 (girls) for overweight and 19.29 (boys) and 19.15 (girls) for obesity [27].

### Time trends

The prevalence of overweight in children in Sweden increased in recent decades until the beginning of the 2000s, when the increase started to level off [28-30]. Historically, a heavy child meant a healthy child. However, the patterns of disease are different today, and obesity is associated with a wide range of serious health complications and an increased risk of premature illness and death [31]. Today, about 15-20% of Swedish children are overweight and 3-5% are obese [3]. During the past twenty years the prevalence of overweight children has doubled, while that of obese children has increased 4-5 times.

### Geographical and social differences

It has been estimated that worldwide, 22 million children under the age of five years are obese and 1 in 10 children is overweight [32]. In Africa and Asia the prevalence of overweight is well below 10%, while the corresponding percentage in Europe and America is above 20% [32]. However, although the prevalence of overweight and obesity in developed countries is about double that in developing countries, the vast majority of affected children live in developing countries. Furthermore, the relative increase in the past two decades has been higher in developing countries (+65%) than in developed countries (+48%) [31].

Obesity prevalence varies across socioeconomic strata. In developed countries, children of low socioeconomic status (SES) are more affected than children from affluent families [33], while the opposite pattern is observed in developing countries [32]. In Sweden, overweight has been shown to be more common in children from lower socioeconomic status groups [34].

## Determinants

Obesity is the consequence of a long-term imbalance between energy intake and energy consumption, determined by food intake and physical activity, and influenced by biological and environmental factors [35]. The pathogenesis of childhood overweight is multifactorial, with interactions between genetic, neuroendocrine, metabolic, psychological, environmental, and socio-cultural factors [32]. Behavioral factors such as consumption of oversized portions, consumption of high calorie foods such as high-fat and low-fibre foods, and intake of sweetened beverages increases the risk of the child becoming overweight. Furthermore, children who overconsume soft drinks also have a lower intake of fruits and vegetables [36]. Television viewing and other sedentary activities have also been related to childhood obesity [32,37]. Availability of fast food and convenience stores near the home increases the risk of children becoming overweight or obese by promoting unhealthy food intake, while presence of sidewalks and green spaces encourages physical activity and reduces the risk of children being overweight or obese [38]. Another strong determinant of child overweight is parental overweight [35,39,40]. This strong association may be explained by genetic, environmental and behavioral factors.

Exposure to certain risk factors or protective factors early in life has been shown to be associated with the development of future overweight. Intrauterine growth patterns play a significant role in the evolution of obesity by modifying fat and lean body mass, neuroendocrine appetite control mechanisms, and pancreatic functional capacities [4]. Longitudinal studies have identified a strong relationship between birth weight and BMI attained in later life [32]. Increasing birth weight has been shown to be independently and linearly associated with increasing prevalence of childhood obesity [39]. In addition, low birth weight babies show a dramatic transition to central adiposity and insulin resistance very early in life [41]. The duration of breastfeeding has been found to be negatively associated with the risk of obesity in later childhood [42-45]. A systematic review of nine studies concluded that breastfeeding seems to have a small but consistent protective effect against obesity in children [46]. Furthermore, studies have shown long-term effects of maternal smoking in pregnancy on the risk of overweight. This effect is hypothesized to be related to long-term effects of nicotine exposure on

neurobehavioral impulse control, which affects satisfaction and appetite and hence leads to increased food consumption, as well as to poor nutrition in the uterus [47,48].

## c) Epidemiology of infectious diseases and antibiotic consumption

### Time trends

Improved hygiene, a gradually extended vaccination program, and better standards of living have all led to a marked decrease in the incidence of serious infectious diseases among children in Sweden over the last two hundred years. However, infectious disease is still the most common cause of short-term morbidity in small children [3]. National data on diagnoses in outpatient care are not comprehensive, and so it is hard to say anything about time trends in infectious diseases overall. However, national data show that the amount of in-hospital care due to infectious disease among children less than 15 years has decreased since the late 1980s [12]. Furthermore, a Swedish study from the county of Kalmar showed a decreasing number of primary healthcare patients with respiratory tract infections during 1999-2005, while the amount of antibiotics prescribed remained constant during this time [49]. Today, about 30% of all children aged 0-6 years are treated with at least one course of antibiotics per year [50]. The development of antibiotics as a treatment for infectious diseases is an important cornerstone in medical history. However, the increased use and the development of more potent antibiotics have led to an increased antimicrobial resistance, which is a threat in the treatment of infectious disease the world over [51]. As in many other countries, the use of antibiotics increased in Sweden throughout the 1980s, without any obvious medical reasons [52]. During 1986–93, antibiotic sales increased by 50% [53]. After this, there was a strong decline, with an especially prominent decrease among pre-school children. [54]. Part of this decrease has been attributed to the work done by the Swedish strategic program against antibiotic resistance (STRAMA). STRAMA is an independent network aiming to minimize the development of antibiotic resistance and has been operating since 1995 [55]. After several years of small changes, 2009 showed a marked decrease in sales of antibiotics, with the greatest reduction in the group of children aged 0-6 years. One suggested reason for this decrease was the increased awareness of infection control issues and hand hygiene connected with the pandemic influenza in 2009 [56].

## Geographical and social differences

From an international perspective, Sweden is a country with low antibiotic use [57]. A European survey from 2003 showed that Greece and France had the highest amounts of outpatient antibiotics sold, while Sweden had a relatively low use of antibiotics [58]. There are also considerable variations in the amount of prescribed antibiotics between counties in Sweden, with the highest amounts found in Stockholm and the southern part of Sweden, and lower amounts in the north [58,59].

Children living in homes with a lower SEP more often experience respiratory infections during their childhood [10,60]. The reasons for this might be multifactorial, including an increased exposure to infectious agents due to crowding, poor nutrition, smoking, or stress [51]. Regarding socioeconomic differences in the use of antibiotics, there are studies that have shown a higher use in lower socioeconomic groups [51,61]. Studies have also shown a higher antibiotic consumption among the children of families experiencing stress, parents with a foreign background [62] and parents in need of support from outside the family [63]. However, there are also studies showing a lower use in low-SEP groups [64].

## Determinants

Infectious diseases are caused by microbes such as bacteria or viruses. Whether or not a given person develops disease when in contact with microbes depends on the aggressiveness of the microbe, but also on individual factors such as genetics, prevalent disease, age, and presence of medical treatments, as well as environmental factors [65]. Exposure to secondhand tobacco smoke during childhood has been shown to be associated with an increased risk for upper and lower respiratory tract infections such as common cold, recurrent ear inflammations, bronchitis, and pneumonia [12,66-69]. A recent systematic review and meta-analysis of 60 studies on the association between secondhand tobacco smoke and lower respiratory infections among small children, showed significant increases in the risk of lower respiratory infection in association with smoking by the mother, father, both parents, and any household member. Prenatal maternal smoking also had a significant effect on lower respiratory infection risk, but this was weaker than the postnatal effect [68]. Furthermore, exposure to maternal smoking during pregnancy has been shown to increase the risk of meningococcal disease during the first year of life [70]. Breastfeeding has been shown to have a protective effect against infectious gastroenteritis [71], recurrent ear inflammation [72], and respiratory tract infections. Some studies have observed a protective

dose/duration-response effect on gastrointestinal or respiratory tract infections [73]. Low birth weight has been shown to be associated with an increased risk for pneumococcal disease during early childhood [74], and an increased risk of pneumonia and bronchitis during the first two years in life [75].

## *The sensitive fetus and child*

The fetus and the growing child are especially vulnerable to environmental factors, due to their rapid growth and development [12]. Organ systems with a prolonged development and maturation, such as the central nervous system, the hormonal system, the reproductive system and the immune system, are more sensitive to unfavorable environmental exposures [12]. For example, the development and maturation of the immune system can be affected by exposure to various environmental factors early in life, leading to a reduced resistance to infection, or a change of direction of the immune system leading to allergic reactions or the development of autoimmunity. However, the mechanisms involved are relatively unknown. Furthermore, small children have immature metabolic pathways and therefore have more difficulties with detoxifying and excreting chemicals [67]. The liver reaches its full capacity first at 3 years of age, while the kidneys do so at the age of 1 year. Another difference between children and adults is that the uptake through the stomach and intestines is relatively higher among infants, due to a slower and more irregular intestine mobility and a slower drain of the stomach content. Finally, compared to adults, children inhale relatively larger volumes of air per kilogram, and so also have a relatively higher uptake through breathing than among adults [67]. All these differences between child and adult physiology lead to a higher vulnerability to environmental factors at a young age.

## *Causal model*

Since it is known that most diseases are multicausal and encompass intertwining chains of biological and social risk factors, an overall megamodel that takes into account all the possible social and biological influences on disease would be far too complex [76]. *Figure 1* shows a simplified hypothetical model of the determinants of childhood health. Childhood health is affected by individual factors (e.g., age, sex, genetic disposition, lifestyle habits), group-related factors (e.g., parental SEP, family, social network and ethnicity) and environmental factors (e.g., housing, day care, physical environment). These factors are also interconnected; for example parental SEP is thought to be related to material conditions (e.g., housing, physical

environment, family finances) as well as the social environment (e.g., family situation, and social network), which in turn might affect health-related behaviors and psychosocial stressors acting through biological mechanisms to affect childhood health.

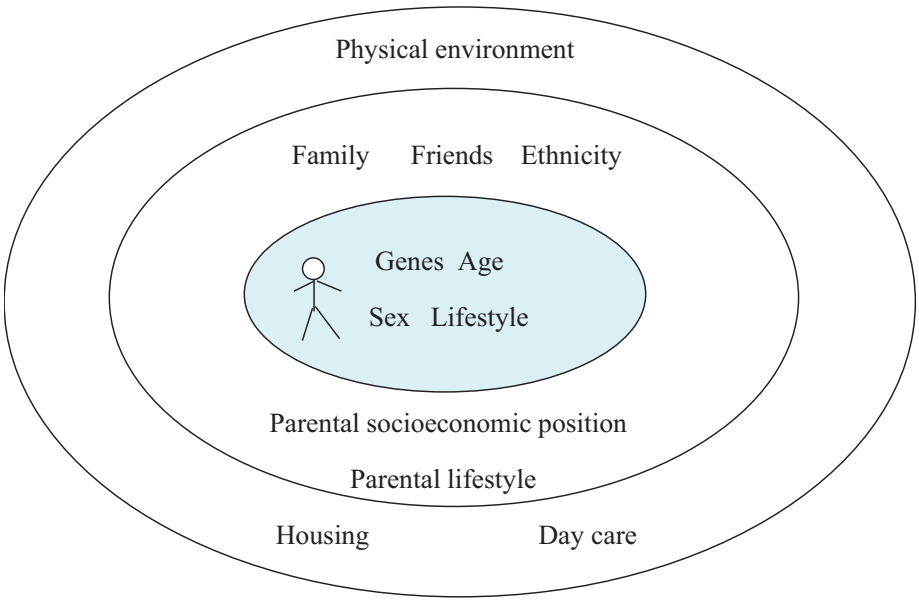


*Figure 1.* Some potential determinants of child health.

The importance of early life circumstances has attracted considerable attention during recent years and there has been growing interest in a temporal perspective on the development of disease [77]. It has been suggested that early development make important echoes in disease risk throughout life. Different conceptual models have been presented for the impact on disease of exposure to health risks early in life; these have been grouped into two broad conceptual models, the critical period model and the accumulation of risk model [78]. The critical period model focuses on the importance of an independent effect of exposure during a specific sensitive period in life, having lasting effects on health [79-81]. The hypothesis by Forsdahl of a lasting effect of adverse environmental conditions during childhood on adult health [82] and the fetal origins hypothesis formulated by Barker and Osmond in the 1980s were based on this model [83]. The fetal origins hypothesis proposes that alterations in fetal nutrition and endocrine status result in developmental

adaptations that permanently change structure, physiology, and metabolism, thereby predisposing individuals to cardiovascular, metabolic, and endocrine disease in adult life [84]. The process whereby a stimulus or insult at a sensitive or critical period of development has long-term effects is termed *programming*. The accumulation of risk model focuses on accumulation of risk during the life course [77-81]. This model assumes that risks to health gradually accumulate as the number, duration and severity of exposures increase. These life course models may operate simultaneously, and can be difficult to distinguish empirically [77]. The studies presented in this thesis were based on the assumption of an influence of various health determinants on childhood health encompassing both theoretical models.

## *Early life factors*

### a) Maternal smoking during pregnancy

Smoking during pregnancy has decreased by more than 20 percentage units during the past 25 years. Today, about 6% of women pregnant in the third trimester smoke daily [3]. Smoking during pregnancy is more common among women living in a household with low educational level and low income [1]. National comparisons using data from the medical birth register at the National Board of Health and Welfare show that the proportion of smokers at enrolment in maternity care (week 8-12 of the pregnancy) ranges between 4% and 9% at the county level and between 0% and 26% at the municipality level. The lowest proportions at the county level were seen in Västerbotten and Jämtland (4%), and the highest proportions in Skåne (8.9%), Sörmland, and Värmland (more than 9%)[85]. During 2005-2007, 8.4% of pregnant women in Malmö were smokers, placing it in the mid 50% of the Swedish municipalities [85]. Maternal smoking during pregnancy has been shown to increase the risk for sudden infant death syndrome (SIDS) [85,86], reduced birth weight [3,67,87], preterm birth [3,67], cleft lip/palate [88], congenital anomalies, decreased lung function [67], childhood obesity [89], colic pain [90], and meningococcal disease during the first years of life [70]. Maternal smoking has also been shown to be associated with wheeze in infancy [91,92] and acute lower respiratory infections during childhood [93]. Some plausible mechanisms for this have been suggested, concerning the negative effects of carbon monoxide on the fetal uptake of oxygen which may affect cell growth and development [85], as well as direct effects of nicotine on fetal development by impairing the maturation of the lungs [67]. Furthermore, children are less able to detoxify and excrete chemicals and are thus more susceptible to such toxic substances [67].

## b) Secondhand tobacco smoke

Tobacco smoke contains thousands of chemical gases or particles. Many of the substances from tobacco smoke are assimilated through the respiratory airways and mucous membranes [12]. For example, small children may assimilate nicotine through inhalation and through breast milk. Swedish national statistics from the Board of Health and Welfare have shown that close to 6% of mothers and more than 11% of fathers smoked during the infant's first month in 2006. The corresponding percentages for children born in 1999 were 9% and 14%, respectively. Among parents of infants aged 8 months, 7% of the mothers and 11% of the fathers were smokers [94]. There are considerable regional differences with regard to secondhand tobacco smoking. The counties of Värmland, Södermanland and Skåne have the highest rates of mothers who smoke during the infant's first month of life, with proportions ranging between 8% and 9 %. The corresponding highest proportions among fathers were seen in Skåne, Örebro and Södermanland with prevalences of 13-15% [94]. Exposure to secondhand tobacco smoke has been shown to be associated with an increased risk of upper and lower respiratory infections [12,66-69,94], impaired lung function [67] and the onset and severity of asthma [18,20,94]. Suggested mechanisms include a toxic effect of tobacco smoke on the child's evolving immune system and also a direct effect on the mucous membrane in the respiratory airways.

## c) Breastfeeding

Between the mid-1930s and the early 1970s, there was a decline in breastfeeding rates. Some explanations for this decline include the introduction of commercial breast milk substitutes and decreased support for breastfeeding as deliveries started to take place in the hospitals instead of at home [94]. Between 1950-1970, the percentage of children being breastfed at the age of 6 months decreased from 40 % to below 10 %. During the 1970s, there was a marked change of attitude in society, advocating the social and medical value of breastfeeding; this resulted in a sharp increase in breastfeeding. The frequency of breastfeeding began to rise again in the early 1990s partly due to the creation of Baby Friendly Hospitals Initiative (BFHI), on the initiative of UNICEF, with the goal to support breastfeeding [94]. The frequency of breastfeeding is high in Sweden. Almost all (97%) infants born in 2007 were being breastfed at the age of 1 week, and 80% were exclusively or partially breastfed at the age of 4 months. At 6 months, 68% were being breastfed. The prevalences for exclusive breastfeeding were 72% at 2 months and 59% at 4 months [94]. In Europe, Norway has the highest frequency of partly breastfed children at 6 months of age, with Sweden coming second. Great Britain and

Belgium are at the bottom of the list [95]. There are also regional differences within Sweden. The proportion of infants born in 2007 being exclusively breastfed at 4 months was about 65% on the island of Gotland and in the county of Västerbotten, about 55% in Skåne, and about 45% in Västmanland [94].

Breastfeeding has been shown to be protective and associated with decreased morbidity in infancy with a lowered incidence of infectious disease [96], asthma [97], childhood overweight [5,98], some childhood cancers [99], and Type 1 diabetes [100], as well as a better cognitive development [101]. There are various potential mechanisms regarding the protective effect of breastfeeding. Human breast milk contains large amounts of IgA, cytokines, fatty acids, and oligosaccharides [96,102]. These factors stimulate the development of the child's immune system and gut flora. The glycans found in breast milk, is thought to function as soluble receptors that inhibit pathogens from adhering to their target receptors on the mucosal surface of the host gastrointestinal tract [102]. Breastfeeding has been shown to be associated with favorable lipid profiles, lower levels of blood glucose, and lower blood pressure in later childhood [94]. Studies have also shown lower levels of serum insulin in infants fed breast milk than children fed with infant formula [98].

## Recommendations

The World Health Organization (WHO) and the World Health Assembly (WHA) recommend exclusive breastfeeding for 6 months, followed by continued breastfeeding with supplementary food for another 24 months or longer. Breast milk contains all necessary nutrition up to the age of 6 months apart from Vitamin D, which needs to be given from the age of 1 month [94]. The Swedish National Food Administration, together with the Swedish Pediatric Committee on Nutrition and in consultation with the National Board of Health and Welfare and the Ministry of Health and Social Affairs, have expressed the following view: "For the first period breast milk is the best nutrition for the child. Most infants manage excellently on breast milk exclusively for the first six months of their lives. From around six months breastfeeding ought for nutritional reasons to be supplemented with other food, but it is advantageous for breast milk to constitute a part of the diet throughout the first year of life or longer" [94,103].

### d) Birth weight

Between 1973 and 2001, the average birth weight in Sweden increased, the number of children with a high birth weight increased, and the number of children with a low birth weight declined. In 2001, this increase reached a plateau and there has since been a small decline in the average birth weight since then [86]. Worldwide, there are large differences in the numbers of children born with a low birth weight between various parts of the world. Statistics from UNICEF during 2000-2007 show the highest prevalences of low birth weight in South Asia (27%), Sub-Saharan Africa (15%), and West and Central Africa (15%), with lower prevalences in the industrialized countries (7%) [104]. There are two main reasons for low birth weight; growth retardation during pregnancy and premature birth. These two often exist together [3]. Today, about 2.5% of all children in Sweden are born with growth retardation and 6% are born preterm. These proportions have been fairly constant over the last decade [3]. Several studies based on different populations and across different measures of SEP inside and outside the Nordic countries have shown an inverse association between birth weight and SEP [105]. Lifestyle factors such as smoking and long-lasting stress could lead to impaired nutritional supply for the fetus during pregnancy, but growth retardation and preterm birth might also be due to the presence of maternal disease [3,106-108]. Being born with a low birth weight has been shown to predict health and health-related outcomes in childhood and later in life, such as, infant mortality, childhood obesity, school-age cognitive performance, adult mortality, and chronic diseases in adulthood such as diabetes, high blood pressure, central obesity and cardiovascular disease [3,98,105,109-115]. The mechanisms of these associations are still relatively unknown, but evidence from animal studies and some human studies have given a few ideas of potential mechanisms. An influence on the neuroendocrine development of the fetus with an activation of the hypothalamic-pituitary-adrenal axis, an impaired development of the pancreas with an impaired development of beta cells, and a deteriorated insulin-like growth factor 1-metabolism have all been suggested to potentially play a role in linking associations between growth restraint early in life and metabolic disease and diabetes later in life [98,116]. Having a high birth weight has also been shown to be associated with various health problems in both childhood and adulthood. High birth weight increases the risk of childhood and adulthood central obesity and there is an increased risk of arm and collarbone fractures at delivery sometimes followed by nerve injuries [98,117,118]. Most of the studies on potential mechanisms between high birth weight and later adiposity come from studies of diabetes during pregnancy [98]. Maternal hyperglycemia leads to excess fetal insulin, which in turn acts as a growth hormone for the fetus. Furthermore, animal studies suggest that fetal hyperinsulinemia can alter expression of hypothalamic neurotransmitters, leading to offspring hyperphagia and increased weight [118].

## *Socioeconomic position*

There is a huge body of literature showing that better health is related to social advantage [119]. Furthermore, it is widely acknowledged that the social position of the family is closely related to the health risks that small children are exposed to, and so the environment in which children grow up is closely associated with their health [120]. The term "socioeconomic position" refers to the social and economic factors that influence the positions individuals or groups will hold within the structure of a society [119]. The family's SEP affects the child's health from the very beginning, through the mother's living conditions and health habits during her pregnancy. The risk of death at delivery and death after the first week of life is highly increased in children to mothers from a household with low income compared to children to mothers of a more affluent background [3]. Parental smoking, short duration of breastfeeding, and low social support are all more common in low-SEP groups, and have been shown to be associated with increased morbidity and mortality rates in infancy [91,96,97,99-101,121,122]. Children from less affluent families are more prone to have or develop various health problems such as asthma, depression and anxiety, infectious diseases, and overweight and obesity, and they also have a higher morbidity and mortality due to injuries from accidents [3,10,65]. Furthermore, children from low-SEP homes are more often admitted to hospitals for respiratory infections or asthma, compared to children from households with a higher SEP, which could be due to a more severe disease condition [123].

There are different indicators of socioeconomic position. In the industrialized part of the world, the most established indicators are those based on educational level, occupational status, and income. For example, parental education is thought to reflect a child's early life circumstances. It reflects the material, intellectual, and other resources of the family, all of which might affect the growing child. Parental educational level might affect the receptivity to health education messages and the ability to communicate with health services [119]. Parental education also affects issues such as the child's performance in primary and secondary school, motivation, self-direction, and manner of speech, which in turn might affect future educational attainment, employment status, and income [119]. The high use of education as an indicator of SEP might partly be due to the fact that it is easy to measure and has high response rates when used in self-administered questionnaires. However, there are also some shortcomings. Educational attainment varies by birth cohort and by country, and a measure of length of education does not say anything about the quality of the education. Even though each of the three abovementioned indicators of SEP measure particular aspects of social stratification, they are all correlated

with each other since they measure aspects of an underlying social stratification [119].

## *Social support*

Although the concept of social support is an old one, it started to gain increased attention during the 1970s. Since then, studies have shown associations between the presence of social support and the ability to withstand stressful life situations [124-126]. Furthermore, low social support has been shown to be associated with more unfavorable health-related behaviors [125-127], chronic disease and increased mortality [124,126]. There has been some discussion of whether lack of social support is a stressor in itself, acting through neuroendocrine reactions or psychological mechanisms, or if social support only exerts an effect by buffering the impact of other stressors [125]. There has been support for both mechanisms [124-126,128]. It is well-known that the wellbeing of a child is closely linked to the physical, emotional and social health of the parents [129]. Poor maternal psychosocial functioning may influence the child's psychosocial and physical health both directly, by inhibiting the mother's ability to nurture and care for the child, and also indirectly through her limited personal resources to help her child by turning to a physician for assistance [130].

# Aims

## General aim

The general aim of this thesis was to examine the associations between sociodemographic factors, early life factors, health, and medical care consumption among small children.

## Specific aims

1. To investigate the associations between antibiotic use among 8-month-old children and characteristics of the child as well as parental sociodemographic characteristics, lifestyle factors, and psychosocial support. (Paper I)

2. To investigate the association between exposure to secondhand tobacco smoke at an early age and presence of allergy/having sought care due to allergic symptoms in 4-year-old children. Furthermore, to examine whether such a potential association was similar in children with heredity for allergy (i.e., with at least one parent having an allergy) and children with no such heredity. (Paper II)

3. To examine the association between early life factors and childhood overweight and obesity, and to investigate whether a potential association between early life factors and childhood overweight persisted after stratification for presence of parental overweight. (Paper III)

4. To examine differences in parental preventive behavior, parental risk behavior, social support, and the use of medical care in small children by maternal educational level. Furthermore, to investigate whether potential differences in child medical care consumption by maternal educational level could be explained by differences in parental behavior and social support. (Paper IV)

# Material and methods

## *The Child health care centers*

The Child Health Care (CHC) centers in Sweden have the common purpose of promoting health and development of all children, providing early identification of any problems with the growth and development of the child, and reducing child morbidity and mortality. According to international comparison, the CHC centers reach almost 100% of all children in the country, and are unique in doing so [131]. Similar solutions reaching the whole society can only be found in other Scandinavian countries and the Netherlands. The CHC centers offer base programs including regular visits, controlling each child's weight, height, hearing, sight, physical and psychological development, and administration of vaccinations according to the base program, until the child is 5-6 years old. The focus is on prevention, visits are voluntary, and the consultations are free of charge. The base program at the CHC centers in Malmö includes 15 visits from age 0 to age 4 years. Some of the visits are conducted with a nurse and some with a nurse and a physician.

## *The "Child health and living conditions study"*

During 1996 the Department of Social Medicine and the CHC in Malmö received an assignment to investigate the health and living conditions among small children in Malmö. This resulted in a self-administered questionnaire that was handed out to the parents of 8-month-old and 4-year-old children in conjunction with their check-up at the CHC centers aiming to reach all children in Malmö in these two age groups. The questionnaire was distributed by the pediatric nurses at the centers, and contained approximately 30 questions about issues such as the parents' education, country of birth, social support, and financial security; and the child's sex, number of siblings, medical care consumption, and housing. It also included questions about maternal smoking during pregnancy, secondhand tobacco smoke, and breastfeeding. A pilot study was conducted to test and validate the questions at some of the CHC centers in Malmö, before the questionnaire was put into use [132]. The results of the pilot study showed that the questions generally were well understood, and the response rates were generally high. However, there was some need for corrections. For example, the number of years of education was added to the items concerning parental educational level and the words "also includes smoking outside" were

added to the questions concerning secondhand tobacco smoke. Furthermore, the results showed that parents born outside the Nordic countries had some difficulty understanding and answering the questions, mostly due to linguistic problems. Thus, there was a need to translate the questionnaire into languages other than Swedish. The questionnaire was after this translated into five different languages: Albanian, Arabic, English, Serbo-Croatian, and Somali [133]. In addition to the information provided by the parents, information was collected from the CHC journal, such as the child's height and weight at 4 years, birth weight, and whether and how often the parents had taken part of the parental educational program. This assignment was later expanded to also include three other municipalities (Svedala, Vellinge, and Trelleborg).

The studies in this thesis were population-based and cross-sectional, and were based on children who visited the CHC centers in Malmö for their 8-month or 4-year checkup and whose parents answered the self-administered questionnaire. Table 1 gives a detailed description of the study population in each paper. The studies were approved by the Regional Ethical Committee at Lund University.

**Table 1.** Study population, measure of exposure, and outcome in each paper.

| Study | Design | Study population | Measures of exposure | Outcome measure |
|---|---|---|---|---|
| I | Cross-sectional | 7,266 boys and girls ages 8 months during 2003-2006 | Parental sociodemographic factors<br>Parental psychosocial factors<br>Parental life style factors<br>Child characteristics | Antibiotic consumption |
| II | Cross-sectional | 4,278 boys and girls ages 4 years during 2006-2008 | Secondhand tobacco smoke at 0 to 4 weeks and 8 months | Allergy |
| III | Cross-sectional | 9,009 boys and girls ages 4 years during 2003-2008 | Secondhand tobacco smoke at 0 to 4 weeks and 8 months<br>Smoking during pregnancy<br>Breastfeeding<br>High birthweight | Overweight<br>Obesity |
| IV | Cross-sectional | 9,289 boys and girls ages 8 months during 2003-2007 | Maternal educational level | Parental preventive behavior<br>Parental risk behavior<br>Medical care consumption |

## Malmö

Malmö is situated in the southwest part of Sweden. It is the third largest town in the country, with a population of about 300 000 inhabitants. Malmö is a multicultural municipality with 171 nationalities represented, and 100 languages spoken [134]. Of the children living in Malmö, more than 50% were born abroad or have parents who were born abroad [1]. The largest groups of immigrants originate from Iraq, Denmark, and the former Yugoslavia. Malmö is an old industrial city with a former expansive ship, textile and lime industry. However, starting with the town's economic crises during the 1970s and 1980s, with the closure of some of the former flourishing industries and a vast reduction in the number of industrial workers, the town has gradually been transformed from an industrial city into what some people call a "city of knowledge". The private sector service has grown in recent years, with companies within areas such as medical technology, information technology, logistics, and retail and wholesale trade. Today, Malmö has its own university college, as well as the Öresundsbron, a bridge between Denmark and Malmö, which connects Malmö with the continent thus facilitating tourism and transport of goods and manpower to and from other European countries. At the same time, Malmö is a segregated town. While 77% of the inhabitants in the more affluent western part of the town district such as Limhamn-Bunkeflo are employed or self-employed, the corresponding proportion in the more deprived eastern parts of the town, in Rosengård is 39% [135,136]. Child poverty in Rosengård is five times the national average, with a vast increase since the beginning of the 1990s [137]. In national comparisons, Malmö has a high proportion of inhabitants born abroad, a relatively low employment rate, a low median income per 1000 inhabitants, a relatively high proportion of child poverty and a relatively low proportion of pupils qualifying for upper secondary school (gymnasieskolan) [85].

## Studied factors

### Measures of early life factors

Exposure to secondhand tobacco smoke during early life (when the child was 0-4 weeks of age) was assessed through self-report by questionnaire and was dichotomized into no (no secondhand smoking) and yes (daily exposure, including smoking outside) based on the question: "Did anyone in the family smoke when the child was 0-4 weeks of age?" The answering alternatives concerned smoking on a daily basis (also including outdoor smoking) by mother/stepmother, father/stepfather, siblings or other person. An identical question was used to assess secondhand smoking at 8 months of age (Papers I-IV). Maternal smoking was

assessed through self-report by questionnaire and dichotomized into ‘yes’ and ‘no’ based on the question of whether the mother smoked during pregnancy (Papers I-IV). Information on birth weight was collected from the CHC journal. Low birth weight was defined as having a birth weight<2500 gram (Paper I, II and IV), while high birth weight was defined as having a birth weight>4000 grams (Paper III). Unfortunately, there was no information on small for gestational age (SGA) or large for gestational age (LGA). Breastfeeding was assessed through self-report by questionnaire. In paper IV breastfeeding was defined based on length of exclusive breastfeeding, while in the other three papers breastfeeding was defined based on length of total (partly and exclusive) breastfeeding. One reason for these differences in categorization is a change in question over time. During the period 2003-2007, breastfeeding was assessed through a question on length of exclusive and partly breastfeeding, respectively. However, in 2008, the question on breastfeeding was changed into one question on total length of breastfeeding without separating length of exclusive and partly breastfeeding.

## *Sociodemographic factors*

Information on sociodemographic variables was assessed through self-report by questionnaire. Parents’ country of origin was categorised into three categories: ‘Both parents born in Sweden’, ‘One parent born in Sweden’, and ‘Both parents born outside Sweden’ (Papers I-IV). Maternal and paternal educational level was categorised by length of education into three groups: ‘9 years or less’, ‘10–12 years’, and ‘more than 12 years’ (Papers I-IV). Earlier studies have shown a more evident association between maternal educational level and childhood health compared to paternal educational level [138] and therefore we focus on maternal educational level in Paper II-IV. Maternal and paternal employment status was categorised into: ‘Parental leave’, ‘Working’ and ‘Other’ (unemployed, studying, retirement, sick leave, working at home) and was used in paper I. Crowded living was defined as a household having more than two persons per room excluding the kitchen and bathroom and was calculated as the number of persons in the household divided by the number of rooms in the house/flat excluding the kitchen and bathroom (Papers II-IV). Position among siblings in the family was dichotomized into firstborn versus secondborn or later (Papers I-IV).

## *Psychosocial factors*

Information on psychosocial variables was assessed through self-report by questionnaire. Social support was operationalized as practical support and emotional support. Practical support concerned the possibility to receive help from someone to look after the child within the same day and was dichotomized into low practical support (i.e., those who answered ‘not for certain’ or ‘no’) and high practical support (i.e., those who answered ‘yes, definitely’ or ‘yes, probably’) (Papers III and IV). Emotional support reflects the individual’s experience of receiving care and personal encouragement, and having feelings of confidence and trust [124,125,127]. Emotional support was assessed with the question: “Do you have someone who can give you proper personal support to cope with life’s stresses and problems?”, and was dichotomized into low emotional support (i.e., those who answered ‘not for certain’ or ‘no’) and high emotional support (i.e., those who answered ‘yes, definitely’ or ‘yes, probably’) (Papers I-IV). The reliability and validity of the measure of emotional support have been assessed in earlier studies [124,125,127,139,140]. Economic stress was assessed with the question "How many times during the past year did you not have enough money to afford the food or clothes that you and your family needed?" with answers being classified into ‘yes’ (‘every month’, or ‘6 months a year’) and ‘no’ (‘very occasionally’ or ‘never) and used in Papers I and III. This measure of economic stress has been shown to be related to poor self-rated health even after adjustment for potential confounders [141].

## *Overweight/obesity*

Children´s height (cm) and weight (kg) was measured by the CHC nurse at the physical examination of the child at the CHC visit at 4 years. Overweight and obesity were assessed via BMI according to the classification by Cole et.al based on large nationally representative cross-sectional growth studies with cut-offs of 17.55 (boys) and 17.28 (girls) for overweight and 19.29 (boys) and 19.15 (girls) for obesity [27]. The parents’ height and weight were self-reported in the questionnarie and overweight was defined by BMI > 25 kg/m$^2$ and obesity >30 kg/m$^2$. Body mass index was calculated as weight (kg)/height (m)$^2$. These variables were used in Paper III.

## *Allergy*

Information on allergic diseases was assessed through self-report by questionnaire. Having an allergy was assessed through parents reporting that the child had allergic diseases (i.e., atopic eczema, hay fever, asthma or food allergies). Nickel and pencillin allergies were not considered. The categories were; 'no allergies', 'suspected allergies', 'confirmed allergy tested positive in prick test, in blood test or by provocation', or 'severe allergy diagnosed by a physician with need of medication for at least three months of the year', and the last category was 'I don´t know'. Those reporting confirmed allergies or having severe allergies were considered as having an allergy. This question came into use in 2006 and was used to assess childhood allergic disease in paper II. Parental allergy was assessed through an identical question, but directed at each biological parent instead. Parents reporting confirmed allergy or having severe allergies were considered as having an allergy. This variable was used to assess parental allergic disease in paper II. In paper I another question assessing child allergy was used, i.e., "Does the child have an allergy?" to which the parent could answer 'Yes' or 'No'. This question was removed from the questionnaire in 2008. Presence of allergy was further assessed by the question if the child had sought medical care in addition to the regular CHC-visits during the last 12 months, due to atopic eczema, food allergies or asthma. This variable was used to assess allergic disease in paper II.

## *Antibiotic consumption*

Information on antibiotic consumption was assessed through self-report by questionnaire. Antibiotic use at the age of 8 months was assessed by the question: 'Has the child been treated with any form of antibiotics during the child's first eight months of life?' The parent could answer 'Yes' or 'No' and also fill in the number of times. This variable was used in paper I.

## *Medical care consumption*

Information on medical care consumption was assessed through self-report by questionnaire. Having sought care from a doctor was categorized into 'Yes' and 'No' based on the question of whether the child had seen a doctor during the last 8 months in addition to the regular CHC visits. In-hospital stay was assessed through the question: "Has the child been admitted to the hospital during the last 8 months?" with response alternatives of 'Yes' and 'No'. These variables were used in paper IV.

## *Other*

Having a pet was based on the question of whether there was a pet in the home and could be answered with 'Yes' or 'No'. This variable was used in paper II. Recurrent infection was assessed through self-report by questionnaire and concerned how often the child had sought medical care in addition to the regular CHC-visits during the last 8 months due to infectious disease. This variable was categorized into '< 3 times' and '3 times or more' and was used in paper I. The child's drinking of sweetened beverages (i.e., soft drinks, syrup or Coca-cola) concerned daily drinking and was dichotomized into 'Yes' (daily drinking) and 'No' (including the following answering alternatives 'at night if he/she wakes up', 'once or twice a week', 'never'). This variable was used in paper III. Difficulties with breastfeeding were assessed through self-report by questionnaire with response alternatives: 'Yes' or 'No' (Paper IV). The types of breastfeeding problems were further assessed through the question: "If yes, what kind of problems?" with response alternatives: "Difficulties getting milk production started"; "Insufficient breast milk"; "Sore nipples"; "The child had difficulty suckling"; "Other, please specify?". More than one type of problem could be reported. These variables were used in paper IV. Having brushed the child's teeth was assessed through self-report by questionnaire with the question: "If the child has any teeth, have you started to brush them?" with response alternatives of "Yes" or "No" (Paper IV). Information on parental training was collected from CHC-journals, in which the nurse stated whether or not the parents had taken part in the parental educational program. This variable was used in papers II-IV. The parental educational program includes information and discussions about issues such as delivery and parenthood. Earlier studies have shown a lower attendance among lower educated parents and among parents born outside Sweden [142] and there are uncertainties regarding the effect from such education with few studies evaluating its health effects [142]. Presence of day care was assessed through self-report by questionnaire and was dichotomized into 'Yes' and 'No' (Paper III).

# Statistics

## *Paper 1*

Odds ratios (OR) and 95% confidence intervals (95% CI) were used to analyse the associations between various child and parental characteristics and antibiotic use. Multiple logistic regression analyses were performed in order to adjust the estimated OR for the influence of potential confounding factors. Model 1 included year and gender; model 2 included year, gender, and parents' country of birth; model 3 included year, gender, parents' country of birth, and maternal educational level; and model 4 included year, gender, parents' country of birth, maternal educational level, and having had recurrent infections. Statistical analyses were performed with version 12.0.1 of SPSS for Windows.

## *Paper II*

Statistically significant differences between various child and parental characteristics by presence of secondhand tobacco smoke early in life were established through estimating the confidence intervals around the differences between the proportions. Logistic regression was used to analyse the associations between secondhand tobacco smoke and the development of an allergy. Multiple logistic regression analyses were performed in order to adjust the estimated OR for the influence of potential confounding factors, i.e., sex, year of investigation, (i.e., 2006, 2007 or 2008), maternal smoking during pregnancy, maternal educational level, parents' country of birth, participation in parental education program, crowded living and having a pet. Furthermore, four groups were constructed based on presence of secondhand tobacco smoke early in life and presence of parental allergy. Potential synergistic effects between presence of secondhand smoke early in life and presence of parental allergy on the development of childhood allergy were tested using logistic regression analysis. Synergi index (SI) = ((OR(AB) – 1)/(OR(Ab) – 1) + (OR(aB) – 1)), where OR = Odds ratio; Ab = exposed to one risk factor; aB = exposed to the other risk factor; AB = exposed to both risk factors. Synergistic interaction was defined to be present if the effect of both exposures was more than additive compared with their independent effects (SI > 1). [143] CI (95%) for the synergy indexes were calculated [144]. Statistical analyses were performed with version 17.0 of SPSS for Windows.

## *Paper III*

Logistic regression was used to analyze the associations between early life factors and presence of overweight/obesity at the age of 4 years. Multiple logistic regression analyses were performed in order to adjust the estimated OR for the influence of potential confounding factors, i.e., sex, year, maternal educational level, parents' country of birth, participation in parental education program, first born, parental overweight, crowded living, intake of sweetened beverages and economic stress. Furthermore, potential synergistic effects between presence of parental overweight and unfavorable early life factors on the development of childhood overweight or obesity were tested using logistic regression analysis. A SI was calculated with the formula SI = ((OR(AB) – 1)/(OR(Ab) – 1) + (OR(aB) – 1)), where OR = odds ratio, Ab = exposure to one risk factor, aB = exposure to the other risk factor and AB = exposure to both risk factors. Synergistic interaction was defined to be present if the effect of both exposures was more than additive compared with their independent effects (SI > 1) [143]. CI (95%) for the synergy indexes were calculated [144]. Statistical analyses were performed with version 17.0 of SPSS for Windows.

## *Paper IV*

Proportions (95 % confidence intervals) of parental preventive behavior (length of exclusive breastfeeding, tooth brushing, participation in parental educational program), parental risk behavior (maternal smoking during pregnancy and secondhand tobacco smoke), social support (low emotional support, low practical support) were analyzed in relation to maternal educational level. The odds of medical care consumption (doctor's visits and in-hospital care), were analyzed in relation to exposure to one, two or three unfavorable parental behavioral factors (exclusive breastfeeding < 4 months, maternal smoking during pregnancy and secondhand tobacco smoke) by logistic regression. Logistic regression was further used to analyze the associations between maternal educational level and the child's medical care consumption. Multiple logistic regression analyses were performed in order to adjust the estimated OR for various covariates. Model 1 included year, sex, parents' country of birth, low birth weight and number of children at home; model 2 included model 1 with additional adjustment for low emotional support and low practical support and model 3 included model 2 with additional adjustment for maternal smoking during pregnancy, secondhand tobacco smoke at 0 to 4 weeks and length of exclusive breastfeeding. Statistical analyses were performed with version 17.0 of SPSS for Windows.

# Results and conclusions

## *Paper I:*

## *Antibiotic use among 8-month-old children in Malmö, Sweden-in relation to child characteristics and parental sociodemographic, psychosocial and lifestyle factors.*

### Aim

To investigate the associations between antibiotic use among 8-month-old children and child characteristics, parental sociodemographic characteristics, psychosocial factors and lifestyle factors.

### Results

The crude odds for antibiotic use were significantly higher in families where both parents were born outside of Sweden, OR= 1.43 (95% CI: 1.24-1.65), compared to families where both parents were born in Sweden. This association remained statistically significant after adjustment for confounders. Using higher educational level (>12 years of education) as a reference group, lower maternal educational level (≤ 9 years of education) was associated with an increased antbiotic use for the child, OR=1.61 (95 % CI: 1.34-1.93). This association was only slightly reduced after adjustment for potential confounders, but turned statistically non-significant in the last model. Daily exposure to secondhand tobacco smoke was associated with an increased antibiotic use. This association remained after adjustment for year, gender, and parents' country of birth, but decreased after adjustments for maternal educational level and recurrent infections. Families experiencing economic stress and reporting low access to emotional support had a significantly increased use of antibiotics among their 8 month-old children, OR=1.55 (95% CI: 1.24-1.93) and OR=1.47 (95% CI: 1.26-1.71), respectively. These associations remained statistically significant after adjustment for potential confounders. Boys had higher odds of use of antibiotics than girls. Having a low birth weight and having siblings also increased the odds for early antibiotic use, while breast feeding seemed to have a protective role, even after adjustment for confounders (*Figure 2*).

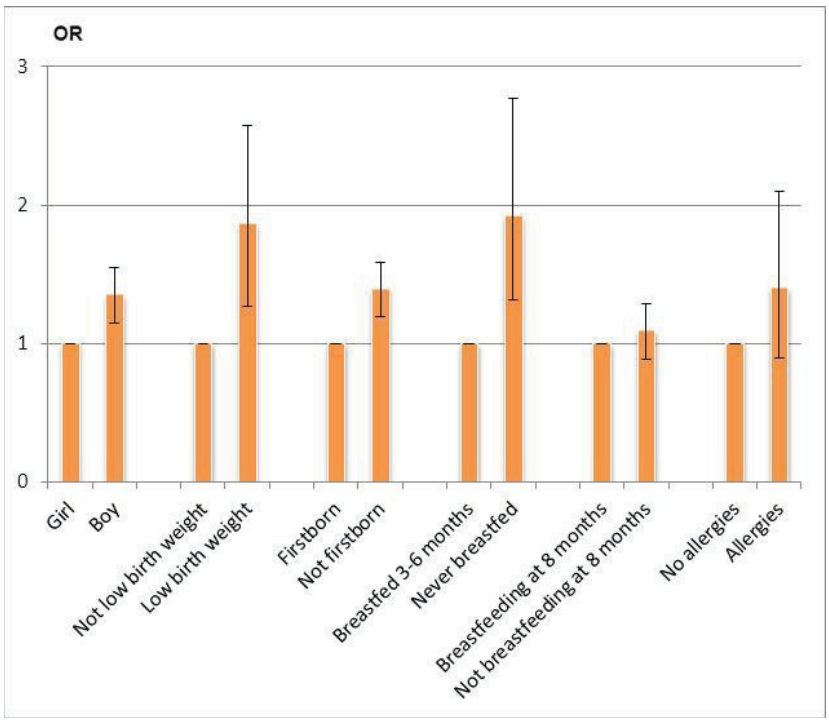


*Figure 2.* Adjusted odds ratios and 95 % confidence intervals of antibiotic consumption in 8-month-old children in Malmö, Sweden, by various child characteristics.

## Conclusions

The use of antibiotics among 8-month-old children was influenced by several factors including parental sociodemographic factors, lifestyle factors, psychosocial support, as well as child-related factors.

# *Paper II:*

# *Early exposure to secondhand tobacco smoke and the development of allergic diseases in 4-year old children in Malmö, Sweden.*

## Aim

To investigate the association between exposure to secondhand tobacco smoke at an early age and presence of allergy/having sought care for allergic symptoms in 4-year old children. Furthermore, to investigate whether such a potential association was similar in children with heredity for allergy (i.e., with at least one parent having an allergy) and children with no such heredity.

## Results

In total, 22 % of the 4-year old children experienced secondhand tobacco smoke during their first month in life. Children with such presence of secondhand tobacco smoke more often had a mother with lower educational level (≤ 9 years of education), had parents not born in Sweden, had a mother who smoked during pregnancy, had a pet, had crowded living, had less often taken part of parental educational programs, less often had a parent with an allergy, had less often been breastfed and were less often firstborn compared to children not exposed to secondhand tobacco smoke early in life. A similar pattern of association was seen for presence of secondhand tobacco smoke at 8 months of age. Children who experienced secondhand tobacco smoke during their first month in life were also to a high degree exposed at the age of 8 months and 4 years.

There was a two to four times increased odds of the child having an allergy or having sought medical care due to allergic symptoms if at least one parent had an allergy, while there were only small increased odds related to presence of tobacco smoke during the child's first month in life or at the age of 8 months (table 2). Constructing four groups based on presence of secondhand tobacco smoke early in life and presence of parental allergy in relation to the child's development of an allergy, indicated a synergistic effect of parental allergy and presence of secondhand tobacco smoke during the first month in life. A similar, but somewhat weaker, pattern of association was seen for presence of secondhand tobacco smoke at 8 months of age. Furthermore, similar analyses, also pointed at synergistic effects

of parental allergy and presence of secondhand tobacco smoke early in life with regard to having sought medical care due to allergic symptoms at the age of 4 years.

**TABLE 2.** Odds ratios (OR) and 95 % confidence intervals (CI) of having an allergy or having sought medical care due to allergic symptoms during the last year in 4-year old children in Malmö, Sweden, by presence of secondhand tobacco smoke and presence of parental allergy.

| | Allergy† | Having sought medical care† due to allergic symptoms |
|---|---|---|
| | *Adjusted model‡* OR; 95 % CI* | *Adjusted model‡* OR; 95 % CI* |
| *Secondhand tobacco smoke* | | |
| Secondhand tobacco smoke during the first month of age (yes vs. no)* | 1.20 (0.83, 1.73) | 1.17 (0.81, 1.69) |
| Secondhand tobacco smoke during eight month of age (yes vs. no) | 1.12 (0.77, 1.64) | 1.39 (0.97, 1.99) |
| *Parents with an allergy* | | |
| At least one parent with an allergy (yes vs. no) | 4.79 (3.51, 6.71) | 2.46 (1.81, 3.34) |
| Mother having an allergy (yes vs. no) | 4.85 (3.58, 6.56) | 2.57 (1.89, 3.49) |
| Father having an allergy (yes vs. no) | 3.51 (2.61, 5.01) | 1.74 (1.25, 2.41) |

* OR, odds ratio; CI, confience interval; Secondhand tobacco smoke was categorized into no (no secondhand tobacco smoke at all) and yes (daily secondhand tobacco smoke, including smoking outside).
† Parents reporting that the child had or had had allergic diseases (i.e., atopic eczema, hay fever, asthma or food allergies). Those reporting confirmed allergies (tested positive in skin prick test, in blood test and by provocation) or having severe allergies were considered as having an allergy;.Allergies were further assessed by the question if the child had sought medical care during the last 12 months, due to eczema, food allergies or asthma.
‡ Adjusted for sex, year, maternal smoking during pregnancy, maternal educational level, parents´country of birth, taken part of parental education program, crowded living and having a pet.

## Conclusions

Children with a family history of presence of allergy and early exposure to secondhand tobacco smoke is a risk group that prevention and intervention should pay extra attention to. The tobacco smoke effect on children is an essential and urgent question considering it not being self-chosen, possibly giving life lasting negative health effects and being possible to reduce.

# *Paper III:*

# *Early life factors and being overweight at 4 years of age among children in Malmö, Sweden.*

## Aim

To investigate the associations between early life factors and childhood overweight and obesity. Furthermore, to investigate whether a potential association between early life factors and childhood overweight persisted after stratification for presence of parental overweight.

## Results

About 15% of the children were overweight and 3% were obese at the age of 4 years. Overweight children were less often boys, more often had overweight parents, more often had a mother who smoked during pregnancy, more often had early exposure to secondhand tobacco smoke, more often had high birth weight and more often had parents who experienced economic stress, compared to children who were normal weight. A similar pattern was seen for obesity at 4 years of age but apart from the mentioned factors associated with overweight, obese children also more often had parents with lower educational level, had parents born outside Sweden, had parents who had not taken part of the parental educational program, lived in crowded conditions, and were less often breastfed compared to children who were not obese.

Having overweight/obese parents was strongly associated with the child being overweight or obese. Furthermore, there were associations between unfavorable early life factors (i.e., mother smoking during pregnancy, presence of secondhand tobacco smoke early in life, high birth weight) and the development of childhood overweight and obesity at 4 years of age, while breastfeeding seemed to have a protective role. The results further showed synergistic effects between parental overweight and exposure to some unfavorable early life factors (i.e., maternal smoking during pregnancy and high birth weight) in the development of childhood overweight and obesity. For example, table 3 presents the odds ratios of child overweight at 4 years of age in relation to presence of maternal smoking during pregnancy stratified by presence of parental overweight. Children whose mothers had smoked during pregnancy and with at least one overweight parent showed highly increased odds of being overweight at 4 years of age, while no such effect

was seen among children with presence of maternal smoking during pregnancy whose parents were normal-weight. These associations were not changed after adjustment for potential confounders. The synergy index was 3.12 (95 % CI: 1.13, 8.63). As this value exceeds 1, it indicates a synergistic effect of the mother's smoking during pregnancy and having overweight parents on the child being overweight at the age of 4 years. Similar, but weaker patterns of associations were seen for not having been breastfed and presence of secondhand tobacco smoke early in life.

**TABLE 3.** Odds ratios (OR) and 95 % confidence intervals (CI) of being overweight at 4-years of age by maternal smoking during pregnancy and presence of parental overweight, Malmö, Sweden.

| | Parents normal-weight | | At least one parent with an overweight* | |
|---|---|---|---|---|
| | Maternal smoking during pregnancy | | Maternal smoking during pregnancy | |
| | No | Yes | No | Yes |
| | OR; 95 % CI* | OR; 95 % CI | OR; 95 % CI | OR; 95 % CI |
| *Adjusted for sex and year* | 1.00† | 0.84 (0.47, 1.50) | 1.73 (1.47, 2.04) | 2.77 (2.16, 3.55)§ |
| *Adjusted model‡* | 1.00† | 0.98 (0.53, 1.92) | 1.75 (1.46, 2.10) | 2.81 (2.11, 3.73)§ |

* OR, odds ratio; CI, confience interval; Parental overweight was defined as having a BMI > 25 kg/m$^2$.
† Reference level.
‡ Adjusted for year, sex, maternal educational level, parents´ country of birth, crowded living, being firstborn, having taken part pf parental educational program, economic stress, and intake of sweetened bewereges.
§ Statistically significantly different ($p<0.05$) from the category: At least one parent with an overweight and no maternal smoking during pregnancy.

## Conclusions

This study shows the importance of early life factors in the development of child overweight and obesity, and thus puts focus on the importance of early targeted interventions. The results further showed a synergistic effect of parental overweight and exposure to some unfavorable early life factors in the development of child overweight and obesity.

# *Paper IV:*

# *Maternal educational level, parental preventive behavior, risk behavior, social support and medical care consumption in 8-month-old children in Malmö, Sweden.*

## Aim

The aim of the present study was to investigate potential differences in parental preventive behavior, risk behavior, social support, and the use of medical care among small children, by maternal educational level. Furthermore to investigate whether potential differences in child medical care consumption by maternal educational level could be explained by differences in parental behavior and social support.

## Results

Children with less-educated mothers were exposed to more health risks than children with higher educated mothers. For example, smoking during pregnancy was five times more common among the less-educated mothers. Less-educated mothers more often experienced low emotional support and low practical support in comparison to mothers with a higher level of education (>12 years of education) and also showed a less health-promoting behavior. Exclusive breast feeding ≥ 4 months was more common among mothers with higher levels of education than among less-educated mothers. A similar pattern of association was seen for tooth brushing and participation in parental educational programs. The differences in breastfeeding duration by maternal educational level could theoretically be due to differences in the frequency of breastfeeding problems. Among mothers without breastfeeding problems, 83 % exclusively breastfed their child for at least 4 months, while the corresponding proportion among mothers with such problems was 42 %. However, there were no differences in the occurrence of breastfeeding problems between maternal educational groups.

The results further showed that increased exposure to unfavorable parental behavioral factors (maternal smoking during pregnancy, secondhand tobacco smoke and exclusive breastfeeding <4 months) was associated with increased odds of in-hospital care and having sought care from a doctor during the last 8 months.

Furthermore, children of less-educated mothers had increased odds of in-hospital care and having sought care from a doctor during the last 8 months. These associations were reduced and turned statistically non-significant after adjustment for unfavorable parental behavioral factors (table 4).

**TABLE 4.** Odds ratios (95 % CI) of doctoral visits and in-hospital stay in relation to maternal educational level.

| | *Doctoral visit beside the regular CHC visits during the last 8 months* | | | *In-hospital stay during the last 8 months* | | |
|---|---|---|---|---|---|---|
| | Model 1† OR (95 % CI)* | Model 2‡ OR (95 % CI)* | Model 3‡ OR (95 % CI)* | Model 1† OR (95 % CI)* | Model 2‡ OR (95 % CI)* | Model 3‡ OR (95 % CI)* |
| Maternal educational level | | | | | | |
| ≥12 years | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| 10-12 years | 1.27 (1.15,1.41) | 1.26 (1.14,1.40) | 1.14 (1.02,1.29) | 1.07 (0.93,1.24) | 1.07 (0.93,1.24) | 1.04 (0.88,1.25) |
| ≤ 9 years | 1.28 (1.09,1.50) | 1.25 (1.06,1.48) | 1.11 (0.91,1.35) | 1.34 (1.08,1.66) | 1.33 (1.06,1.65) | 1.16 (0.89,1.51) |

* OR, odds ratio; CI, Confidence interval
† Adjusted for year, sex, parents country of birth, low birth weight and number of children at home.
‡ Model 1 with additional adjustment for low emotional support and low practical support.
§ Model 2 with additional adjustment for maternal smoking during pregnancy, secondhand tobacco smoke at 0-4 weeks of age and exclusive breastfeeding less than 4 months .

## Conclusions

In conclusion, the results showed that children with less-educated mothers were exposed to more health risks, fewer health-promoting factors, worse social support and had higher medical care consumption than children with higher-educated mothers. Furthermore, the differences in medical care consumption by maternal educational level emphasize the notion that children's health seems to be influenced by the characteristics of the families into which they are born. Thus, improving children's health calls for policies that target the parent's health-related behaviors and social support.

# General discussion

## *Findings*

### Antibiotic use among small children

The results from Paper I showed that use of antibiotics among 8-month-old children was influenced by several factors including parental sociodemographic factors, lifestyle factors, psychosocial support, as well as child-related factors. In our study, antibiotic consumption was significantly higher among children whose parents were less well educated. Similar results have been seen in other studies [51,61,145]. One explanation might be related to the fact that low educational level and unemployment among parents have been shown to be associated with a higher risk of lower respiratory infectious disease and ear inflammation. Even though many of these diseases are of viral origin, antibiotics might be needed in case of subsequent bacterial infections. Furthermore, socioeconomic position might influence the decision of the physician to prescribe antibiotics [51]. A study from Italy with the purpose to check the pediatricians-parents relationships in request for pharmaceutics (mainly antibiotics) during a visit showed that lower educated mothers requested more antibiotics and concluded that this could be due to more anxiety. They also concluded that these mothers were in need of more information, attention and more time given them during the visits [145]. However, there are also studies showing a similar or lower use of antibiotic use among children of less educated parents [64,146]. Potential explanations of such an association include limited economic resources or the fact that these families less often attended day care. The use of antibiotics was also higher in families where both parents were born outside Sweden, a finding supported by other studies [62,108]. This could partly be due to differences in cultural traditions in the case of disease. The finding of a protective role from breastfeeding on antibiotic use is supported by other studies [63,147,148] and might be due to the protective effect of breast milk on infectious disease. Our study further showed a higher antibiotic consumption among parents with low emotional support and among those experiencing economic stress. In accordance with these results, other studies have found a higher antibiotic consumption among children of families experiencing stress and parents in need of support from outside the family [51,63]. In Paper I, children born with a low birth weight had more use of antibiotics compared to children born with a normal weight. This could be due to a higher frequency of lower respiratory infections and wheezing difficulties among children born with a low birth weight and it could also

be that disorders of fetal growth affect the immune function [149]. As in other studies [51,63], boys were more often prescribed antibiotics than girls. Such an effect might perhaps partly be explained by sex differences in air way structures and fetal lung development [150], predisposing boys to more frequent lower respiratory tract infections. Earlier studies have shown an association between exposure to secondhand tobacco smoke and increased antibiotic use [147,151]. We found a similar pattern of association, but the association was reduced after adjustment for maternal educational level.

## Early exposure to secondhand tobacco smoke and the development of allergy

The results in Paper II showed that early exposure to secondhand tobacco smoke tended to be associated with increased odds of reported allergies although the associations were non-significant. However, children with heredity for allergies and with presence of secondhand tobacco smoke during early life had highly increased odds of developing an allergy or having sought medical care due to allergic symptoms. Early exposure to secondhand smoking has been shown to be associated with the development of asthma and wheezing episodes, allergic sensitization and the development of atopic eczema [14,17-19]. However, there are also negative studies [15,152-154]. Furthermore, studies have shown an increased risk of developing an allergy if the parents have an allergy [13-16]. This is consensus with established theories of allergy heredity. The Swedish BAMSE-study, a prospective birth cohort study among children ages 1-14 years in four areas in Stockholm concluded that there is a 55 % risk for future asthma and allergies if both the parents are allergic [97]. The effect of smoking has also been suggested to be stronger in genetically susceptible children and it has even been suggested that some genetic markers could indicate increased susceptibility to environmental factors and identification of these markers might be interesting for future research [13]. There are only few earlier studies showing a synergistic effect of secondhand smoke and heredity on the development of an allergy [13-16]. In the study by Krämer et al. there was an association between cotinine to creatinine ratio (CCR) as a measure of secondhand tobacco smoke and sensitization against house dust mites among children with parental atopy [14]. The fact that children's metabolic pathways, especially directly after birth, are immature and still developing and the fact that children's ability to detoxify and excrete chemicals differs from that of adults, makes children more vulnerable to inhaled toxic substances. Furthermore, children inhale greater volumes of air per kilogram weight than adults do and therefore inhale relatively greater amounts of air pollutants [67]. This together with the notion that there seem to be a genetic predisposition to the harmful effects of

tobacco smoke - not everyone who smokes develop chronic pulmonary disease, i.e., genetic factors play a role in determining the susceptibility to the harmful effects of tobacco smoke [67], makes children and especially children with heredity for allergy more susceptible to the toxic effects of secondhand tobacco smoke.

## Early life factors and childhood overweight/obesity

The results in Paper III showed that having overweight/obese parents was strongly associated with the child being overweight or obese. This result is in line with the results from earlier studies [35,39,40,155-158]. Such an association could be due to genetic factors as well as environmental and/or behavioral factors [159]. Environmental factors have been suggested to contribute to geographic and cultural differences in overweight/obesity and trends over time [158]. According to Silventoinen et al., both genetic background and the environment around the child seem to play an important role in determining whether he or she becomes obese. This observation was demonstrated by comparing twins and adoptees [159]. It is well-known that parents play an important role in the development of their children's food preferences and energy intake [160].

The results in Paper III further showed an association between unfavorable early life factors and the development of childhood overweight and obesity, while breastfeeding seemed to have a protective effect. Early life has been seen as a critical period for the development of obesity. Early life factors such as secondhand tobacco smoke [69,161], maternal smoking during pregnancy [47,48,161-166], impaired fetal growth [35,167], high birth weight [39,168], and low breastfeeding levels [5,42-46,98,163,169-171] have in previous studies been shown to be associated with childhood overweight and obesity. However, the mechanisms underlying the developmental origins of disease remain poorly defined [167]. Maternal smoking during pregnancy was associated with both overweight and obesity at the age of 4 years. The mechanism behind this association could be related to impaired skeletal growth and effects on growth and adiposity hormones such as growth hormones, leptin and gherelin responsive pathways and also a direct stimulation of the fetal hypothalamic pituitary axis, leading to increased levels of adrenocorticotropic hormones with chronic changes in the proportion of body fat [89]. There might also be long-term effects of nicotine exposure on neurobehavioral impulse control affecting satisfaction and appetite [172,173]. The results from Paper III also showed an association between high birth weight and childhood overweight and obesity. Ideas on potential mechanisms behind such an association come from studies of maternal diabetes during pregnancy. Maternal hyperglycemia has been shown to lead to excess of fetal insulin, which in turn acts as a growth hormone for the fetus [118], i.e., the developing fetal pancreas responds to a

glucose load by producing additional insulin. As insulin acts as a fetal growth hormone, exposure to that could lead to fetal adiposity [174,175]. Breastfeeding was found to protect against childhood obesity. One mechanism behind the protective role of breastfeeding could be related to the higher protein/nitrogen content of infant formula compared with breast milk, which may cause increased insulin and insulin-like growth factor-1 secretion leading to excessive weight gain [169,176,177], but has also been suggested to affect energy intake regulation [178]. It could also be that compared with mothers who bottle feed their babies, mothers who breastfeed may be more responsive to the infant's signals for frequency and volume of feeding [179]. The process which links reduced fetal growth with childhood overweight/obesity has been suggested to stem from adrenal overactivity initiated by early growth restraint [180] and by early postnatal catch-up growth resulting in an acceleration of growth that overshoots the genetic trajectory [47]. Secondhand tobacco smoke has been suggested to be related to overweight via its association with low socioeconomic position and less healthy food patterns [181]. However, in Paper III, the association with childhood overweight and obesity persisted even after adjustment for maternal educational level.

Paper III showed a synergistic effect between presence of parental overweight and some unfavorable early life factors (i.e., high birth weight and maternal smoking during pregnancy). There are no previous studies specifically investigating this. However, it is an important topic considering the fact that parental obesity might reflect adverse eating and physical activity patterns, and might be related to both early life factors and later obesity. Furthermore, genes shared by the parents and child might also be associated with both early life factors and later obesity [98].

## Maternal educational level, parental preventive behavior, risk behavior, social support and child medical care consumption

The results in Paper IV showed that children of less-educated mothers were exposed to more health risks, fewer health-promoting factors, and worse social support than children with higher educated mothers. Earlier studies have shown that parental behavior is influenced by material resources and knowledge of favorable life styles [3]. Parental smoking, short duration of breast feeding and low social support have in earlier studies been shown to be more common in lower socioeconomic groups, and have all been shown to be associated with increased morbidity in infancy [18,96,99,101,121,122]. The results in Paper IV further showed that children with less educated mothers had higher consumption of medical care than children with mothers of a higher educational level. Similar

results have been shown in earlier studies [182], but there are also studies with no socioeconomic differences in consultations with a physician or use of health services [146] and also an opposite pattern where children in families with low social status were less likely to have paid a visit to a physician because of an acute infection compared to children with higher social status [64]. The difference in medical consumption by maternal educational level in paper IV was reduced after adjustments for parental behavioral factors such as maternal smoking during pregnancy, exposure to secondhand tobacco smoke as well as duration of breastfeeding. There may be different theoretical mechanisms underlying the association between such behavioral factors and medical care consumption. Earlier studies have shown breastfeeding to be protective and associated with decreased morbidity in infancy with a lowered incidence of infectious diseases, asthma, overweight, Type I diabetes, some childhood cancers, as well as a better cognitive development [94,96-101]. Maternal smoking during pregnancy has been shown to increase the odds for having a child with congenital anomalies, cleft lip/palate, decreased lung function, colic pain, and meningococcal disease [3,17,67,70,90]. Furthermore, a recent review showed that secondhand tobacco smoke was associated with both the onset and severity of asthma, as well as respiratory and middle ear infections among children [20]. Low emotional and practical support have in previous studies been shown to be associated with health care seeking [130,184]. However, in our study, adjustment for low social support did not affect the socioeconomic differences in medical care consumption shown in Paper IV.

# *Methodological issues*

## Representativity

All CHC-centers in Malmö have taken part of the 'Child health and living conditions' investigation since 1998 when the investigation started, apart from the CHC-centers that were formed after that year [133]. Malmö had 18 child health care centers in 2003 and 19 child health care centers in 2008. During the study period they served about 3000 children aged 8-months per year and 2500 children aged 4-years per year. During the period 2003 to 2008, the proportion of parents who answered the questionnaire was about two thirds of those who received the questionnaire (68% among the 4-year-old children (Paper III)). The corresponding proportions for the period 2003 to 2006 among the 8-month-old children was 64% (Paper I), 67% for the period 2006 to 2008 among the 4-year old children (Paper II) and 65% for the period 2003 to 2007 among the 8-month-old children (Paper IV). An earlier study showed only small differences between the participants and the general population with regard to maternal educational level, while there was an underrepresentation of parents born outside Sweden [133]. Such an underrepresentation might affect absolute descriptive measures such as prevalences and proportions. However, when studying associations and using effect estimates, it is more important that the relation between exposure and disease is the same for those who participate in the study, and those who are theoretically eligible for the study, including those who do not participate, rather than a strict criteria of representativity [185]. If the latter would be the case, then every population and also every generation would require its own battery of epidemiological studies [185]. The likelihood of such selection bias in a given study is often assessed by subjective reasoning.

## Study design

The four papers described in this thesis were based on rather large samples aiming to address all children in Malmö in the two age groups (8 months and 4 years) with fairly good response rates. Data sampling was cross-sectional, which could make it difficult to draw conclusions regarding causal relationships. In prospective studies, the temporal sequencing between exposure and outcome is more evident, since the level of exposure is measured before the onset of disease. Even though the studies include self-reported retrospective information on exposure to various early life factors such as maternal smoking during pregnancy, breastfeeding, and secondhand tobacco smoke during the child's first month in life and at the age of 8 months, this

information was reported at the same time as the self-reported outcome measures. Such reporting could include recall bias and underreport of exposures known to be undesired [186].

## Synergy index

Rothman's model of synergism used in our studies, is based on the theory of two causes being component causes in the same sufficient cause. The criterion for interaction is a departure from additivity, and the reference group for the comparisons is the group unexposed to either factor [143]. Rothman's model of synergism is based on additive models and was recommended in a review on how to evaluate interaction by Hallqvist et al. [187]**.** This model has the advantages in that information from different types of studies can be employed, it has a theoretical background , and there is methodology to obtain confidence intervals from multiple regression software [187]. Synergy index = (OR (AB) – 1)/((OR (Ab) – 1) + (OR (aB) – 1)), where OR = odds ratio, Ab = exposed to one risk factor, aB = exposed to the other risk factor and AB = exposed to both risk factors. Synergistic interaction was defined to be present if the effect of both exposures was more than additive compared to their independent effects (synergy index > 1). Furthermore, confidence intervals were calculated [144].

## Validity of measures of breastfeeding

Retrospective report on length of breastfeeding might be prone to recall error due to factors such as stress and sleep deprivation during the child's first year and might also be overestimated due to social pressures to breastfeed [188]. There are previous studies on the validity of self-reported breastfeeding [188-191]. A review on the validity and reliability of maternal recall of breastfeeding practice concluded that maternal recall is a valid and reliable estimate of breastfeeding duration, especially when the duration of breastfeeding is recalled after a shorter period (≤ 3 years) [190]. However, validity and reliability of maternal recall for the age at introduction of food and fluids other than breast milk was less satisfactory [190]. Other studies have reported high correlations for associations between previously recorded breastfeeding durations and that recalled by mothers [192,193]. Thus, there may be some bias with regard to self-reported length of breastfeeding in the present studies. However, such bias is most likely to attenuate the true associations between breastfeeding and the outcome measure towards the null.

## Validity of measures of smoking habits

Self-reported smoking habits might be prone to various types of information bias such as recall bias and underreport of smoking to avoid criticism [194]. However, self-reported information on smoking status among adults has been shown to have high validity in epidemiological studies [194,195]. Self-reported smoking has been validated through various methods, e.g., measurements of serum-cotinine, exhaled carbon monoxide, hair nicotine, urine cotinine and serum thiocyanate. A Danish study showed high validity of self-reported smoking among parents during pregnancy and early childhood validated through exhaled CO (carbon monoxide) [194]. Nafstad et al. further reported high correlations for child hair nicotine and urine cotinine with reported smoking rates among parents of children ages between 12 and 36 months [196]. Similar results have been found in other studies [197]. Questionnaire information on presence of secondhand tobacco smoke in early childhood has also been validated through blood samples measuring cotinine and thiocyanate with good agreement between high and low levels of biomarkers and daily- and non-smoking mothers [196]. However, a recent review found a tendency of underestimation of self-reported smoking, especially when smoking was seen as undesirable, e.g., during pregnancy [198]. Such an underestimation would most likely lead to a dilution of the true associations between smoking habits and the outcome measure.

## Validity of measures of allergy

Self-reported allergy might be connected with bias. Parents who suffer from allergies may be more alert in seeking medical care for their children based on recognition of symptoms. Furthermore, there might be vague symptoms not recognised as symptoms of allergic disease. Asthma definitions relying on self-report has been shown to be associated with high specificity, but low sensitivity, i.e., an increased fraction of false negatives. Such bias has been shown to be associated with the severity of disease where mild cases are less prone to report their asthma or seek medical care due to allergic symptoms [199]. The questions used in Paper II to code the children as having an allergy included children with rather severe allergic problems (i.e., allergy confirmed through skin prick test, blood sample, or by provocation or requiring medication at least three months of the year or having sought medical care due to allergic symptoms in addition to the regular CHC-visits).

## Confounding

In all the four papers, the possibility of confounding was considered. The results were therefore presented as unadjusted and adjusted measures of effect. Confounding is a distortion in the estimated exposure effect that result from differences in risk between the exposed and unexposed that are not due to exposure [200]**.** A confounding factor can be defined as a risk factor for a disease that is associated with the exposure under study. However, a confounding factor must not be affected by the exposure, i.e., it cannot be an intermediate step in the causal chain between exposure and disease [200]**.** The definition of a factor as a confounding factor is often based on theoretical assumptions from causal models and previous results. The decision to adjust for a confounding factor may be based on quantitative criterions such as the change-in-estimate criteria. For example, if a change in odds ratio of 5 % after adjustment for a certain variable is regarded as important, then this variable should be adjusted for. However, there is no exact cutoff [200]**.** The decision to regard variables as confounders in the present studies was based on evidence from studies of factors that might affect the specific outcomes used and studies of factors that might be associated with the exposure. In the papers presented in this dissertation, most of the variables adjusted for were considered as confounders, while some may be regarded as intermediate factors in the same causal chain.

In study I, all multiple logistic regression models on the associations between various child and parental characteristics and antibiotic use were adjusted for the following confounding factors: year, gender, parents' country of birth, maternal educational level and recurrent infections. In these analyses, recurrent infection should be regarded an intermediate variable rather than a confounder. Controlling for such an intermediate factor would theoretically lead to an underestimated effect of an exposure variable on the outcome variable.

In study II, all multiple logistic regression models on the associations between secondhand tobacco smoke and the development of an allergy, were adjusted for: sex, year of investigation, maternal smoking during pregnancy, maternal educational level, parents' country of birth, participation in parental educational program, crowded living and having a pet. In the analyses on synergistic effects of secondhand tobacco smoke and presence of parental allergy on the development of childhood allergy, the results were stratified for parental allergy.

In study III, all multiple logistic regression models on the associations between early life factors and overweight and obesity were adjusted for: year of investigation, sex, maternal educational level, parents' country of birth, crowded living, being firstborn, participation in parental educational program, economic

stress, parental overweight and the child's intake of sweetened bevereges. In the analyses on synergistic effects of early life factors and parental overweight, the results were stratified for parental overweight instead of adjusted. A limitation of Paper III is that the questionnaire contained only one question on nutrition and no question on physical activity. Even though earlier studies have concluded that it is hard to measure nutrition and physical activity in large scale studies, as the instruments used for measuring are too crude to allow the drawing of conclusions [35], it would still be desirable to have more information on such variables.

In study IV, all multiple logistic regression models on the associations between maternal educational level and in-hospital care and doctor's visits were adjusted for: year, sex, parents' country of birth, low birth weight, number of children at home, low emotional support, low practical support, maternal smoking during pregnancy, secondhand tobacco smoke at 0-4 weeks of age and exclusive breastfeeding for less than 4 months. In these analyses, year of investigation, sex and parents' country of birth may be regarded as potential confounders, while the other variables could theoretically be regarded as intermediate factors between maternal educational level and medical care consumption. Thus, changes in OR after adjustments encompassing model 2 given in the paper (i.e., model 1 with additional adjustment for low emotional support and low practical support) and model 3 (i.e., model 2 with additional adjustment for maternal smoking during pregnancy, secondhand tobacco smoke at 0 - 4 weeks; and length of exclusive breastfeeding) could be regarded as changes potentially mediated by these intermediate factors.

## *Implications for future research*

The results in paper I showed that antibiotic consumption was influenced by several factors including parental sociodemographic factors, lifestyle factors, psychosocial support, as well as child-related factors. The increased use and the development of more potent antibiotics have led to an increased antimicrobial resistance, which is a threat in the treatment of infectious disease the world over [51]. Given the fact that systemic antibiotics account for a high proportion of the prescriptions of all pre-school children [51], it is important to identify factors associated with such use to better be able to reduce it. In study II, it was shown that children with heredity for allergies and with presence of secondhand tobacco smoke during early life had highly increased odds of developing an allergy or having sought medical care due to allergic symptoms. Similar results have been shown in earlier studies [13,16]. Some of the potential mechanisms involved might be related to the fact that children have immature metabolic pathways and inhale greater volumes of air per kilogram weight than adults making children more vulnerable to inhaled toxic substances. [12,67]. This fact together with the notion that the effect of smoking has been suggested to be stronger in genetically susceptible children [13], makes children and especially children with heredity for allergy more susceptible to the toxic effects of secondhand tobacco smoke than adults. However, the results from study II were based on cross-sectional data and it would be interesting to investigate the association between secondhand tobacco smoke, allergic heredity and the development of an allergy using a prospective study design. The results from study paper III showed that having overweight/obese parents was strongly associated with the child being overweight or obese. This result is in line with the results from earlier studies [35,39,40,155-158]. Such an association could be due to genetic factors as well as environmental and/or behavioral factors [159]. The results in Paper III further showed an association between unfavorable early life factors and the development of childhood overweight and obesity, while breastfeeding seemed to have a protective effect. Early life has also in earlier studies been seen as a critical period for the development of obesity [35,43,47,70,98,118,161,162, 167,170]. An unfavorable environment in early life is thought to elicit a range of physiological and cellular adaptive responses in key organ systems [171]. Paper III further showed a synergistic effect between presence of parental overweight and some unfavorable early life factors (i.e., high birth weight and maternal smoking during pregnancy). There are no previous studies specifically investigating this association. However, it is an important topic considering the fact that parental obesity might reflect adverse eating and physical activity patterns, and might be related to both early life factors and later obesity. Furthermore, genes shared by the parents and child might also be associated with both early life factors and later obesity [171]. A limitation of paper III is that the questionnaire only contained one

question on nutrition and no question on physical activity. Even though earlier studies have concluded that it is hard to measure nutrition and physical activity in large scale studies [35], it would still be desirable to have more information on such variables and also to be able to confirm our findings in a study with prospective design. The results in Paper IV showed that children of less-educated mothers were exposed to more health risks, fewer health-promoting factors, and worse social support than children with higher educated mothers. Earlier studies have shown that parental behavior is influenced by material resources and knowledge of favorable life styles [3]. Paper IV further showed that children with less educated mothers had higher consumption of medical care than children with mothers of a higher educational level. Similar results have been shown in earlier studies [182], but there are also studies showing an opposite pattern [64]. One important conclusion of Paper IV is that improving children's health calls for policies that target the parents' health-related behaviors and social support.

In conclusion, the results presented in this thesis show that the health among small children is to a high degree influenced by the socioeconomic position and living conditions of the family as well as parental health. Furthermore, unfavorable early life exposures seem to be associated with the development of disease and medical care consumption later in childhood. It has been suggested that early development can make important echoes in disease risk throughout life [171] and this is important to bear in mind when forming interventional strategies. Thus, a life course perspective seems to increase our understanding of childhood health and the needs for intervention.

# Conclusions

- Antibiotic use among small children is associated with several parental factors such as sociodemographic, lifestyle, and psychosocial factors, but also various child characteristics.
- Children with heredity for allergies and with presence of secondhand tobacco smoke during early life, have highly increased odds of reported allergies and allergic symptoms at the age of 4 years.
- Having overweight or obese parents is strongly associated with the child becoming overweight or obese at 4 years of age. Furthermore, unfavorable early life factors (such as maternal smoking during pregnancy, early exposure to secondhand tobacco smoke, high birth weight and no breastfeeding) are all associated with child overweight or obesity at 4 years of age. There are also synergistic effects between presence of parental overweight and exposure to unfavorable early life factors on the development of childhood overweight or obesity.
- Children of less-educated mothers are exposed to more health risks, fewer health-promoting factors, worse social support and have a higher medical care consumption than children of higher educated mothers.

# Populärvetenskaplig sammanfattning

Svenska barn har en god hälsa i internationella jämförelser. Spädbarnsdödligheten är bland den lägsta i världen, dödligheten till följd av olyckor är relativt låg, och en hög andel barn vaccineras mot olika sjukdomar. Samtidigt har man sett en ökning av andelen barn med astma, hösnuva och eksem under de senaste femtio åren. Astma och andra allergiska sjukdomar är idag den vanligaste kroniska sjukdomen under barndomen, medan infektionssjukdomar bland barn är den vanligaste orsaken till akut sjukdom. Vidare har andelen barn med övervikt dubblerats och andelen barn med fetma ökat än mer under de senaste tjugo åren. Barnets hälsotillstånd varierar beroende på föräldrarnas socioekonomiska position, vilket bland annat kan relateras till skillnader i levnadsförhållanden, levnadsvanor samt psykosociala faktorer. Senare års studier har visat på betydelsen av exponering för riskfaktorer tidigt i livet (under fosterstadiet samt under de första levnadsåren) för utvecklandet av kronisk sjukdom i vuxenlivet. Det finns olika teoretiska modeller för att förklara dessa samband. Barkerhypotesen är en välkänd sådan modell där man hävdar att ofördelaktiga intrauterina miljöfaktorer banar väg för framtida sjukdom genom dess negativa inverkan på cellernas respektive organens bildande. Däremot finns det långt färre studier av sambandet mellan tidiga riskfaktorer och barns hälsa. Syftet med avhandlingen var att undersöka sambandet mellan sociodemografiska faktorer, tidig exponering för riskfaktorer och barns hälsa och vårdsökande. Det empiriska underlaget utgjordes av data från den enkät som kontinuerligt delats ut i anslutning till BVC-kontroll (vid 8 månader respektive 4 år) för att följa barns hälsa och levnadsförhållanden under perioden 2003-2008 i Malmö.

Syftet med den första studien (Paper I) var att undersöka sambandet mellan antibiotikaanvändning bland barn i åldern 8 månader och olika karakteristika hos barnen respektive sociodemografiska faktorer, levnadsvanor och psykosociala faktorer bland föräldrarna. Resultaten visade på ett samband mellan såväl sociodemografiska faktorer (pojke, förekomst av syskon, föräldrar med låg utbildningsnivå, föräldrar födda utomlands), psykosociala (lågt emotionellt stöd, ekonomisk stress) samt vissa tidiga riskfaktorer (låg födelsevikt, frånvaro av amning) och tidig antibiotika användning.

Syftet med den andra studien (Paper II) var att undersöka sambandet mellan passiv rökning och förekomst av allergi bland 4-åriga barn. Resultaten visade bland annat att exponering för passiv rökning var vanligare bland barn vars föräldrar hade låg utbildning och bland barn vars föräldrar var födda utomlands. Vidare hade barn till allergiska föräldrar ett två till fyra gånger ökat odds att själva utveckla en allergi. Resultaten visade även på ett tydligt samband mellan tidig exponering för passiv rökning och allergiutveckling bland barn med hereditet för allergi. En slutsats i

studien är att med tanke på att tidig exponering för passiv rökning inte är självvald och med tanke på dess tidiga hälsokonsekvenser är det av stor vikt att reducera andelen rökare bland småbarnsföräldrar.

Syftet med den tredje studien (Paper III) var att studera sambandet mellan exponering för riskfaktorer tidigt i livet (rökning under graviditet, tidig exponering för passiv rökning, hög födelsevikt, samt frånvaro av amning) och förekomst av övervikt och fetma i 4-års åldern. Resultaten visade på ett samband mellan exponering för vissa tidiga risk faktorer (rökning under graviditet, passiv rökning samt hög födelsevikt) och förekomst av övervikt/fetma i åldern 4 år. Dessa samband kunde inte förklaras av skillnader i förekomst av andra uppmätta riskfaktorer för utvecklande av övervikt såsom föräldrarnas utbildningsnivå eller förekomst av övervikt bland föräldrarna. Vidare visade resultaten en tydligare effekt av exponering för vissa tidiga risk faktorer bland barn vars föräldrar var överviktiga. Exponering för ofördelaktiga faktorer tidigt i livet förefaller således sammanhänga med en ökad förekomst av övervikt senare i barndomen. En viktig slutsats i studien är att det är av stor vikt att arbeta förebyggande för att minska en sådan exponering tidigt i livet. En begränsning med studien är dock att det enbart fanns bristfällig information om nutrition och fysisk aktivitet. Resultaten bör således konfirmeras i ytterligare studier med mer utförlig information om nutrition samt fysisk aktivitet.

I den fjärde artikeln (Paper IV) studerades skillnader i små barns exponering för hälsofrämjande faktorer respektive riskexponering utifrån moderns utbildningsnivå. Vidare studerades socioekonomiska skillnader i små barns vårdkonsumtion. Resultaten visade bland annat på tydliga skillnader i riskexponering, socialt stöd, exponering för hälsofrämjande faktorer samt vårdkonsumtion beroende på moderns utbildningsnivå. Andelen barn vars mor rökte under graviditeten var fem gånger så hög bland barn till lågutbildade mödrar jämfört med barn till mödrar med hög utbildning, medan andelen som helammade sina barn under minst fyra månader var betydligt lägre i den förra gruppen. De skillnader man såg i vårdkonsumtion kunde till stor del förklaras av skillnader i tidig exponering för olika hälsorisker

Slutsatsen man kan dra av denna avhandling är att små barns hälsa i hög grad påverkas av familjens socioekonomiska position, levnadsförhållanden och av föräldrarnas hälsa. Vidare förefaller små barns hälsa att påverkas av exponering för riskfaktorer tidigt i livet. Fostret och det växande barnet är speciellt känsligt för en sådan tidig riskexponering till följd av dess snabba tillväxt och utveckling. Genom att studera sambandet mellan tidiga faktorer och barns hälsa ges en möjlighet att identifiera eventuella tidiga stadier av en begynnande kronisk sjukdom samt att studera tidsförloppet mellan tidig exponering och effekt. En ökad kunskap om en sådan effekt av tidig exponering ökar vidare möjligheterna till tidiga preventiva insatser.

# Acknowledgements

I wish to express my deepest gratitude to everyone involved in my education, work and completion of this thesis. In particular I would like to thank:

Maria Rosvall, my principal supervisor, for introducing me to the world of science and sharing all your wonderful knowledge with me. You have always been there for me when I needed help and I really do appreciate your scientific and your pedagogical skills. Thanks for all your constructive criticism, support, guidance and help. I am so thankful for getting the chance to be your doctoral student!

Professor Martin Lindström, my co-supervisor, for your support, constructive criticism, rapid reading and you have always been available for discussion.

Mahnaz Moghaddassi, biostatistician at the Department of Social Medicine and Global Health, for giving your time into helping me with the statistics in the first paper.

I also want to express my gratitude to two of my co-authors: Anna Wremp Malmö University, with whom I wrote my first article and it was a pleasant time we shared together and I greatly do appreciate working together with you! Kristina Hansen, my co-author, thanks for a great job!

Anne Wennick at the Malmö University, for giving me teaching opportunities at the university and for being a good example of how to be a great lecturer.

I want to thank my previous boss Maria Wallström, who did a great job in encouraging me to start with my thesis and also a great thanks to my current boss Lars Olofsson. Thanks for giving me time off from my duties in order to have time to finish my thesis. I also want to thank my assistant manager Sara, who supported me and helped me practically with issues concerning sharing my time at the CHC center with the work on my thesis.

Eva Valind, my previous colleague at the Lindängen CHC center, thanks for being an encourager and an inspiration to me at work. I highly appreciated working and sharing time with you!

Jenny and Carina, my two wonderful colleagues at the Lindängen CHC center, thanks for all the great time I have shared with you and thanks for helping me when I needed to work on my thesis.

All my other great colleagues at Lindängen Primary Health care center, I really do appreciate all of you guys and I am so thankful for your support and encouragment. Especially thanks to Inga, who supported and pushed me into doing this thesis. You are a great encourager!

All my great friends, Rebecka, Emily, Ana-Maria, Kristina, Nicole, Linda, Sofia and Gunilla. Thanks for being my great friends and continuing to support and encourage me in doing this thesis. Your friendship is precious and valuable to me!

My grandmas “mormor” and “farmor”, who both have been a great support and encouragment, in doing this thesis!

My parents in-law in India! Thanks for your support!

My precious sisters Kristina, Malin and Hanna. Thanks for being great loving and caring sisters! Thanks for sharing your time and giving me help with practical stuff, such as looking after our children while writing and working on this thesis. And thanks for supporting and encouraging me!

My wonderful parents, thanks for being the great parents that you are! You are great examples to me and I do appreciate that you encouraged me to reach for the highest in life! And thanks for giving priority to look after our three children.

My dear husband Wilfred, thanks for supporting me in doing this work and thanks for conveying a sense of that it is possible to achieve high goals! Thanks for all the help with the technical parts, I really do appreciate your help and hopefully I won’t be as busy in the future!

Thanks to our dear three children, Rachel, Isabella and Gabriel! You really mean so much to me and you give a lot of meaning and purpose to my life! Hope this thesis inspires you to achieve everything that you are destined to do!

I would also like to thank all the involved CHC nurses and also the participants in the “Child health and living conditions study” for their time and contributions to this work.

Finally, I want to express my deepest appreciation to the God of my life! Who keeps my life together and helps me to achieve all that you destined for me to do!

# References


1. Upp till 18. Fakta om barn och ungdom. Barnombudsmannen rapporterar BR 2010:01. Statistiska centralbyrån, Stockholm, 2010. (In Swedish).

2. Currie C, Gabhainn SN, Godeau E, Roberts C, Smith R, Currie D et al. Inequalities in young people's health. Health behaviour in school-aged children (HBSC) study. International report from the 2005-2006 survey. Copenhagen: World Health organization. Regional office for Europe; 2008.

3. National Board of Health and Welfare. Public Health Report 2009. (In Swedish).

4. Kuh D, Davey-Smith G. The life course and adult chronic disease: a historical perspective with particular reference to coronary heart disease. In: Kuh D, Ben-Shlamo Y, eds. A life course approach to chronic disease epidemiology, 2004.

5. National Board of Health and Welfare. Public Health Report 2005. (in Swedish)

6. Rosvall M, Chaix B, Lynch J, Linström M, Merlo J. Similar support for three different life course socioeconomic models on predicting premature cardiovascular mortality and all-cause mortality. BMC Public Health 2006;6:203.

7. Bjerg A, Sandström T, Lundbäck B, Rönmark E. Time trends in asthma and wheeze in Swedish children 1996–2006: prevalence and risk factors by sex. Allergy 2010;65:48–55.

8. Asher MI, Montefort S, Björksten B, Lai CK, Strachan DP, Weiland SK, et al. ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006;368:733-743.

9. Pearce N, Sunyer J, Cheng S, Chinn S, Björksten B, Burr M et al. Comparison of asthma prevalence in the ISAAC and the ECRHS. ISAAC Steering Committee and the European Community Respiratory Health Survey. International Study of Asthma and Allergies in Childhood. Eur Respir J. 2000;16:420–6

10. Ruijsbroek A, Wijga AH, Kerkhof M, Koppelman GH, Smit HA, Droomers M. The development of socio-economic health differences in childhood: results of the Dutch longitudinal PIAMA birth cohort. BMC Public Health 2011;12:225.

11. Almqvist C, Pershagen G, Wickman M. Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. Clin Exp Allergy 2005;35:612-8.

12. Socialstyrelsen. Miljöhälsorapport 2005. (In Swedish)

13. Jaakkola JJ, Nafstad P, Magnus P. Environmental tobacco smoke, parental atopy, and childhood asthma. Environ Health Perspect 2001;109:579-82.

14. Krämer U, Lemmen CH, Behrendt H, Link E, Schäfer T, Gostomzyk J, et al. The effect of environmental tobacco smoke on eczema and allergic sensitization in children. Br J Dermatol 2004;150:111-8.

15. Raherison C, Pénard-Morand C, Moreau D, Caillaud D, Charpin D, Kopferschmitt C, et al. Smoking exposure and allergic sensitization in children according to maternal allergies. Ann Allergy Asthma Immunol 2008;100:351-7.

16. Keil T, Lau S, Roll S, Grüber C, Nickel R, Niggemann B. Maternal smoking increases risk of allergic sensitization and wheezing only in children with allergic predisposition longitudinal analysis from birth to 10 years. Allergy 2009;64:445-51.

17. Lannerö E, Wickman M, van Hage M, Bergström A, Pershagen G, Nordvall L. Exposure to environmental tobacco smoke and sensitisation in children. Thorax 2008;63:172-6.

18. Strachan DP, Cook DG. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. Thorax 1998;53:204-12.

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

20. Wigle DT, Arbuckle TE, Turner MC, Berube A, Yang Q, Liu S, et al. Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. J Toxicol Environ Health B Crit Rev. 2008;11:373-517.

21. Matson AP, Thrall RS, Rafti E, Puddington L. Breast milk from allergic mothers can protect offspring from allergic airway inflammation. Breastfeed Med. 2009;4:167-74.

22. Kull I, Wickman M, Lilja G, Nordvall SL, Pershagen G. Breastfeeding and allergic diseases in infants -a prospective birth cohort study. Arch Dis Child 2002;87:478-81.

23. Lombardi E, Simoni M, La Grutta S, Viegi G, Bisanti L, Chellini E, et al. Effects of pet exposure in the first year of life on respiratory and allergic symtoms in 7-yr-old children. The SIDRIA -2 study. Pediatr Allergy Immunol. 2010;21:268-76.

24. Brauer M, Hoek G, Smit HA, de Jongste JC, Gerritsen J, Potsma DS, et al. Air pollution and development of asthma, allergy and infections in a birth cohort. Eur Respir J. 2007;29:879-88.

25. Melen E, Nyberg F, Lindgren CM, Berglind N, Zucchelli M, Nordling E, et al. Interactions between glutathione S-transferase P1, tumor necrosis factor, and traffic- related air pollution for development of childhood allergic disease. Environ Health Perspect. 2008;116:1077-84.

26. Salam MT, Islam T, Gilliland FD. Recent evidence for adverse effects of residential proximity to traffic sources on asthma. Curr Opin Pulm Med. 2008;14:3-8.

27. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240-3.

28. Lager A.Övervikt bland barn – system för nationell uppföljning. 2005-2006 års uppföljning. Statens folkhälsoinstitut and Centre for Health Equity Studies (CHESS), Stockholms Universitet/Karolinska Institutet, 2007.

29. Socialstyrelsen. Folkhälsa- Lägesrapport 2006. Stockholm 2007. (in Swedish)

30. Mårild S, Bondestam M, Bergström R, et al. Prevalence trends of obesity and overweight among 10-year-old children in western Sweden and relationship with parental BMI. Acta Paediatr. 2004; 93:1588-95.

31. de Onis M, Blössner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. Am J Clin Nutr. 2010;92:1257-64.

32. Raj M, Kumar RK. Obesity in children & adolscents. Indian J Med Res. 2010;132:598-607.

33. Strauss RS, Pollack HA. Epidemic increase in childhood overweight, 1986-1998. JAMA 2001;286:2845–8.

34. Jälminger A-K, Marmur A, Callmer E. Min Matdagbok – en matvaneundersökning bland barn i årskurs tre från områden med olika socioekonomiska förhållanden i Stockholms län. Centrum för tillämpad näringslära, rapport 27, Stockholms läns landsting. (in Swedish)

35. Kleiser C, Schaffrath Rosario A, Mensink GB, Prinz-Langenohl R, Kurth BM. Potential determinants of obesity among children and adolescents in Germany: results from the cross-sectional KiGGS study. BMC Public Health 2009; 9:46.

36. Linardakis M, Sarri K, Pateraki MS, Sbokos M, Kafatos A. Sugar-added beverages consumption among kindergarten children of Crete: effects on nutritional status and risk of obesity. BMC Public Health 2008;8:279.

37. Plachta-Danielzik S, Landsberg B, Johannsen M, Lange D, Müller MJ. Determinants of the prevalence and incidence of overweight in children and adolscents. Public Health Nutr. 2010;13:1870-81.

38. Rahman T, Cushing RA, Jackson RJ. Contributions of built environment to childhood obesity. Mt Sinai J Med. 2011;78:49-57.

39. Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, et al. Early life risk factors for obesity in childhood: cohort study. BMJ 2005;330:1357.

40. Danielzik S, Czerwinski-Mast M, Langnäse K, Dilba B, Müller MJ. Parental overweight, socioeconomic status and high birth weight are the major determinants of overweight and obesity in 5–7 y-old children: baseline data of the Kiel Obesity Prevention Study (KOPS) Int J Obes Relat Metab Disord. 2004;28:1494–502.

41. Ibáñez L, Ong K, Dunger DB, de Zegher F. Early development of adiposity and insulin resistance after catch-up weight gain in small-for-gestational-age children. J Clin Endocrinol Metab. 2006;91:2153–8.

42. von Kries R, Koletzko B, Sauerwald T, von Mutius E, Barnert D, Grunert V, von Voss H. Breastfeeding and obesity: cross sectional study. BMJ 1999;319:147-50.

43. Gillman MW, Rifas-Shiman SL, Camargo CA Jr, Berkey CS, Frazier AL, Rockett HR. Risk of overweight among adolescents who were breastfed as infants. JAMA 2001; 285:2461-7.

44. Liese AD, Hirsch T, von Mutius E, Keil U, Leopold W, Weiland SK. Inverse association of overweight and breast feeding in 9 to 10-y-old children in Germany. Int J Obes Relat Metab Disord. 2001;25:1644-50.

45. Agras WS, Kraemer HC, Berkowitz RI, Hammer LD. Influence of early feeding style on adiposity at 6 years of age. J Pediatr. 1990;116:805–9.

46. Arenz S, Rückerl R, Koletzko B, von Kries R. Breastfeeding and childhood obesity-a systematic review. Int J Obes Relat Metab Disord. 2004;28:1247–56.

47. Vik T, Jacobsen G, Vatten L, Bakketeig LS. Pre- and post-natal growth in children of women who smoked in pregnancy. Early Hum Dev. 1996; 45:245-55.

48. Suzuki K, Ando D, Sato M, Tanaka T, Kondo N, Yamagata Z. The Association between maternal smoking during pregnancy and childhood obesity persists to the age of 9-10 years. J Epidemiol. 2009 19:136-42.

49. Neumark T, Brudin L, Engström S, Mölstad S. Trends in number of consultations and antibiotic prescriptions for respiratory tract infections between 1999 and 2005 in primary healthcare in Kalmar County, Southern Sweden. Scand J Prim Health Care 2009;27:18-24.

50. The Swedish Strategic Programme for the Rational use of antimicrobial Agents and The Swedish Institute for Infectious Disease Control. SWEDRES 2009. A report on Swedish Antibiotic Utilisation and Resistance in Human Medicine 2010; Stockholm, Sweden. (In Swedish)

51. Thrane N, Olesen C, Schønheyder HC, Sørensen HT. Socioeconomic factors and prescription of antibiotics in 0- to 2- year-old Danish children. J Antimicrob Chemother. 2003;51:683-9.

52. Högberg L, Oke T, Geli P, Lundborg CS, Cars O, Ekdahl K.Reduction in outpatient antbiotic sales for pre-school children: interrupted time series analysis of weekly antibiotic sales data in Sweden 1992-2002. J Antimicrob Chemother. 2005;56:208-15.

53. The Swedish Strategic Programme for the Rational use of antimicrobial Agents and The Swedish Institute for Infectious Disease Control. *SWEDRES* 2001. A report on Swedish Antibiotic Utilisation and Resistance in Human Medicine 2002; Stockholm, Sweden. (In Swedish)

54. Mölstad S, Cars O. Major change in the use of antibiotics following a national programme: Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA). Scand J Infect Dis. 1999;31:191–5.

55. http://www.strama.se (In Swedish)

56. The Swedish Strategic Programme for the Rational use of antimicrobial Agents and The Swedish Institute for Infectious Disease Control. SWEDRES 2010. A report on Swedish Antibiotic Utilisation and Resistance in Human Medicine 2011; Stockholm, Sweden. (In Swedish)

57. Cars O, Mölstad S, Melander A. Variation in antibiotic use in the European Union. Lancet 2001;357:1851-3.

58. The Swedish Strategic Programme for the Rational use of antimicrobial Agents and The Swedish Institute for Infectious Disease Control. *SWEDRES 2006.* A report on Swedish antibiotic utilization and resistance in human medicine. 2007; Stockholm, Sweden. (In Swedish.)

59. Melander E, Landgren M. Antibiotikaanvändningen fortfarande hög hos skånska barn -är detta rimligt? Smittskydd Skåne, Region Skåne. 2007:2. (In Swedish)

60. Patel S, Schroeder JW Jr. Disparities in children with otitis media: the effect of insurance status. Otolaryngol Head Neck Surg. 2011;144:73-7.

61. Andre M, Hedin K, Håkansson A, Mölstad S, Rohde N, Petersson C. More physician consultations and antibiotic prescriptions in families with high concern about infectious illness--adequate response to infection-prone child or self-fulfilling prophesy? Fam Pract. 2007;24:302-7.

62. Mangione-Smith R, Elliott MN, Stivers T, Mcdonald L, Heritage J, McGlynn EA. Racial /ethnic variation in parent expectations for antibiotics: implications for public health campaigns. Pediatrics 2004;113:385-94.

63. Louhi-Pirkanniemi K, Rautava P, Aromaa M, Ojanlatva A, Mertsola J, Helenius H. Factors of early infancy and recurrent use of antibiotic therapy. Acta Paediatr. 2004;93:1386-90.

64. Hjern A, Haglund B, Rasmussen F, Rosén M. Socio-economic differences in daycare arrangements and use of medical care and antibiotics in Swedish preschool children. Acta Paediatr. 2000;89:1250–6.

65. National Board of Health and Welfare. Public Health Report 2001. (in Swedish)

66. Pershagen G. Accumulating evidence on health hazards of passive smoking. Acta Paediatr.1999;88:490–2.

67. Cheraghi M, Salvi S. Environmental tobacco smoke (ETS) and respiratory health in children. Eur J Pediatr. 2009;168:897-905.

68. Jones LL, Hashim A, McKeever T, Cook DG, Britton J, Leonardi-Bee J. Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in infancy: systematic review and meta-analysis. Respir Res. 2011;12:5.

69. Hawkins SS, Berkman L. Increased tobacco exposure in older children and its effect on asthma and ear infections. J Adolesc Health 2011;48:647-50.

70. Sørensen HT, Labouriau R, Jensen ES, Mortensen PB, Schønheyder HC. Fetal growth, maternal prenatal smoking, and risk of invasive meningococcal disease: a nationwide case-control study. Int J Epidemiol. 2004;33:816-20.

71. Walker A. Breast milk as the gold standard for protective nutrients. J Pediatr 2010;156:S3-7

72. Pelton SI, Leibovitz E. Recent advances in otitis media. Pediatr Infect Dis J 2009;28:S133-7.

73. Duijts L, Ramadhani MK, Moll HA. Breastfeeding protects against infectious diseases during infancy in industrialized countries. A systematic review. Matern Child Nutr 2009;5:199-210.

74. Mahon BE, Ehrenstein V, Nørgaard M, Pedersen L, Rothman KJ, Sørensen HT. Perinatal risk factors for hospitalization for pneumococcal disease in childhood:a population-based cohort study. Pediatrics. 2007;119:804-12.

75. Shaheen S, Sterne JA, Tucker JS, Florey CD. Birth weight, childhood lower respiratory tract infection, and adult lung function. Thorax 1998;53:549-553.

76. Marmot M. Multilevel approaches to understanding social determinants. In: Berkman L, Kawachi I. eds. Social Epidemiology. Oxdord: Oxford University Press, 2000.

77. Kuh D, Ben Shlamo Y. Introduction. In: Kuh D, Ben-Schlamo Y. A life course approach to chronic disease edidemiology, 2004.

78. Smith GD. Life-course approaches to inequalities in adult chronic disease risk. Proc Nutr Soc. 2007;66:216–36.

79. Hallqvist J, Lynch J, Bartley M, Lang T, Blane D. Can we disentangle life course processes of accumulation, critical period and social mobility? An analysis of disadvantaged socio-economic positions and myocardial infarction in the Stockholm Heart Epidemiology Program. Soc Sci Med. 2004;58:1555–62.

80. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. J Epidemiol Community Health 2005;57:778–83.

81. Pollitt P, Rose K, Kaufman J. Evaluating the evidence for models of life course socioeconomic factors and cardiovascular outcomes: a systematic review. BMC Public Health 2005;5:7.

82. Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? Br J Prev Soc Med. 1977;31:91–5.

83. Barker DJ, Osmond C. Infant mortality, childhood nutrition and ischaemic heart disease in England and Wales. Lancet 1986;1:1077–81.

84. Godfrey KM, Barker DJ. Fetal nutrition and adult disease. Am J Clin Nutr. 2000;71:1344-52.

85. Öppna jämförelser 2009. Folkhälsa. (In Swedish) www.skl.se/vi_arbetar_med/oppnajamforelser/oppnajamforelser_folkhalsa

86. Graviditeter, förlossningar och nyfödda barn. Rapport, Socialstyrelsen, 2011. (in Swedish)

87. Chertok IR, Luo J, Anderson RH. Association between changes in smoking habits in subsequent pregnancy and infant birth weight in West Virginia. Matern Child Health J. 2011;15:249-54.

88. Chung KC, Kowalski CP, Kim HM, Buchman SR. Maternal cigarette smoking during pregnancy and the risk of having a child with cleft lip/palate. Plast Reconstr Surg. 2000;105:485-91.

89. Durmus B, Kruithof CJ, Gillman MH, Willemsen SP, Hofman A, Raat H, et al. Parental smoking during pregnancy, early growth, and risk of obesity in preschool children: the Generation R study. Am J Clin Nutr 2011;94:164-71.

90. Shenassa ED, Brown MJ. Maternal smoking and infantile gastrointestinal dysregulation: the case of colic. Pediatrics 2004;114:497-505.

91. Strachan DP, Cook DG. Health effects of passive smoking 1, Parental smoking and lower respiratory illness in infancy and early childhood. Thorax 1997;52:905-914.

92. Li YF, Langholz B, Salam MT, Gilliland FD. Maternal and grandmaternal smoking patterns are associated with early childhood asthma. Chest 2005;127:1232-41.

93. Moore HC, de Klerk N, Richmond P, Lehmann D. A retrospective population-based cohort study identifying target areas for prevention of acute lower respiratory infections in children. BMC Public Health 2010;10:757.

94. National board of health and welfare. Breast-feeding and smoking habits among parents of infants born in 2007. Official statistics of Sweden. Stockholm, 2009. (In Swedish)

95. Cattaneo A, Yngve A, Koletzko B, Guzman LR. Promotion of Breastfeeding in Europe project: Protection, promotion and support of breastfeeding in Europe: current situation. Public Health Nutr. 2005;8:39-46.

96. Wold AE, Adlerberth I. Breast feeding and the intestinal microflora of the infant – implications for protection against infectious diseases. Adv Exp Med Biol. 2000;478:77-93.

97. BAMSE projektet går vidare. Vårdal Nytt Nr 1 2003. (in Swedish)

98. Gillman MW. A life course approach to obesity. In: Kuh D, Ben-Shlamo Y, eds. A life course approach to chronic disease epidemiology, 2004.

99. Martin RM, Gunnell D, Owen CG, Smith GD. Breast-feeding and childhood cancer: a systematic review with metaanalysis. Int J Cancer 2005;117:1020-31.

100. McKinney PA, Parslow R, Gurney KA, Law GR, Bodansky HJ, Williams R. Perinatal and neonatal determinants of childhood type 1 diabetes. A case-control study in Yorkshire, U.K. Diabetes Care 1999;22:928-32.

101. Angelsen NK, Vik T, Jacobsen G, Bakketeig LS. Breast feeding and cognitive development at age 1 and 5 years. Arch Dis Child 2001;85:183-8.

102. Morrow AL, Ruiz-Palacios GM, Jiang X, Newburg DS. Human-milk glycans that inhibit pathogen binding protect breast-feeding infants against infectious diarrhea. J Nutr. 2005;135:1304-7.

103. Axelsson I, Finkel Y, Michaelsen K, Hernell O, Jakobsson I, Perhagen J, et al. Introduktionen kan vänta till sex månaders alder, men inte längre. Läkartidningen 2004;101:195-197. (in Swedish)

104. http://www.childinfo.org/low_birthweight_profiles.php (cited 2011-09-06)

105. Mortensen LH, Diderichsen F, Arntzen A, Gissler M, Cnattingius S, Schnor O, et al. Social inequality in fetal growth: a comparative study of Denmark, Finland, Norway and Sweden in the period 1981-2000. J Epidemiol Community Health 2008;62:325-31.

106. Cnattingius S, Haglund B. Decreasing smoking prevalence during pregnancy in Sweden: the effect on small-for-gestational-age births. Am J Public Health 1997;87:410-3.

107. Borders AE, Grobman WA, Amsden LB, Holl JL. Chronic stress and low birth weight neonates in a low-income population of women. Obstet Gynecol 2007;109:331-8.

108. Sanders-Phillips K, Settles-Reaves B, Walker D, Brownlow J. Social inequality and racial discrimination : risk factors for health disparities in children of color. Pediatrics 2009;124:176-86.

109. Forouhi N, Hall E, McKeigue P. A life course approach to diabetes. In: A life course approach to chronic disease epidemiology, 2004.

110. Barker DJ. Fetal origins of coronary heart disease. BMJ 1995;311:171.

111. Barker M, Robinson S, Osmond C, Barker DJ. Birth weight and body fat distribution in adolscent girls. Arch Dis Child 1997;77:381-3.

112. Okosun IS, Liao Y, Rotimi CN, Dever GE, Cooper RS. Impact of birth weight on ethnic variations in subcutaneous and central adiposity in American children aged 5-11 years. A study from the Third National Health and Nutrition Examination Survey. Int J Obes Relat Metab Disord. 2000;24:479-84.

113. Choi CS, Kim C, Lee WJ, Park JY, Hong SK, Lee MG, Park SW, Lee KU. Association between birth weight and insulin sensitivity in healthy young men in Korea: role of visceral adiposity. Diabetes Res Clin Pract. 2000;49:53-9.

114. Kuh D, Hardy R, Chaturvedi N, Wadsworth ME. Birth weight, childhood growth and abdominal obesity in adult life. Int J Obes Relat Metab Disord. 2002;26:40-7.

115. Canoy D, Pouta A, Ruokonen A, Hartikainen AL, Saikku P, Järvelin MR. Weight at birth and infancy in relation to adult leukocyte count: a population-based study of 5619 men and women followed from the fetal period to adulthood. J Clin Endocrinol Metab. 2009;94:1916-22.

116. Phillips DI: Birth weight and the future development of diabetes. A review of the evidence. Diabetes Care. 1998;21 Suppl 2:B150-5.

117. Parsons TJ, Power C, Manor O. Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: longitudinal study. Br Med J. 2001;323:1331-5.

118. Gillman MW, Rifas-Shiman SL, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, birth weight, and adolescent obesity. Pediatrics 2003;111:221–6.

119. Galobardes B, Shaw M, Lawlor D, Davey Smith G, Lynch J. Indicators of socioeconomic position. In: Methods in social epidemiology. Eds:Oakes J, Kaufman J. Published by Jossey-Bass, 2006.

120. Irwin LG, Johnson JL, Henderson A, Dahinten VS, Hertzman C. Examining how contexts shape young children´s perspectives of health. Child Care Health Dev. 2007;33:353-9.

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

122. Wright RJ. Epidemiology of stress and asthma: from constricting communities and fragile families to epigenetics. Immunol Allergy Clin North Am. 2011;31:19-39.

123. Geyer S, Peter R, Siegrist J. Socioeconomic differences in children´s and adolscents´ hospital admissions in Germany:a report based on health insurance data on selected diagnostic categories. J Epidemiol Community Health 2002;56:109-14.

124. Hanson BS. Social network, social support and health in elderly men. A population study. Thesis. Department of Community Medicine, Lund University, Malmö, Sweden 1988.

125. Östergren P-O. Psychosocial resources and health. With special reference to social network, support and cardiovascular disease. Thesis. Department of Community Medicine, Lund University, Malmö, 1991.

126. Berkman L, Glass T. Social integration, social networks, social support, and health. In: Berkman L, Kawachi I, eds. Social epidemiology. Oxford: Oxford University Press, 2000.

127. Lindström M: Social participation, social capital and socioeconomic differences in health-related behaviours . An epidemiological study. Thesis. Department of Community Medicine, Lund University, Malmö, 2000.

128. Cohen S, Wills TA: Stress, social support, and the buffering hypothesis. Psychol Bull 1985;98:310-57.

129. Schor EL, American Academy of Pediatrics Task Force on the Family. Family Pediatrics: Report of the task force on the family. Pediatrics 2003;111:1541-71.

130. Janicke DM, Finney JW, Riley AW. Children's health care use: A prospective investigation of factors related to care-seeking. Med care 2001;39:990-1001.

131. Magnusson M, Blennow M, Hagelin E, Sundelin C. Barnhälsovård- att främja barns hälsa. Stockholm, Liber AB, 2009 (in Swedish)

132. Olivius G, Hanson BS. Barns hälsa och levnadsförhållanden i Malmö. Pilotstudie vid BVC. Malmö 1997. (in Swedish)

133. Rosvall M, Falck S, Moghaddassi M, Köhler M, Östergren P-O. Rapport 2007: Barns hälsa och levnadsförhållanden. Socialmedicinska Enheten, Malmö, Region Skåne, 2007. (in Swedish).

134. http://www.malmo.se (in Swedish)

135. http://www.malmo.se/Kommun--politik/Om-oss/Stadsdelar/Rosengard/Fakta-om-Rosengard.html

136. http://www.malmo.se/download/18.3964bd3611d8d4a5d1c800010954/12.LIMHAMN-BUNKEFLO+rev.+081119.pdf

137. Barnfattigdomen i Sverige. Årsrapport 2010. Rädda barnen. Stockholm, Wallén och Co Grafiska AB, 2010. (In Swedish)

138. Devlieger H, Martens G, Bekaert A. Social inequalities in perinatal and infant mortality in the northern region of Belgium (the Flanders). Eur J Public Health 2005;15:15-9.

139. Östergren P-O, Lindbladh E, Isacsson S-O, Odeberg H, Svensson SE. Social network, social support and the concept of control - a qualitative study concerning the validity of certain stressor measures used in quantitative social epidemiology. Scand J Soc Med. 1995;23:95-102.

140. Hanson BS, Östergren PO, Elmståhl S, Isacsson SO, Ranstam J. Reliability and validity assessments of measures of social networks, social support and control - results from the Malmö Shoulder and Neck study. Scand J Soc Med. 1997;25:249-257.

141. Olivius G, Ostergren PO, Hanson BS, Lyttkens CH. Parental economic stress: evidence of an overlooked public health risk among Swedish families. Eur J Public Health 2004;14:354-60.

142. Waldenström U, Bergström M, Fabian H. Föräldrautbildning under graviditet måste omprövas. Läkartidningen 2011;108:979-983. (In Swedish)

143. Rothman KJ. Interaction between causes. In: Modern Epidemiology. Ed: Rothman K. Boston: Little, Brown; 1986.

144. Hosmer DW, Lemeshow S: Confidence interval estimation of interaction. Epidemiology 1992;3:452-6.

145. Zaffani S, Cuzzolin L, Meneghelli G, Gangemi M, Murgia V, Chiamenti G, et al. An analysis of the factors influencing the paediatrician-parents relationship:the importance of the socio-demographic characteristics of the mothers. Child Care Health Dev. 2005;31:575-80.

146. Hjern A, Haglund B, Rosen M. Socioeconomic differences in use of medical care and antibiotics among schoolchildren in Sweden. Eur J Public Health 2001;11:280-3.

147. Dubois L, Girard M. Breastfeeding, day-care attendance and the frequency of antibiotic treatments from 1,5 to 5 years: a population-based longitudinal study in Canada. Soc Sci Med. 2005;60:2035-44.

148. Sabirov A, Casey JR, Murphy TF, Pichichero ME. Breastfeeding is associated with a reduced frequency of acute otitis media and high serum antibody levels against NTHi and outer membrane protein vaccine antigen candidate P6. Pediatr Res. 2009; 66:565-70.

149. Caudri D, Wijga A, Gehring U, Smit HA, Brunekreef B, Kerkhof M, et al. Respiratory symtoms in the fisrt 7 years of life and birth weight at term:the PIAMA birth cohort. Am J Respir Crit Care Med. 2007;175:1078-85.

150. Clarke JR, Salmon B, Silverman M. Bronchial responsiveness in the neonatal period as a risk factor for wheezing in infancy. Am J Respir Crit Care Med. 1995;151:1434-40.

151. Nilsson P, Köhler M, Ostergren PO, Khan FA. Children exposed to environmental smoking have a higher antibiotic consumption. Vaccine 2007;25:2533-5.

152. Strachan DP, Cook DG. Health effects of passive smoking. 5. Parental smoking and allergic sensitisation in children. Thorax 1998;53:117-23.

153. Ribeiro SA, Furuyama T, Schenkman S, Jardim JR. Atopy, passive smoking, respiratory infections and asthma among children from kindergarten and elementary school. Sao Paulo Med J. 2002;120:109-12.

154. Murray CS, Woodcock A, Smillie FI, Cain G, Kissen P, Custovic A. Tobacco smoke exposure, wheeze, and atopy. Pediatr Pulmonol. 2004;37:492-8.

155. Schaefer-Graf UM, Pawliczak J, Passow D, Hartmann R, Rossi R, Bührer C, et al. Birth weight and parental BMI predict overweight in children from mothers with gestational diabetes. Diabetes Care 2005;28:1745-50.

156. Hernández-Valero MA, Wilkinson AV, Forman MR, Etzel CJ, Cao Y, Bárcenas CH, et al. Maternal BMI and country of birth as indicators of childhood obesity in children of Mexican origin. Obesity 2007;15:2512-9.

157. Hirschler V, Buzzano K, Erviti A, Ismael N, Silva S, Dalamon R. Overweight and lifestyle behaviours of low socioeconomic elementary school children in Buenos Aires. BMC Pediatr. 2009;9:17.

158. Semmler C, Ashcroft J, van Jaarsveld CH, Carnell S, Wardle J. Development of overweight in children in relation to parental weight and socioeconomic status. Obesity 2009;17:814-20.

159. Silventoinen K, Rokholm B, Kaprio J, Sørensen TI. The genetic and environmental influences on childhood obesity: a systematic review of twin and adoption studies. Int J Obes. 2010;34:29-40.

160. Scaglioni S, Salvioni M, Galimberti C. Influence of parental attitudes in the development of children eating behaviour. Br J Nutr. 2008;99:22-5.

161. Mizutani T, Suzuki K, Kondo N, Yamagata Z. Association of maternal lifestyles including smoking during pregnancy with childhood obesity. Obesity 2007;15:3133-9.

162. Griffiths LJ, Hawkins SS, Cole TJ, Dezateux C, Millenium Cohort Study Child Health Group. Risk factors for rapid weight gain in preschool children: findings from a UK-wide prospective study. Int J Obes 2010;34:624-32.

163. Martorell R, Stein AD, Schroeder DG. Early nutrition and later adiposity. J Nutr. 2001; 131:874S-880S.

164. Dubois L, Girard M. Early determinants of overweight at 4,5 years in a population-based longitudinal study. Int J Obes. 2006;30:610-7.

165. Oldroyd J, Renzaho A, Skouteris H. Low and high birth weight as risk factors for obesity among 4 to 5- year-old Australian children : does gender matter? Eur J Pediatr. 2011;170:899-906.

166. Gorog K, Pattenden S, Antova T, Niciu E, Rudnai P, Scholtens S, et al. Maternal smoking during pregnancy and childhood obesity. Matern Child Health J. 2011;15:985-92

167. Ozanne SE, Constância M. Mechanisms of disease: the developmental origins of disease and the role of the epigenotype. Nat Clin Pract Endocrinol Metab 2007;3:539-46.

168. Sørensen HT, Sabroe S, Rothman KJ, Gillman M, Fischer P, Sørensen TI. Relation between weight and length at birth and body mass index in young adulthood: cohort study. BMJ 1997;315:1137.

169. Hediger ML, Overpeck MD, Kuczmarski RJ, Ruan WJ. Association between infant breastfeeding and overweight in young children. JAMA 2001;285:2453-60.

170. Huus K, Ludvigsson JF, Enskär K, Ludvigsson J. Exclusive breastfeeding of Swedish children and its possible influence on the development of obesity: a prospective cohort study. BMC Pediatr. 2008;8:42.

171. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science 2004;305:1733-6.

172. Matijasevich A, Brion MJ, Menezes AM, Barros AJ, Santos IS, Barros FC. Maternal smoking during pregnancy and offspring growth in childhood:1993 and 2004 Pelotas cohort studies. Arch Dis Child 2011; 96:519-25.

173. Balaban G, Silva GA. Protective effect of breastfeeding against childhood obesity. J Pediatr. 2004;80:7-16.

174. Pedersen J. Weight and length at birth of infants of diabetic mothers. Acta Endocrinol. 1954;16:330-42.

175. Freinkel N. Banting lecture 1980: Of pregnancy and progeny. Diabetes 1980;29:1023-35.

176. Lucas A, Sarson DL, Blackburn AM, Adrian TE, Aynsley- Green A, Bloom SR. Breast vs bottle : endocrine responses are different with formula feeding. Lancet 1980;1:1267-9.

177. Lucas A, Boyes S, Bloom SR, Aynsley-Green A. Metabolic and endocrine responses to a milk feed in six-day-old term infants: differences between breast and cow´s milk formula feeding. Acta Paediatr Scand. 1981;70:195-200.

178. Treviño-Garza C, Bosgues -Padilla FJ, Estrada-Zúñiga CM, Mancillas-Adame L, Villarreal-Pérez JZ, Abrego-Moya V, et al. Typical leptin fall is mitigated by breastfeeding in female infants. Arch Med Res 2010; 41:373-7.

179. Birch LL, Fisher JO. Development of eating behaviours among children and adolscents. Pediatrics 1998;101:539-49.

180. Law CM, Barker DJ, Osmond C, Fall CH, Simmonds SJ. Early growth and abdominal fatness in adult life. J Epidemiol Community Health 1992;46:184-6.

181. Apfelbacher CJ, Loerbroks A, Cairns J, Behrendt H, Ring J, Krämer U. Predictors of overweight and obesity in five to seven-year-old children in Germany: results from cross sectional studies. BMC Public Health 2008;8:171

182. Roberts H, Smith SJ, Bryce C. Children at risk? Safety as a social value. Buckingham: Oxford University Press. 1995.

183. Cooper R, Hyppönen E, Berry D, Power C. Associations between parental and offspring adiposity up to midlife:the contribution of adult lifestyle factors in the 1958 British Birth Cohort Study. Am J Clin Nutr. 2010;92:946-53.

184. Raphael JL, Zhang Y, Liu H, Giardino AP. Parenting stress in US families: implications for paediatric healthcare utilization. Child Care Health Dev. 2010;36:216-24.

185. Rothman K, Greeenland S. Precision and validity in epidemiological studies. In: Modern Epidemiology. Eds: Rothman K, Greenland S. Philadelphia: Lippincott-Raven, 1998

186. Bonita R, Beaglehole R, T Kjellström. Basic epidemiology. World Health Organization . 2006.

187. Hallqvist J, Ahlbom A, Diderichsen F, Reuterwall C. How to evaluate interaction between causes: a review of practices in cardiovascular epidemiology. J Intern Med. 1996;239:377-82.

188. Gillespie B, d'Arcy H, Schwartz K, Bobo J, Foxman B. Recall of age of weaning and other breastfeeding variables. Int Breastfeed J. 2006;1:4.

189. Troy LM, Michels KB, Hunter DJ, Spiegelman D, Manson JE, Colditz GA, Stampfer MJ, Willett WC. Self-reported birthweight and history of having been breastfed among younger women: an assesment of validity. Int J Epidemiol. 1996;25:122-7.

190. Li R, Scanlon KS, Serdula MK. The validity and reliability of maternal recall of breastfeeding practice. Nutr Rev. 2005;63:103-10.

191. Cupul-Uicab LA, Gladen BC, Hernandez-Avila M, Longnecker MP. Reliability of reported breastfeeding duration among reproductive -aged women from Mexico. Matern Child Nutr. 2009;5:125-37.

192. Promislow JH, Gladen BC, Sandler DP. Maternal recall of breastfeeding duration by elderly women. Am J Epidemiol. 2005;161:289-96.

193. Eatons-Evans J, Dugdale AE. Recall by mothers of the birth weights and feeding of their children. Hum Nutr Appl Nutr. 1986;40:171-5.

194. Christensen AE, Tobiassen M, Jensen TK, Wielandt H, Bakketeig L, Host A. Repeated validation of parental self-reported smoking during pregnancy and infancy: a prospective cohort study of infants at high risk for allergy devlopment. Paediatr Perinat Epidemiol. 2004;18:73-9.

195. Vartianen E, Seppälä T, Lillsunde P, Puska P: Validation of self-reported smoking by serum cotinine measurement in a community-based study. J Epidemiol Community Health 2002;56:167-70.

196. Nafstad P, Kongerud J, Botten G, Urdal P, Silsand T, Pedersen BS, et al: Fetal exposure to tobacco smoke products: a comparison between self-reported maternal smoking and concentrations of cotinine and thiocyanate in cord serum. Acta Obstet Gynecol Scand. 1996;75:902-7.

197. Oddoze C, Dubus JC, Badier M, Thirion X, Pauli AM, Pastor J, et al: Urinary cotinine and exposure to parental smoking in a population of children with asthma. Clin Chem. 1999;45:505-9.

198. Gorber SC, Schofield-Hurwitz S, Hardt J, Levasseur G, Tremblay M: The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. Nicotine Tob Res. 2009;11:12-24.

199. Toren K, Palmqvist M, Löwhagen O, Balder B, Tunsäter A: Self-reported asthma was biased in relation to disease severity while reported year of asthma onset was accurate. J Clin Epidemiol. 2006;59:90-3.

200. Greenland S, Rothman K. Introduction to stratified analyses. In: Modern Epidemiology. Eds: Rothman K, Greenland S. Philadelpia, Lippincott-Raven, 1998.

# Appendix