An epidemiological study on the associations between preeclampsia exposure, growth and physical activity in preschool age and subsequent allergy, asthma and lung function in late childhood

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Scientific environment

This PhD work uses data from "The Stavanger Study" performed at the Paediatric Department at Stavanger University Hospital. During the work I have been a member of The Research group for Women and Child Health at Stavanger University Hospital, including members from both the Department of Gynaecology and Obstetrics and The Paediatric Department and led by Professor Knut Øymar. The project has also been discussed in minor groups in several occasions.

The project has been performed in cooperation with several co-workers and authors, for the first Paper with dr. philos Bjørn Øglænd who collected the data in "The Stavanger Study", who was also a co-supervisor for this part of the PhD-project. For the remaining papers, post doc Petur Juliusson at The Department of Clinical Science, University of Bergen has been a co-worker, especially regarding anthropometric aspects, and co-supervisor for the thesis. Professor Michele Forman, during the writing of the thesis working at different universities in USA and currently at Purdue University, Indiana, has been involved in the original planning of "The Stavanger study" and a valuable co-worker during my work, especially regarding epidemiological aspects. During the whole period, Professor Geir Egil Eide at University of Bergen has been an active participant and co-author for the statistical aspects. For Paper IV, Associate Professor of University of Bergen and consultant paediatrician at Stavanger University Hospital Ingvild Bruun Mikalsen has been involved.

Knut Øymar, Professor at the Department of Clinical Science, University of Bergen has been the main supervisor of this thesis. As a PhD candidate I have been affiliated to the Department of Clinical Science, University of Bergen.
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Abbreviations

b	Regression coefficient
BMI	Body Mass Index (kg/m^2)
CD4	Cluster of Differentiation 4
CI	Confidence Interval
CLASP	Collaborative Low-dose Aspirin Study in Pregnancy
DAG	Directed Acyclic Graph
DOAD	Developmental Origins of Adult Disease
DOHaD	Developmental Origins of Health and Disease
EAACI	European Academy of Allergy and Clinical Immunology
ERS	European Respiratory Society
ERV	Expiratory Reserve Volume
FEF	Forced Expiratory Flow
FEV_1	Forced Expiratory Volume during the first second of FVC
FIF	Forced Inspiratory Flow
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GEE	Generalized Estimating Equations
GINA	Global Initiative for Asthma
GLI	Global Lung Function Initiative
HELLP	Haemolysis, Elevated Liver enzymes and Low Platelet count
IC	Inspiratory Capacity
IgE	Immunoglobulin E
IOTF	International Obesity Task Force
IRV	Inspiratory Reserve Volume
ISAAC	International Study of Asthma and Allergies in Childhood
kU/l	Kilo Units per Litre
LR	Likelihood Ratio
mmHg	Millimetres of mercury
MFPR	Multiple Fractional Polynomial Regression
OR	Odds Ratio

PEF	Peak Expiratory Flow
Q_1	Lower quartile
Q_3	Upper quartile
RAST	Radio-Allergo-Sorbent Test
RV	Residual Volume
SD	Standard Deviation
SDS	Standard Deviation Score
Th	T-helper lymphocyte
TLC	Total Lung Capacity
Tregs	T regulatory lymphocytes
TV	Tidal Volume
VC	Vital Capacity

Summary of thesis

Background

An adverse intrauterine environment may affect offspring immunology, including allergies, asthma and lung function, as well as offspring metabolism, including growth and development. A few studies have been reported on the associations between preeclampsia and these outcomes, but they have shown conflicting results. Furthermore, a possible association between childhood excessive weight/obesity and physical activity with allergies, asthma and lung function has been suggested, but, again, previous studies show conflicting results, and few longitudinal studies exist.

Objectives

(1) To study the associations of preeclampsia exposure with atopic sensitization, allergic rhinoconjunctivitis, atopic dermatitis, asthma and lung function in late childhood. (2) To study the associations of preeclampsia exposure with length/height, weight and body mass index (BMI) at several ages from birth to late childhood and waist circumference, waist-to-height ratio and skinfolds in late childhood. (3) To study the associations of weight-related anthropometric measurements at several ages from birth to late childhood and physical activity with allergies and asthma in late childhood. (4) To study the associations of weight-related anthropometric measurements at several ages from birth to late childhood with lung function in late childhood.

Methods

In a nested case control study, 229 children were exposed to preeclampsia (mild/moderate: n = 164, severe: n = 54, unknown severity: n = 11) and 385 were unexposed. Length/height were abstracted from medical records at birth, 3 and 6 months, 1 and 4 years, and measured along with waist circumference and skinfolds at 10.8 years (girls), 11.8 years (boys) and 12.8 years (both genders). Questionnaires on maternal and child data were administered to the mothers when the children were at

the age of 10.8/11.8 years (girls/boys) and to the children at the age of 12.8 years (both genders). Specific IgE in serum and lung function were measured at the age of 12.8 years (both genders). Multiple regression analyses were performed to analyse the associations of mother's preeclampsia, child weight, child BMI, and childhood physical activity with childhood growth, atopic sensitization, allergic rhinoconjunctivitis, asthma, atopic dermatitis and lung function.

Results

Severe preeclampsia exposure was associated with high-level atopic sensitization (sum of specific IgE in serum ≥ 3.9 *kU*/l; the lower quartile of all sensitized children in the study) and with allergic rhinoconjunctivitis in the offspring. We did not find any association of preeclampsia with allergic rhinoconjunctivitis, atopic dermatitis or lung function.

In boys, mild/moderate preeclampsia exposure was positively associated with length/height after 0.5 years; however, severe preeclampsia exposure was negatively associated with length/height at all ages. In girls, preeclampsia was negatively associated with length/height until 12 years of age. In both genders, preeclampsia exposure was in general negatively associated with weight and BMI during infancy and early childhood, but the association became positive in later childhood, except that for boys exposed to severe preeclampsia the negative association remained throughout childhood. Severe preeclampsia exposure was positively associated with waist-to-height ratio at 10.8/11.8 (girls/boys) years of age. We did not find any associations of preeclampsia exposure with skinfolds or waist circumference.

BMI at 1 year of age and low physical activity at 3–6 years of age were positively associated with atopic sensitization at 12.8 years of age. Change in BMI from 1 to 4 years, BMI at 4 years and high physical activity at 6–10 years of age were positively associated with ever being diagnosed with atopic dermatitis at the age of 10.8/11.8 years (girls/boys). Low physical activity at 3–6 and 6–10 years of age were positively associated with ever being diagnosed with asthma at the age of 10.8/11.8 years (girls/boys). We did not find any associations of weight, BMI and physical activity with ever being diagnosed with allergic rhinoconjunctivitis at the age of

10.8/11.8 years (girls/boys), and current asthma at the age of 12.8 years (both genders), nor did we find any non-straight-line associations of the predictors with any of the outcomes of atopic sensitization, allergic rhinoconjunctivitis, atopic dermatitis or asthma.

Birthweight and BMI at different ages throughout childhood were positively associated with forced vital capacity in percent of predicted (FVC %) and forced expiratory volume in the first second of predicted (FEV_1 %) at 12.8 years of age. BMI, waist circumference, waist-to-height ratio and skinfolds at 12.8 years of age and the change in BMI from early to late childhood were positively associated with FVC % and FEV_1 % and negatively associated with FEV_1/FVC and forced expiratory flow at 25–75% of FVC/FVC. Interaction analyses showed that positive associations between anthropometrics other than BMI and lung function were mostly present in girls. Inverse U-shaped associations were found between BMI at the ages of 10.8/11.8 (girls/boys) and 12.8 years (both genders) and FVC % and FEV_1 % at 12.8 years of age.

Conclusions

Preeclampsia exposure was positively associated with atopic sensitization and allergic rhinoconjunctivitis in late childhood, but not with atopic dermatitis, asthma or lung function. From birth to adolescence, length/height, weight and BMI trajectories differed between the genders depending on the severity of preeclampsia exposure. In general, preeclampsia exposure was negatively associated with length/height, and in girls positively associated with weight and BMI. BMI and physical activity in early childhood were positively associated with atopic sensitization, atopic dermatitis and asthma in late childhood. Body composition through childhood may influence lung function in late childhood, which may be physiological or associated with air flow limitation. Non-straight-line associations suggest a differential impact on lung function in normal-weighted and overweight children.

Our results suggest that foetal life is a particularly sensitive period for subsequent growth and development of the immune system, and that growth during

childhood may further influence allergic disease and lung function in late childhood. Understanding the impact of early life risk factors may enable preventing the development of allergic disease and unfavourable lung function and promote healthy growth.

List of publications

Byberg, K.K., Ogland, B., Eide, G.E. & Oymar, K. (2014): "Birth after preeclamptic pregnancies: association with allergic sensitization and allergic rhinoconjunctivitis in late childhood; a historically matched cohort study", BMC Pediatrics, Vol 14: 101

Byberg, K.K., Øymar, K., Eide, G.E., Forman, M.F., Júlíusson, P.B. (2017): "Exposure to preeclampsia *in utero* affects growth from birth to late childhood dependent on child's sex and severity of exposure: follow-up of a nested case control study", Plos One, Vol. 12: 5.

Byberg, K.K., Eide, G.E., Forman, M.R., Júlíusson, P.B., Øymar, K. (2016): "Body mass index and physical activity in early childhood are associated with atopic sensitization, atopic dermatitis and asthma in later childhood", Clinical and Translational Allergy, Vol. 6: 3.

Byberg, K.K., Mikalsen, I.B., Eide, G.E., Forman, M.F., Júlíusson, P.B., Øymar, K. (2017): "The associations between weight-related anthropometrics during childhood and lung function in late childhood; a historical cohort study", Submitted.

1. Introduction

1.1 Background

Allergy and allergic diseases are becoming increasingly common worldwide (1-3). They represent the most common chronic medical conditions in children, and they impose a considerable burden on the involved children and their families. Today, more than one-third of all Norwegian school children have at least one allergic sensitization (4).

Allergies seem to have affected humans since ancient times. The earliest medical description of allergy is of King Menses of Egypt, who died of anaphylaxis in 2641 BC; furthermore, Emperor Octavianus Augustus (born in 63 BC) was the most famous allergic individual of this era, with the whole allergic triad including allergic rhinitis, asthma and eczema and positive family history of allergy (5).

One of the milestones in the understanding of allergic diseases is the simultaneous discovery of IgE by Johansson and Bennich in Uppsala, Mrs and Mr Ishizaka in Denver and Humphrey and Stanworth in the UK in 1967 (6-8). IgE is the immunoglobulin involved in hypersensitivity type 1, and it manifests in allergy and allergic diseases (9). During the past few decades, as increasing knowledge has been gained about allergies, an epidemic of allergy and allergic diseases has also been seen, especially in the developed world.

Over the last 2000 years, various terms have been used for describing allergies. However, only in 1906 did Clemens von Pirquet introduce the term ‘allergy’ (from the Greek ‘*allos*’ meaning ‘other’ and ‘*ergon*’ meaning ‘reaction’) to describe a hypersensitivity reaction. In 1923, the American allergists Coca and Cooke introduced the term atopy to characterize familial-type hypersensitivity reactions such as asthma, seasonal allergic rhinitis and others (10).

The worldwide allergy epidemic cannot be explained by inheritance alone. Increasingly, environmental factors are being studied to find an explanation. In particular, early-life factors, both *in utero* and during the first years of life, seem to

play an important role. Increasing evidence suggests that pregnancy and early childhood are sensitive periods for environmental risk factors for the development of allergy and allergic disease (11).

A hostile intrauterine environment could potentially affect the developing foetus, especially in terms of lung development and the immune system, which develop both *in utero* and in early childhood (12, 13).

Preeclampsia affects 3%–5% of pregnancies, and it may create a hostile intrauterine environment (14). Associations between preeclampsia exposure *in utero* and subsequent allergic sensitization and allergic disease have been suggested (15-17).

Adaptive responses to low birth weight due to a hostile intrauterine environment could be a risk factor for subsequent obesity and metabolic diseases (18). The prevalence of obesity has increased in parallel with allergy and allergic diseases, and an association has been suggested (19). The association between obesity and asthma in adults has been established, and some studies indicate the same for children (20, 21). However, studies on the association between obesity and allergy in childhood show conflicting results (22, 23).

A possible association between preeclampsia exposure and allergic sensitization, allergic disease and lung function could be mediated through a changed growth pattern in affected children. It is already known that children exposed to preeclampsia (especially of the severe type) have low birthweight, and at least some of them have an increased risk of overweight in adolescence (24, 25). However, how preeclampsia exposure affects growth between birth and adolescence remains unknown, and the effect on height has not been studied according to the severity of preeclampsia. To address these issues could improve the understanding of the complex relations of early life predictors and outcomes in the other papers of this thesis.

After the submission of the first paper of in this thesis in February 2014, new studies about preeclampsia, growth, allergic sensitization, allergic diseases and lung function have been published. Our study aimed to address questions based on the current knowledge at that time. Consequently, when addressing topics related to our

hypotheses, the general introduction will refer to articles published before our papers. More recent knowledge will be addressed in the discussion section.

1.2 Preeclampsia

Preeclampsia is a maternal disorder of pregnancy occurring after 20 weeks of gestation. It can either be of severe type with onset at early pregnancy or with slowly developing, milder symptoms later during pregnancy. The mother shows hypertension, renal involvement, coagulation disturbances and reduced organ perfusion. The most severe form often results in preterm delivery, intrauterine growth restriction or even foetal death. Preeclampsia is the most common cause of maternal and foetal morbidity and mortality in the developed world (14).

1.2.1 Definition

The word preeclampsia is derived from the words 'pre' and 'eclampsia'. 'Eclampsia' is a Greek noun meaning a 'light burst', and it is used metaphorically in this context to mean 'sudden occurrence'.

Preeclampsia may be defined in various ways, and it could probably be characterised as a syndrome rather than as one disorder. However, most preeclampsia cases have some common features, and in this study, we have used the criteria of the Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) (26), which is described in greater detail in Chapter 3.

1.2.2 Epidemiology

Despite advancements in perinatal care, the incidence of preeclampsia has increased during the last two decades (27), and it is seen globally in 3%–5% of all pregnancies (14). However, the increased incidence has not been accompanied by any increased risk of maternal and infant morbidity and mortality. In healthy nulliparous women, this condition is mostly mild and near-term, and it poses a negligible risk of adverse outcomes for the offspring. However, the prevalence and risk is higher in women with multifetal gestation, hypertension, previous preeclampsia, diabetes mellitus and

thrombophilia (14). Obesity is a risk factor for preeclampsia, and the worldwide increase in obesity is likely to increase the prevalence of preeclampsia (14).

1.2.3 Pathophysiology

The causes of preeclampsia are largely unknown. It may be caused by a faulty maternal response to placentation, in which inflammatory signals (depending on the foetal genes) and the maternal response to these signals (depending on maternal genes) lead to the maternal syndrome (14).

Lam et al. described the difference between abnormal placentation in preeclampsia and normal placentation, and it is illustrated in Figure 1 (28).

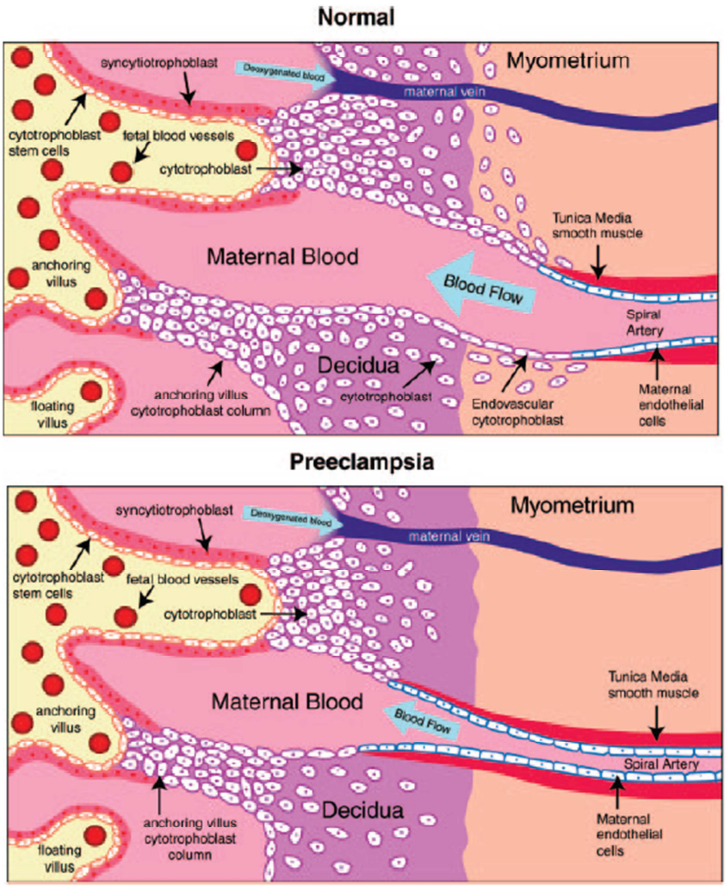


Figure 1 Abnormal placentation in preeclampsia. With permission from Lam et al, Hypertension, 2005. In normal placental development, invasive cytotrophoblasts of foetal origin invade the maternal spiral arteries, transforming them from small-calibre resistance vessels capable of providing adequate placental perfusion to sustain the growing foetus. During vascular invasion, the cytotrophoblasts differentiate from an epithelial phenotype to an endothelial phenotype (upper panel). In preeclampsia, cytotrophoblasts fail to adopt an invasive endothelial phenotype. Instead, invasion of the spiral arteries is shallow, and they remain small-calibre resistance vessels (lower panel).

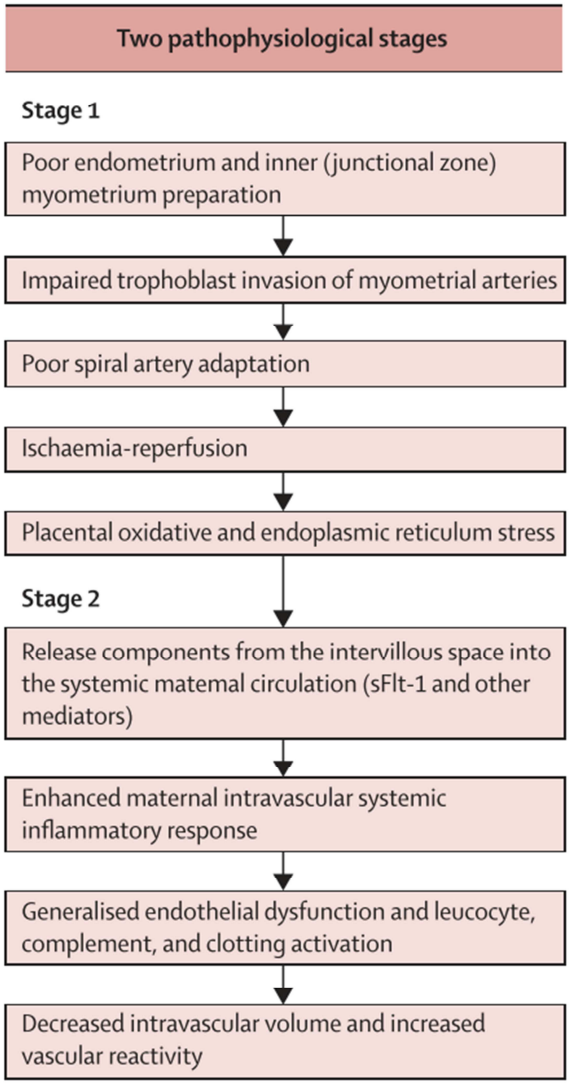


Figure 2 Two possible pathophysiological stages of preeclampsia. Modified from Steegers et al., Lancet, 2010, with permission.

Impaired remodelling of the spiral artery has been considered an early event in the development of preeclampsia (Figure 2). Vascular changes occur in the inner myometrium followed by trophoblast invasion with associated remodelling. The interaction of trophoblasts with uterine natural killer cells and/or dendritic cells is considered important in the regulation of invasion. The intervillous flow starting at 8 weeks of gestation in connecting channels appears between spiral arteries and lacunae

in the wall of the implanted blastocyst, and the embryo is protected from high oxygen concentrations by early trophoblast plugging. The premature loss or insufficient lateral spread of these plugs could result in extensive chorionic regression, a small placenta and intrauterine growth restriction and/or preeclampsia depending on the timing (29).

Impaired invasion of myometrial spiral arteries in preeclampsia might result from maternal flow defects.

The first stage of preeclampsia might be an excessive or atypical maternal immune response to trophoblasts and thus a failed interaction between two genetically different organisms (Figure 2). Consequently, very shallow placentation occurs.

The second stage (Figure 2) involves exaggerated endothelial activation and a hyperinflammatory state. The components of the intervillous space are released into the systemic maternal circulation, thereby producing the maternal inflammatory response. These components include anti-angiogenic factors (29).

The two types of preeclampsia might actually be two different phenotypes, where the severe type is mostly early onset whereas the mild/moderate types are mostly late onset. The mechanisms linking these two stages of faulty placentation in preeclampsia vary between the different phenotypes. Severe (or early onset) preeclampsia is more common in normal-weight mothers, and it is characterized by a small placenta owing to angiogenic imbalance, with a higher degree of inflammation. Mild/moderate (or late onset) preeclampsia is characterized by normal placentation, in which cardiovascular and metabolic syndromes might still set off a cascade of placental inflammation (29, 30).

1.2.4 Clinical characteristics and treatment

Maternal organ systems susceptible to excessive inflammation and endothelial damage include the central nervous system, lungs, liver, kidneys, systemic vasculature, heart and the blood coagulation mechanism. The placenta and foetus are also at risk. The numbers of complications for the mother and foetus depend on the number of organ systems involved. Maternal symptoms may be mild ones like nausea

and vomiting even at the onset of severe preeclampsia. Significant maternal morbidity is encountered in ~15% of women with severe preeclampsia, which may be accompanied by complications including retinal detachment, cerebrovascular bleeding and haemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome). In particular, early-onset, or severe-type, preeclampsia is associated with foetal growth restriction. Eclampsia occurs in 1%–2% of severe preeclampsia cases, and causes tonic-clonic seizures either during pregnancy or shortly after delivery (29).

Commonly, the following signs or symptoms might be present: hypertension, proteinuria, headache, visual disturbance, epigastric pain, vomiting, reduced foetal movements and an infant that is small for the gestational age.

There is no universal standard of care for mothers with preeclampsia, although standardized assessment and surveillance, avoidance and management of severe hypertension, prevention and treatment of seizures and avoidance of overhydration help reduce morbidity/mortality risk. Women at term are best managed by induction of labour, whereas for those remote from term, expectant management could be attempted, although the definite treatment is delivery of the baby (29).

Preeclampsia is the most common indication for premature delivery (23%), with several consequences for the offspring (31).

The timing of delivery depends on foetal well-being as assessed by ultrasound and cardiotocography.

1.2.5 Associations between preeclampsia and subsequent disease in the child

The epigenetic modification of foetal vascular tissue owing to mother's preeclampsia might have consequences for the child's future cardiovascular and reproductive health. Individuals exposed to preeclampsia *in utero* have an increased risk of having (or fathering) a future pregnancy with preeclampsia. Children exposed to preeclampsia have an increased risk of hypertension, altered start of puberty, metabolic syndrome and cardiovascular disease (29, 32-34). Preeclampsia exposure

may have a negative effect on intellectual development in children, and it is positively associated with mental, mood or anxiety disorders; epilepsy and lower motor competence (35).

Microchimerism refers to a small number of cells or DNA harboured by one individual that originate in a genetically different individual. The most common source is from maternal-foetal trafficking across the placenta during pregnancy (36). Microchimerism may have an impact on the long-term health of both the mother and the offspring. The offspring may have maternal cells and DNA in their body; this is called maternal microchimerism, and it is positively associated with inflammatory conditions during the entire life. Maternal cells have proliferative potential (37). During preeclampsia, the transfer of cells between the mother and the foetus is higher than during normal pregnancies, and an increased risk of the mother harbouring foetal microchimerism has been found (38). Therefore, the foetus could also have an increased risk of maternal microchimerism after pregnancies with preeclampsia. Maternal microchimerism is also a risk factor for autoimmune diseases; therefore, it could also give rise to other non-communicable diseases like atopy. To the best of our knowledge, no publications exist on the possible association between maternal microchimerism and atopy; however, one report suggests a negative association between maternal microchimerism and asthma in children (39).

The risk of some types of cancer is suggested to be affected by preeclampsia. Women born after preeclamptic pregnancies have a reduced risk of breast cancer (40). Men born after pregnancies with severe and mild preeclampsia have a reduced and increased risk of testicular cancer, respectively (41).

A few studies have assessed the associations of preeclampsia with allergy, asthma and lung function before the submission of our first paper in the beginning of 2014. Further details are introduced in Chapters 1.5–1.6.

1.3 Childhood growth

It is estimated that up to 80% of the final height of individuals is dependent on their genetic potential (42); however, normal endocrine function and adequate nutrition are

also prerequisites for normal growth and development (43). Generally, childhood growth is a sensitive parameter of general health, and chronic diseases and psychosocial deprivation may negatively affect linear growth (44). Additionally, as stated by Tanner, children's growth reflects prevalent conditions in society (45).

Secular trends in childhood growth in Norway were summarized from the Bergen Growth Study in the Journal of the Norwegian Medical Association in 2009 (46). The authors found that Norwegian school children were generally taller than children 30 years ago; overweight had increased in children above five years of age, and those in the upper percentiles were mainly affected; toddlers had the same growth as 20 years ago; and Norwegian children had higher birthweight, childhood length/height, head circumference and weight than the World Health Organization international standard (46).

1.3.1 Normal childhood growth

Genotype and maternal factors are most important for foetal growth (47, 48). Placental function is crucial, and pregnancy disorders weakening the placenta will affect foetal growth negatively (49). The placenta exerts endocrine functions by producing growth-regulating hormones. Normal foetal growth also depends on an adequate supply of nutrients, oxygen and insulin (48, 50).

Postnatal growth is divided into three stages: infancy, childhood, and puberty, also called the ICP model (Figure 3) (51). The first stage, infancy, is characterized by a fast but decelerating growth during the first 2–3 years of life. Foetal growth factors are most important in this period. The second stage, childhood, starts at ½–1 year of age, and it adds to infant growth. From 3 years of age, the childhood stage is the most important, with the main growth factors being the thyroid and growth hormones. The third and last stage, puberty, adds to childhood growth at puberty, and it adds up to 20–25 cm for girls and 25–30 cm for boys, independent of ethnicity and age of puberty onset. As childhood growth wanes, the total growth in puberty is lower the later puberty starts. The earlier puberty starts, the larger will be the total growth during puberty. The final height in children with early- or late-onset puberty therefore

remains normal as the actual height at puberty onset is either higher or lower compared to that of children entering puberty at an average age. Growth during puberty is regulated by sex hormones, both directly and through the modification of the secretion and effect of growth hormone. The maximal growth velocity is frequently seen 2 years after puberty onset (51).

The crossing of percentiles during the first 2 years of life is frequently normal, and the child usually finds its new growth channel during this period (52). Crossing percentiles is almost universal in puberty, but it is especially prominent in constitutionally delayed growth and development (52).

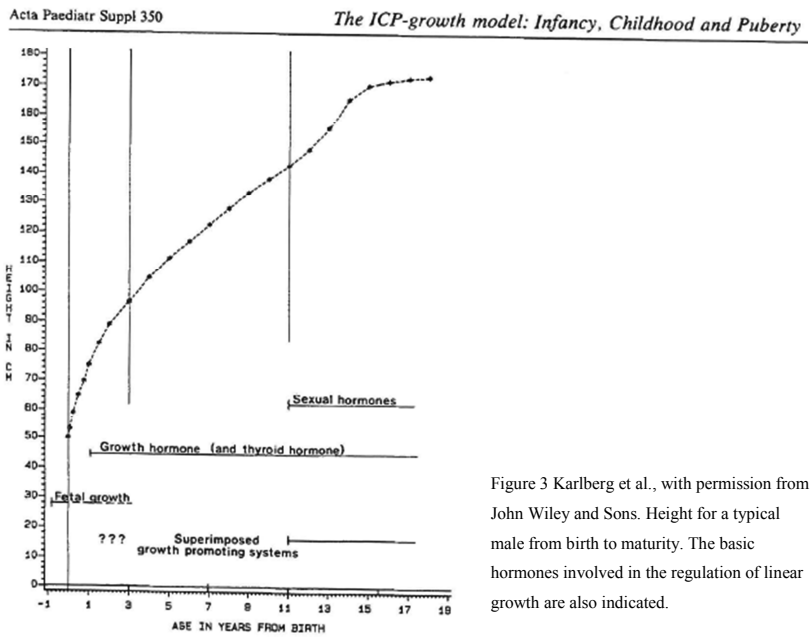


Figure 3 Karlberg et al., with permission from John Wiley and Sons. Height for a typical male from birth to maturity. The basic hormones involved in the regulation of linear growth are also indicated.

1.3.2 Catch-up growth

The definition of catch-up growth varies, but it is typically characterized by above-normal height velocity for 1 year following a period of less growth. The change in height standard deviation score of 0.67 is frequently used, as it corresponds to the distance between two lines in the growth curve. Complete catch-up results in a mean final height close to the mean target height (53).

Small for gestational age (SGA) is usually defined as a birthweight <-2 standard deviation scores (SDS) (54). However, intrauterine growth retardation is defined as a failure to achieve the growth potential of a foetus that is promised by the genetic constitution (49).

Most, but not all, children show catch-up growth following intrauterine growth retardation. Catch-up seen in children born SGA is associated with being overweight and obese later in life. Although only 14 % of children born SGA remain short at 18 years of age (54), these children frequently show more catch-up in weight than in height (55). The unfavourable metabolic consequence of being born SGA and/or experiencing catch-up growth is indicated by the association with increased abdominal adiposity (56).

1.3.3 Overweight epidemic

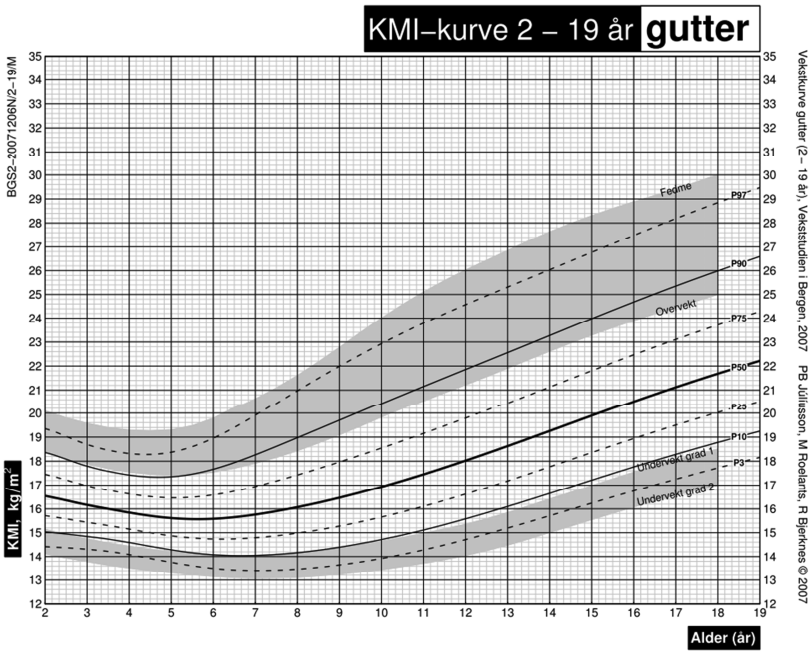
The prevalence of overweight and obese children has increased worldwide during the last few decades (57). However, there are large variations across countries. For example, the following numbers have been reported in Europe. In England, overweight in 4- to 11-year-old boys increased from 7.8% in 1974 to 21.4% in 2002, and in Spain, overweight in 6- to 7-year-old boys increased from 21% in 1985 to 34% in 1996, with a similar increase being found in girls (58). The annual increases in overweight and obesity prevalence in Europe increased from below 0.5% in the 1980s to over 1.0% in the late 1990s (58). In the Bergen Growth Study from Norway, the prevalence of overweight and obesity was found to increase from 1971 to 2007, with an overall mean increase in weight for height of 0.48 kg/m (boys) and 0.92 kg/m (girls) (59). The prevalence of overweight including obesity found in the Bergen Growth Study in 2009 was 13.8% in all children (60).

The importance of early-life risk factors in the development of childhood obesity is increasingly emphasized, and obesity is a risk factor for excessive morbidity across the life course for those affected (61).

Overweight and obesity are due to an energy imbalance, with excess energy stored as fat. However, genes, metabolism, behaviour and environment influence body weight

and composition (42). Sleep disturbances and social risks are associated with obesity (62, 63). A sedentary, modern lifestyle is a risk for overweight/obesity. Medication, diet and lifestyle could influence gut flora and thus play a role in obesity, allergy and allergic diseases (64, 65)

Cut-off points for BMI (unit: kg/m^2) for thinness grades 1, 2 and 3 and overweight and obesity in children between 2 and 18 years by gender for exact age corresponding to BMI of 25 and 30 kg/m^2 at 18 years of age are shown in Figures 4–5 (46, 66). However, BMI is not an accurate measurement of obesity; it is actually influenced by both lean and fat mass. Therefore, other measurements of body composition are also used. Waist circumference and waist-to-height ratio are strongly related to BMI and cardiovascular risk factors, whereas measurements of skinfold thickness do predict the percentage of body fat better than BMI (67). However, it is not certain whether skinfolds predict health risks better than BMI does (68).



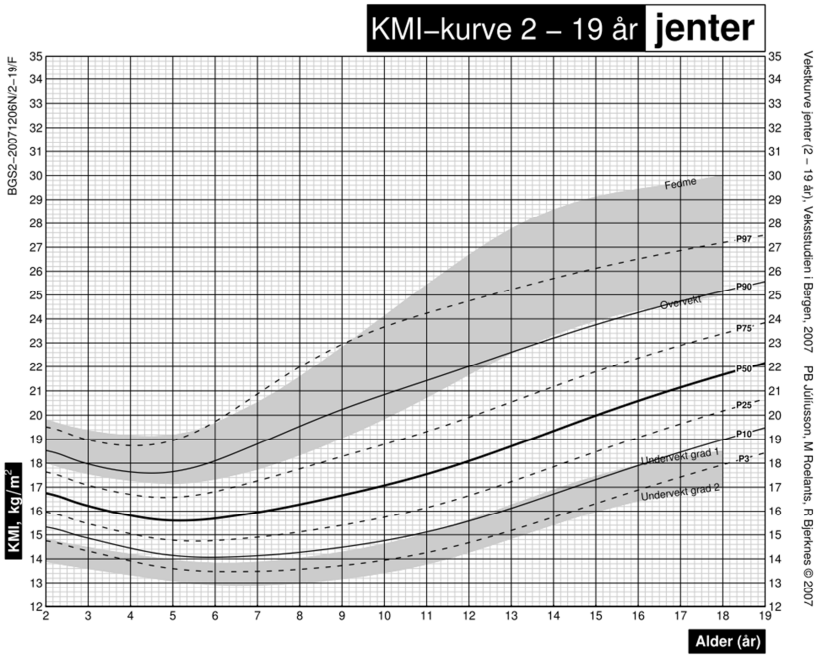


Figure 4. Juliusson et al., Bergen Growth Study. Body mass index curves for boys (upper panel) and girls (lower panel). The limits for thinness grade 1 and 2 are respectively indicated by the top and bottom of the lower grey area and those for obesity and overweight, by the top and bottom of the upper grey areas.

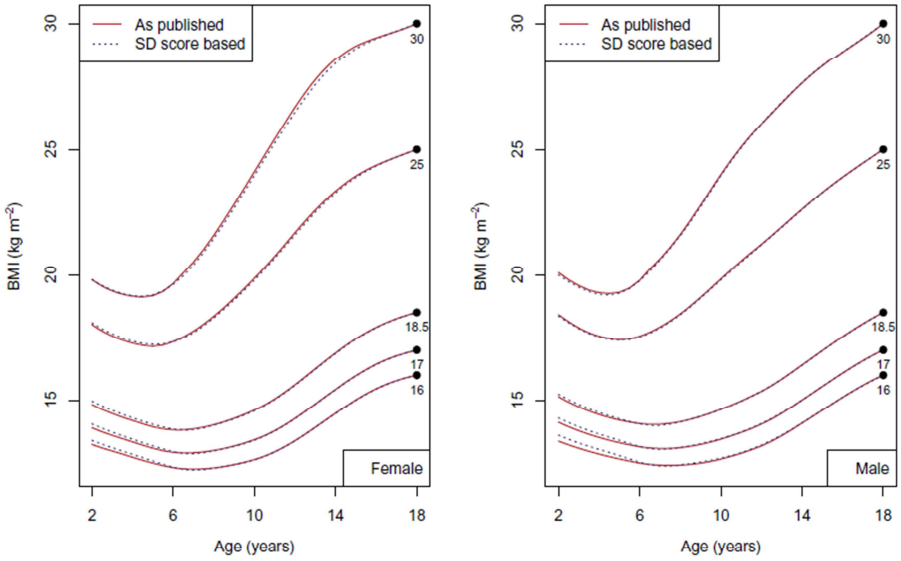


Figure 5. Cole & Lobstein 2012, with permission from John Wiley and Sons. Original international cut-offs (red solid lines) and those as derived from the more recent L, M and S curves (blue dotted lines).

1.3.4 Developmental origins of health and disease

The developmental origins of adult disease (DOAD) or the Barker hypothesis is based on many studies providing evidence for the hypothesis that birth weight is related to disease risk later in life (18, 69). The more modern term, Developmental Origins of Health and Disease (DOHaD) is now used, because several early stressors in life increase disease risk later in life, and it has been discovered that chronic malnutrition, changes in social condition and adverse early-life experiences may epigenetically change phenotypes and contribute to long-lasting risk of disease (70).

Foetal growth is generally limited by maternal constraints, and it is aggravated by small placental size or poor perfusion, short maternal stature, young or old maternal age, first pregnancy or multiple pregnancies, unbalanced maternal diet or excessive maternal thinness or fatness. Furthermore, foetal development is impaired by poor placental function or maternal disease. Subsequent rapid childhood growth appears to have negative effects on later health. The relation between prenatal nutrition and later metabolic disease is likely to be U-shaped, with increased risks at both ends of the birth-weight curve. Genetic expressions seem to be modified by prenatal factors. These epigenetic modifications involve a small set of enzymes, and they may include changes in the methylation of nucleotides in promoter regions of specific genes (71). Intrauterine growth restriction, severely preterm birth and food restriction *in utero* are associated with increased appetite and carbohydrate intake and lower physical activity, and these food preferences persist into adulthood (72).

1.3.5 Preeclampsia and growth

Severe preeclampsia frequently results in poor nutrient supply or, in the most severe cases, poor perfusion, and therefore, it may influence foetal growth (73, 74). Preeclampsia is the most frequent indication of preterm delivery (31). As intrauterine growth restriction and preterm birth may affect the appetite of the offspring (72), preeclampsia could, via epigenetics, affect appetite (71) and even the growth of the offspring in the long term.

Some studies have been conducted on preeclampsia exposure *in utero* and its association with subsequent growth.

Odegard et al. found that preeclampsia is negatively associated with foetal growth (25). Ogland et al. found that preeclampsia exposure in girls is associated with higher BMI and larger waist circumference in late childhood, but only if the mothers had high BMI (24). In a study of 90 children exposed to preeclampsia (differentiated by early or late onset) and 50 controls, the height and weight of exposed children at 7–11 years of age did not differ from those of the controls (75). Similarly, in a study of >9000 16-year-old adolescents in Finland, preeclampsia exposure (not differentiated by severity) was not associated with BMI or waist circumference (76). However, in another Finnish study of 144 individuals who were born SGA, men who were exposed to preeclampsia (not differentiated by severity) *in utero* had higher weight and BMI at 20–25 years of age than unexposed men; however, no difference in height was found (77). In the same publication, 139 individuals born to term were studied, and preeclampsia exposure was not associated with height, weight or BMI at 20–25 years of age (77). In a Norwegian study of 23 children exposed to preeclampsia and 17 controls at 5–8 years of age, no significant differences in BMI, waist circumference, hip circumference and waist-to-height ratio were found (78). Larger studies have shown that preeclampsia exposure (not differentiated by severity) was associated with low birthweight, catch-up growth in infants (79) and high weight and BMI in adolescence (32, 80). However, no studies have focused on growth trajectories or length/height in children after preeclampsia exposure. Furthermore, few studies on preeclampsia and growth have differentiated by the severity of preeclampsia.

1.3.6 Growth and atopy

The prevalence of obesity and allergies/allergic diseases has increased in parallel worldwide (57), and studies have been conducted on the associations between these conditions. The associations between obesity and allergy, asthma and lung function are described in further detail in Chapters 1.5.6 and 1.6.1.

1.4 Physical activity

Physical activity in children consists of spontaneous and everyday movement, as well as targeted exercise. Everyday activity plays the most important part in the youngest age groups. Children's activity level is closely linked to their body composition and is also associated with various health aspects (81). The recommended minimum of activity, for example, during play, is 60 min per day for children. Most Norwegian children aged 6–9 years, but only half of those aged15years, achieved the recommended levels of physical activity in 2012 (82). The levels of physical activity for 9-year-old children was increased from 2000–2005, but those in 15-year-olds remained constant (83).

Exercise has been suggested to diminish the unfavourable metabolic profile of children who have experienced intrauterine growth retardation (84). The favourable effects of physical activity may be due to the negative association with leptin (thus regulating appetite) (85). On the other hand, activity behaviour may be influenced by *in utero* conditions, as suggested by animal experiments, where poor nourishment *in utero* was associated with sedentary behaviour in postnatal life, despite adequate nutrition postnatally (86).

Physical activity increases growth hormone levels and improves bone strength (87). A sedentary lifestyle in children is strongly associated with obesity (88); thus the effects of physical activity and obesity on general health could be difficult to distinguish. Tremblay et al. reviewed the role of a sedentary lifestyle in children (81), and they found that it was positively associated with concerns about body shape, depressive symptoms, behavioural problems, poorer academic achievements, serum cholesterol levels, blood pressure, glycated haemoglobin, fasting insulin, insulin resistance and metabolic syndrome. Furthermore, a sedentary lifestyle was negatively associated with musculoskeletal, cardiovascular and aerobic fitness; self-esteem; and perceptions of self-worth. The authors reported that a decrease in sedentary time in favour of more physical activity reversed several of the negative health effects described above (81).

Several studies have suggested the immunological effects of physical activity; for example, acute exercise increases the levels of natural killer cells and proinflammatory cytokines, before they decrease shortly thereafter (89-91). Studies have shown that after a long period of exercise, proinflammatory cytokines are reduced whereas natural killer cells are increased (92, 93). Furthermore, in a small study of allergic individuals, circulating levels of IgE were reported to be significantly altered by the acute steady state of moderate exercise (94).

Asthmatic subjects experienced better disease control after aerobic training (95). Further studies on the association between physical activity and atopy are described in the chapters about atopy.

1.5 Atopy

1.5.1 Definitions

Johansson et al. published a nomenclature for allergy in a position statement for the European Academy of Allergy and Clinical Immunology (EAACI) in 2001 (96). It is presented in Table 2 along with the definition of asthma from the 2014 Global Initiative for Asthma (GINA) strategy report for asthma control (97).

Table 2:

Current definitions of allergy	
Hypersensitivity	Objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons. Hypersensitivity reactions include several phenomena, as summarized in Figure 6.
Atopy	Personal and/or familial tendency, usually in childhood or adolescence, to become sensitized and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. Consequently, these persons can develop typical symptoms of asthma, rhinoconjunctivitis or eczema.
Atopic	Allergic symptoms in a person with an atopic constitution, as in atopic rhinoconjunctivitis.
Allergy	A hypersensitivity reaction initiated by immunologic mechanisms. This could be IgE-mediated or non-IgE-mediated (cell-mediated), but only those who produce IgE towards an allergen could be atopic (Figure 7).
Allergens	Antigens stimulating hypersensitivity mediated by allergy. These are mostly proteins, but in certain circumstances, pure carbohydrates could be allergens. In rare instances, low-molecular-weight chemicals could work as allergens for IgE antibodies, and certain drugs are recognized by T cells.
Allergic diseases	Asthma, allergic rhinoconjunctivitis and atopic eczema/dermatitis.
Asthma	According to the latest GINA guidelines; 'a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation'.
Allergic rhinitis	Symptoms resulting from an immunologically mediated hypersensitivity reaction in the nose (Figure 8)
Allergic conjunctivitis	Similar to allergic rhinitis, but occurs in the conjunctiva. It often accompanies allergic rhinitis, then it is called allergic rhinoconjunctivitis (Figure 9)
Atopic dermatitis or atopic eczema/dermatitis syndrome	Eczematous hypersensitivity reactions of the skin, analogous to rhinitis in the nose and asthma in the lung. The term 'atopic dermatitis' allows for the definition of one distinct form of dermatitis (skin inflammation) where 'atopic' has a different meaning than 'atopy' as defined above, because it is actually possible to select patients with atopic dermatitis in whom no IgE-associated mechanism is involved (Figure 10)

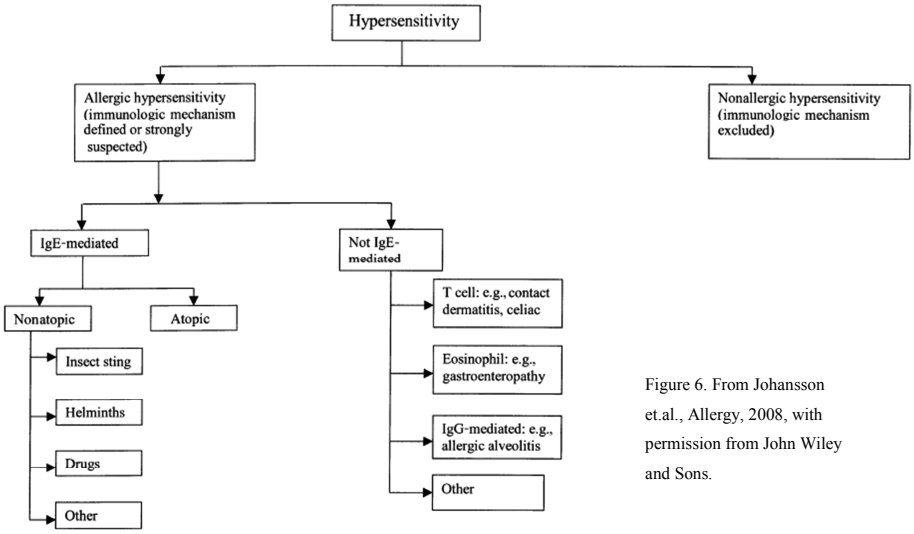
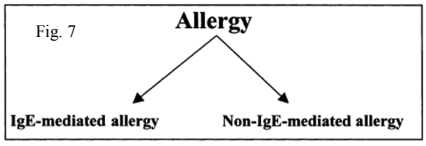
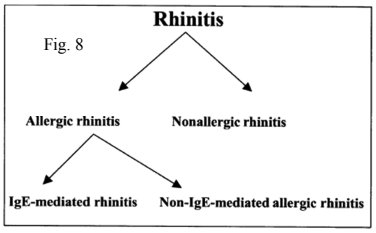
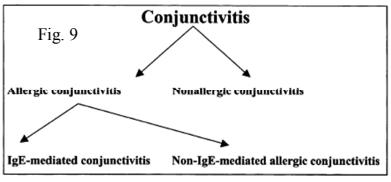


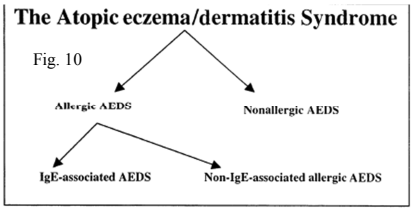
Figure 6. From Johansson et.al., Allergy, 2008, with permission from John Wiley and Sons.

Figures 7–10: From Johansson et al., Allergy, 2008, with permission from John Wiley and Sons.









1.5.2 Epidemiology

The prevalence of atopic sensitization has increased worldwide during the last 50 years. In 2005–2006, the prevalence of atopic sensitization in USA was 36.2% in preschool children and 44.6% in schoolchildren (98). The prevalence was higher than that in 1976–80, when 23.6% of individuals aged 6–24 years had atopic sensitization

(99). Similarly, the prevalence of atopic sensitization in Swedish schoolchildren increased from 21% in 1996 to 30% in 2006 (100).

The prevalence of asthma, allergic rhinoconjunctivitis and atopic eczema increased worldwide from 1995 to 2003; according to the International Study of Asthma and Allergies in Childhood (ISAAC), it varies from 20- to 60-fold across countries (101, 102). In countries with the highest prevalence rates, there was little change or even a decrease in prevalence in all three conditions (102). In a metaanalysis from 2015 based on ISAAC questionnaires (103), the prevalence of atopy and allergic diseases worldwide was reported, and with large differences were observed between centres. The mean prevalence of childhood asthma, atopic dermatitis and allergic rhinitis worldwide was reported to be approximately 12%, 8% and 13%, respectively (103).

The prevalence of asthma has also increased worldwide in the last 50 years. For children in developed countries, the prevalence has increased from 4%–5% in 1955 to approximately15% in 2010, although with great variation (104). In Scotland, the prevalence of wheezing in school children doubled from 10% to 20% between 1965 and 1989 (3). The World Health Organisation estimates that with the current global trend of asthma increase, the number of affected individuals will increase from 300 million in 2013 to 400 million by 2025 (3). A publication from the ISAAC phase III study showed that the worldwide differences in asthma symptom prevalence are decreasing, and that the prevalence is decreasing in English-speaking countries but increasing in countries with lower prevalence (105). In the ISAAC phase I study, the prevalence of asthma varied 15-fold from 2.1% to 32.2% between countries, and in the ISAAC phase III study, the differences between countries had decreased (3). The prevalence of asthma ever in northern Norwegian schoolchildren was 7.3%–9.3% in 1985, and it increased to13.8% in 2000 and 17.6% in 2008 (106, 107). Asthma is now the most common chronic non-communicable disease among children (108).

Epidemiological studies show that the prevalence of allergic rhinoconjunctivitis continues to increase worldwide. In the USA and Europe, the prevalence is 3%–19 %, and 4%–32%, respectively (3). In northern Norwegian schoolchildren, the prevalence of allergic rhinoconjunctivitis was 15.9%–16.5% in 1985, and it increased to 29.6%

in 2000 and decreased to 24.5% in 2008 (106, 107). In Trondheim, Norway, 3% of 2-year-old children had allergic rhinoconjunctivitis in 2003–2005 (109).

Generally, the incidence of atopic dermatitis has increased two-to three-fold during the past 30 years (3). In northern Norwegian schoolchildren, the prevalence of atopic dermatitis was 12.2%–13.4% in 1985, and it increased to 20.8% in 2000 and decreased to 19.3% in 2008 (106, 107). In Trondheim, Norway, 17% of 2-year-old children had atopic dermatitis in 2003–2005 (109). In 45% of children, the onset of atopic dermatitis occurred during the first 6 months of life; 60% of children were affected during the first year and 85%, before 5 years of age (3).

The prevalence of atopy is higher in boys until puberty, after which it is higher in girls; this indicates that sex hormones influence the development of atopy (110, 111).

Allergic rhinitis, atopic dermatitis and asthma are global health problems affecting people of all ages and ethnic and socioeconomic groups, and they cause major illness and disability, thereby affecting social life, sleep, school and work and having a major economic impact (101, 112).

The increased prevalence of atopy must be attributable to non-genetic factors, as described in Chapter 1.5.5.

1.5.3 The atopic march

Atopy starts early in life, and therefore, early-life factors play an important role in its development. Sometimes, the term ‘the atopic march’ is used, meaning that there is a progression from atopic dermatitis to food allergy, and, subsequently, allergic rhinitis and asthma (113). Approximately half of the children with atopic dermatitis develop asthma, and two-thirds develop allergic rhinoconjunctivitis (114). The associations with atopic dermatitis are probably due to concomitant atopic dermatitis and atopic sensitization, and not due to atopic dermatitis without sensitization (115). Atopic dermatitis is suggested to increase the risk of food sensitization, and food sensitization may occur through the skin (113). The oral route is considered more tolerogenic (113). The Dual- Allergen Exposure hypothesis suggests that allergic sensitization to foods occurs through cutaneous exposure, whereas tolerance occurs

as a result of oral exposure to food (116). It is unknown whether food allergy is actually a step in the atopic march (113).

When allergic rhinitis develops in the 'atopic march', the risk of asthma is present. Many patients with allergic rhinitis also have lower airway hyperreactivity. Nasal symptoms, airflow and inflammation markers correlate with lower airway markers like forced expiratory volume in 1 second. Allergic rhinitis and asthma have very common pathogeneses, and three-fourths of patients with asthma report having allergic rhinitis (113).

1.5.4 Pathophysiology of atopy

According to the T-helper (Th) 1/Th2 paradigm, atopy is a decreased Th1 response to antigens that skews the balance of Th1/Th2 cells in favour of Th2 cells. Atopy is associated with a Th2–type inflammation, as described below (117). Several subsets of $CD4^+$ Th lymphocytes have been discovered after the Th1/Th2 paradigm was established; including T regulatory cells (Tregs) and the proinflammatory Th17 and Th9 cells. Tregs regulate the induction of allergen-specific T-cells and suppress the effector cells of allergy (Figure 11) (118).

The phase of allergic sensitization begins with the allergen captured by the antigen-presenting cells of the epidermis, gut and airway mucosa, which in turn migrate to lymph tissues and promote Th2 immunity. Furthermore, Th2 cells produce cytokines that lead to B-cell immunoglobulin E (IgE) production, and IgE binds to high-affinity receptors (FcεRI) on the surface of mast cells and basophils in the skin, gut and respiratory and cardiovascular systems, thereby readying them for reactivity the next time exposure to the allergen occurs (Figure 11). The next phase, elicitation, occurs within minutes after allergen exposure when mast cells with IgE become activated (Figure 11) (113, 119), and it causes symptoms in all the mentioned organ systems through the release of various mediators (112, 120).

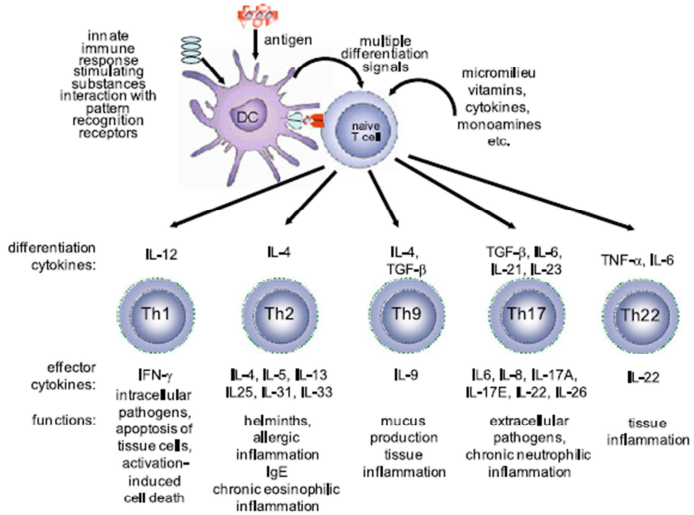


Figure 11. From Jutel, Current Allergy and Asthma Reports 2011, with permission from Springer. The figure shows the differentiation of naïve T-cells. Depending on the adjuvanticity of the substances co-exposed with the antigen and status of the cells and cytokines in the microenvironment, naïve T-cells can differentiate into T-helper (Th) 1, Th2, Th9, Th17 and Th22 T cells. Based on their respective cytokine profiles, responses to chemokines and interactions with other cells, these T-cell subsets can promote different types of inflammatory responses. *IFN*: interferon, *IL*: interleukin, *TGF*: transforming growth factor, *TNF*: tumour necrosis factor.

IgE, which was discovered in 1967, is the fifth and final class of human antibody(8). Gould and Sutton reviewed the role of IgE in allergy in 2008 (121). The activity of IgE is associated with a network of proteins, especially FcεRI, CD23, galectin-3 and several co-receptors for CD23, CD21 and various integrins. IgE and mast cells are concentrated in the mucosal membranes. Thus, IgE is among the first defence molecules that an invading pathogen may encounter; however, it plays an important role in allergy. The cross-linking of IgE-FcεRI on mast cells leads to the elicitation phase of allergy, involving mast cell degranulation and synthesis of lipid mediators. Cytokines and chemokines liberated in this early phase initiate the late phase, which peaks some hours later and involves the recruitment and activation of inflammatory cells at sites sensitive to the allergen. Allergens also activate IgE-sensitive antigen presenting cells (APC), which in turn promote IgE production by B cells to replenish the IgE consumed in the allergic reaction, thereby maintaining mast-cell and APC sensitization. FcεRI is upregulated by IgE from local B cells, and is only expressed on mucosal mast cells. Any excess IgE is mostly directed into secretions, rather than into the circulation (121). Figure 12 shows the steps involved in the allergic response,

with an emphasis on the role of IgE. It shows that IgE is synthesized and secreted by B cells that have switched from producing IgM. (121).

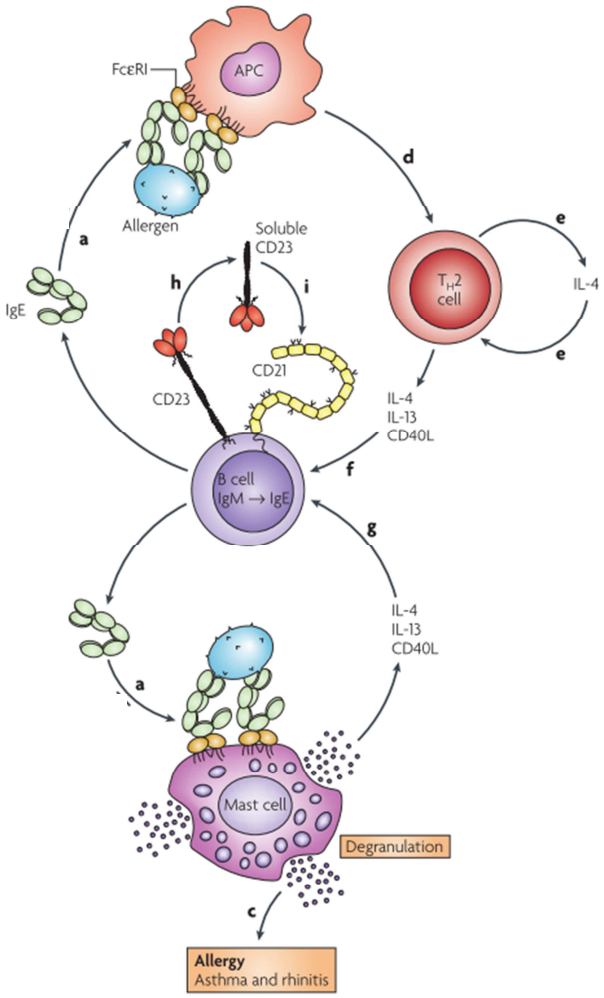


Figure 12. Modified from Gould, 2008, with permission from Nature Publishing Group. IgE binds to FcεRI on mast cells and APCs (a) and sensitizes these cells to allergens. Allergen binding to IgE triggers mast-cell degranulation to cause an allergic response (c). Allergen binding to the APC leads to the presentation of allergenic peptides to Th2 cells (d). The allergen-activated Th2 cells secrete interleukin-4 (IL-4) (e) to maintain the Th2 –cell lineage and recruit more Th cells into this lineage (e). The Th2 cells also secrete IL-13 and express CD40 ligand (CD40L), which, together with IL-4, stimulates switching to IgE (f). The allergen-activated mast cells contribute to the production of IL-4 and IL-13 (and express CD40L), which may also stimulate the expression of CD23 and the release of soluble CD23 (h). Soluble CD23 may upregulate IgE synthesis and secretion through interaction with CD21 (i). Thus, the allergen plays a role in the pump-priming of the allergic response.

1.5.5 Early-life risk factors

As reviewed by Prescott et al. in 2013 (122), studies have shown that allergy may occur during the first months of life in some individuals. Therefore, non-genetic risk factors for allergy may play a role early in infancy or *in utero*; these include diet, pollutants, microbial patterns and stress, all of which promote inflammation (Figure 12). The environment, both during pregnancy and in early childhood, can determine

the physiologic, structural, immune, metabolic and behavioural development and modify the response patterns influencing future disease susceptibility. Evidence suggests that the effects on the immune system that lead to atopy must begin *in utero*.

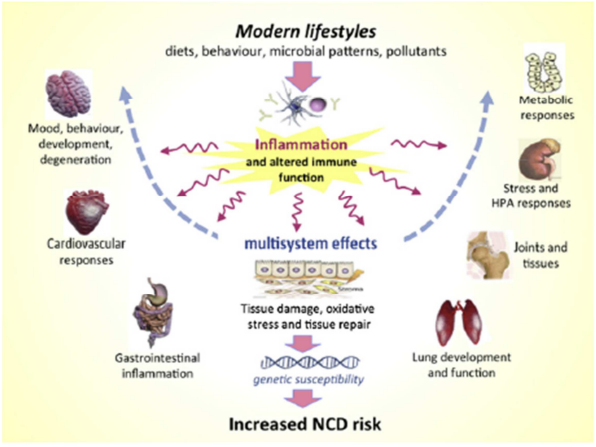


Figure 12. From Prescott, 2013, with permission from Elsevier. The figure shows that inflammation is a common element in many non-communicable diseases (NCD). HPA: hypothalamic-pituitary-adrenal axis.

Supplements of omega-3 fatty acids (with anti-inflammatory properties) to pregnant women and infants aged 0–6 months are negatively associated with allergic sensitization and atopic dermatitis in offspring.

The manipulation of gut microbiota can prevent allergy and obesity, and there is evidence that these effects are mediated through the immune system (Figure 13). The positive effects of exercise on general health are partly mediated through the same pathways (122).

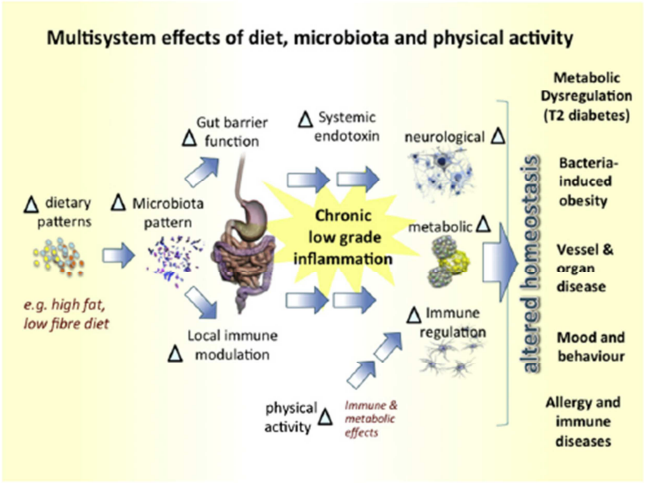


Figure 13. From Prescott, 2013, with permission from Elsevier. This figure shows the central role of the immune system in mediating the multisystem effects of diet, physical activity, and microbiota.

The hygiene hypothesis suggests that lack of exposure to microorganisms skews the Th1/Th2 balance towards an immune response to allergens with Th2 overweight (123). The dermal microbiome in atopic dermatitis probably plays an important role in creating an immune response with Th2 overweight (113). Studies have shown that growing up on a farm is protective against atopy, and this mechanism is suggested to act via bacterial endotoxins from farm animals suppressing the Th2 response toward allergens via specific enzyme induction (124). Studies have shown that gut microbiota play an important role in protection against the development of atopy, and they are influenced by factors such as the mode of birth (exposure to maternal vaginal microbiota), feeding (breastmilk promotes healthy gut microbiota), maternal exposure to pets or livestock during pregnancy and maternal exposure to antimicrobials during pregnancy (125).

Childhood diet is probably an important environmental factor related to the development of atopy. A Mediterranean diet seems to protect against atopy development (126), and a positive association between fast food and atopy has been reported (127). In a study of cord blood omega-3 fatty acids, negative associations with atopy were reported (128). In the LEAP study, the early introduction of peanuts

in high-risk infants was negatively associated with the development of a peanut allergy even if the children avoided peanuts for a longer period at a later age, further underlining the tolerogenic role of the oral route for introducing allergens (129).

Positive associations between outdoor air pollution *in utero* and later atopy have been reported (130), and poor indoor air quality, including stuffy odour, mould contamination, and exposure to environmental tobacco smoke during the first two years of life, could contribute to atopy development (131).

1.5.6 Risk factors for atopy in the current studies

The following risk factors for atopy are studied: preeclampsia exposure *in utero*, weight and BMI from birth to late childhood, physical activity in early childhood and weight-related anthropometrics in late childhood. Previous studies have reported on these associations before our articles did, as described in this chapter.

Nafstad et al. reported positive associations between complications during pregnancies (but not preeclampsia) and both childhood asthma and allergic rhinoconjunctivitis (15, 16). In a study of 378 children delivered by caesarean section, Keski-Nisula et al. reported a positive association between preeclampsia exposure *in utero* and adolescent allergic sensitization (17). Furthermore, Gagliardi et al. reported positive associations between preeclampsia and both respiratory distress syndrome and bronchopulmonary dysplasia in preterm children, and wheezing in preschool children (132). To the best of our knowledge, no further studies have focused on preeclampsia exposure, especially not according to severity, and subsequent allergic diseases. Furthermore, the long-term effect of preeclampsia exposure on lung function in the offspring was unknown.

Positive associations have been found between obesity and asthma in several studies, where obesity precedes asthma (133), although the causal pathway of this association remains unclear (134). On the other hand, the association between obesity and allergy was less consistent (135-137).

Positive associations have been reported between an accelerated weigh gain in early childhood and atopic sensitization, allergic rhinitis (12) and asthma (138, 139);

however, no associations with atopic dermatitis have been found. Childhood physical activity may be associated with atopy either directly or through an effect on body composition. In the ISAAC phase III study, positive associations were reported between vigorous physical activity and a sedentary lifestyle and childhood asthma, allergic rhinoconjunctivitis and atopic dermatitis (135). Although childhood obesity and physical activity and associations with atopy have been studied, few longitudinal studies apart from register studies exist (133, 140, 141). Furthermore, it is not known whether accelerated weight gain from birth is associated with an increased risk of atopy or whether the positive association between BMI and asthma is limited to atopic children.

1.6 Lung function

Figure 14 shows how the various volumes of the lung can be measured by plethysmography.

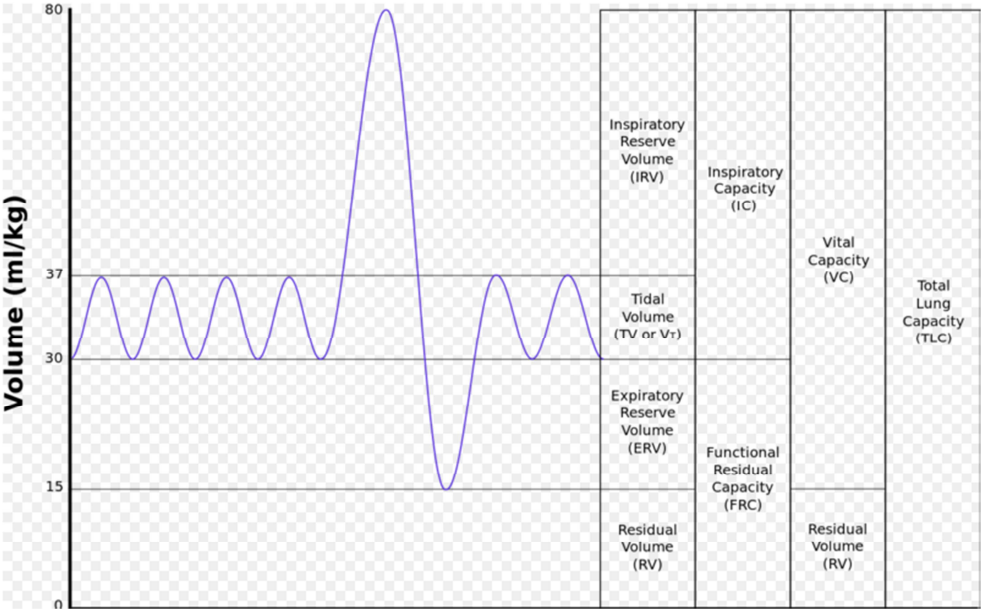


Figure 14. Total lung capacity and its subdivisions. Reprinted from Wikimedia Commons.

Total lung capacity (TLC) is the volume in the lungs at maximal inflation; it is the sum of the residual volume (RV) and the vital capacity (VC). The RV is the remaining volume in the lungs after maximum expiration. The VC is the volume inspired starting from maximum expiration up to maximum inspiration. The functional residual capacity (FRC) is the lung volume at the end of a normal expiration, that is, under the mechanical equilibrium of the opposite forces exerted by the lung tissue and thorax. The inspiratory capacity (IC) is the volume of air that can be maximally inspired starting from FRC. The expiratory reserve volume (ERV) is the volume of air exhaled by maximum expiration starting from FRC, and it is used to derive RV from FRC. The tidal volume (TV) is the volume of air moved during normal breathing. The inspiratory reserve volume (IRV) is the maximal volume that can be inhaled from the end-inspiratory level (142).

Spirometry is used to measure the volume of air exhaled from the lungs during a maximal expiratory manoeuvre, and it is usually shown as a flow-volume curve (Figure 15). Forced vital capacity (FVC) is the maximal volume of air exhaled with maximally forced effort from a position of maximal inspiration, that is, the VC, with a maximally forced expiratory effort, and it is expressed in litres. The forced expiratory volume during the first second of FVC (FEV_1) is the volume of air exhaled during the first second of the performance of FVC. The peak expiratory flow (PEF) is the largest expiratory flow achieved with a maximally forced effort from a position of maximal inspiration, and it is expressed in litres/second (143). $FEF_{25\%}$ is the forced expiratory flow after the first 25% of the FVC has been expired, and it is expressed in litres/second. $FEF_{50\%}$ and $FEF_{75\%}$ are the FEFs after 50%, and 75% of the FVC, respectively, has been expired. $FEF_{25\text{-}75\%}$ is the average of the flow when 25% to 75% of the VC has been expired, and it represents the flow in the mid-portion of the VC (144). The curve below the x-axis of the flow-volume curve represents the inspiratory curve, where the forced inspiratory flow (FIF) measurements correspond to the FEF measurements above the x-axis.

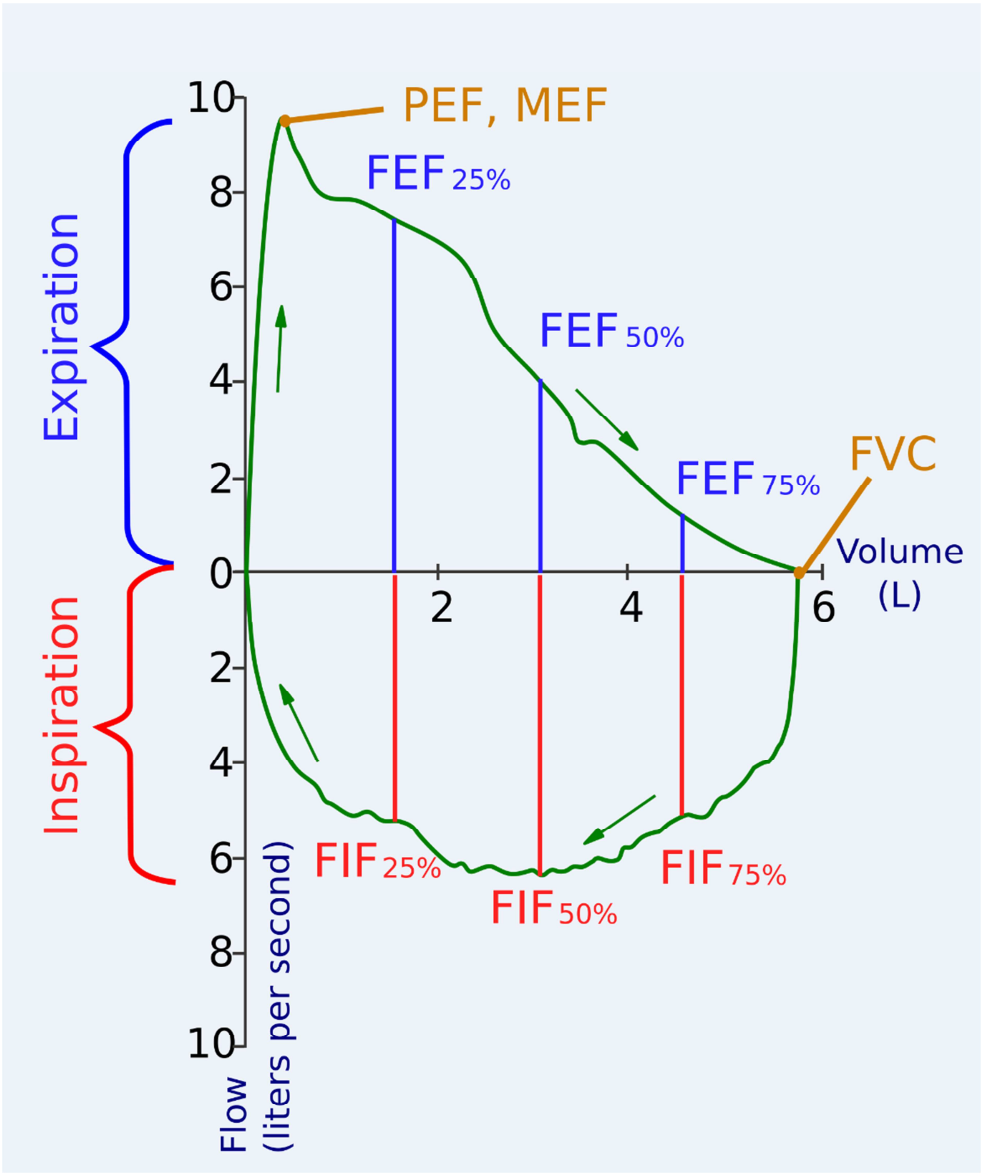


Figure 15. Flow-volume loop as measured by spirometry, reprinted from Wikimedia Commons.

The use of predicted values for lung function measurements yields standardized values relative to gender, age, height and ethnicity. Several types of reference equations have been published, with the most recent one being the Global Lung Function Initiative (GLI) references (145).

Obstructive lung function can be assessed using spirometry, and it may be graded according to severity as described by Paton (144): Mild: FEV_1 in percent of predicted (%) =70–100; Moderate: FEV_1 % = 50–70; Severe: FEV_1 % = 34–50; Very severe: FEV_1 % < 34. The maximal expiratory airflow rates reduce in the presence of an obstruction, and there is a reduction of the maximal airflow from the lung compared to the FVC, which is usually expressed as a reduction in the FEV_1/FVC ratio.

The earliest change with flow limitation in small airways is shown as a slowing in the terminal portion of the flow volume curve, and it gives an increasingly convex curve (convex to the x-axis) in late expiration.

Flow measurements in small airways ($FEF_{25\%}$, $FEF_{50\%}$ and $FEF_{75\%}$) are sensitive to inadequate patient effort, as they measure the flow at specific moments. However, $FEF_{25-75\%}$, as the mean between the two, is more robust, and therefore, it is used more often to describe small airway obstruction; it may be more sensitive in children than FEV_1/FVC (144).

1.6.1 Associations between growth and lung function

Lung function is dependent on normal development from foetal life and onwards. Sonnenschein-van der Voort et al. recently found that foetal length, infant weight development and lower infant length growth were positively associated with airway resistance (146). These authors also reported a positive association between faster weight gain across childhood and FVC and FEV_1 values (139).

In a recent metaanalysis, Den Dekker et al. reported that children with younger gestational age at birth had lower FEV_1, FEV_1/FVC ratio and $FEF_{75\%}$; whereas those who were born SGA had lower FEV_1 but higher FEV_1/FVC ratio. Greater infant weight gain was associated with higher FEV_1 but with lower FEV_1/FVC ratio and lower $FEF_{75\%}$ in childhood (147).

Several studies have reported that birth weight is positively associated with lung function (148-150). Barker suggested that an adverse environment and poor growth *in utero* may lead to impaired growth of the airways and subsequently reduced airway calibre (151). Cross-sectional studies in children and adolescents have shown that

weight-related anthropometrics are positively associated with FEV_1 and FVC but negatively associated with FEV_1/FVC ratio (152-155). Studies on the association between change in weight over time and lung function have reported different results at different ages (139, 156, 157).

Some studies have shown that reduced lung volume is related to the degree of obesity (158). Others have noted negative associations between weight-related anthropometrics and lung function (154). However, a review has noted discrepancies among studies (159).

In prematurely born children, increased soluble antiangiogenic factor might influence future lung function (160). Furthermore, infants with intrauterine growth restriction may have a congenital reduction in airway calibre and compliance, leading to poor lung function (150).

Preeclampsia is the most frequent medical indication for delivering a baby prematurely. Although preeclampsia has been shown to be positively associated with respiratory distress syndrome and bronchopulmonary disease in preterm infants and with recurrent wheezing in preschool children (132), no studies exist on a possible long-term association between preeclampsia exposure and lung function.

1.7 Summary

The prevalence of atopy has increased substantially worldwide during recent decades (98), and early-life environmental factors and lifestyle may be important risk factors for this increase (122). Preeclampsia is, like atopy, a condition characterized by inflammation (29, 113). The incidence of preeclampsia is also increasing (27). Previous studies on the association between preeclampsia exposure and atopy and lung function in early childhood have been assessed in a few studies, (15-17, 132). However, the role of preeclampsia exposure in atopy and lung function development until late childhood is not known.

There is an increased focus of the impact of early childhood lifestyle on atopy (122). The incidence of obesity is also increasing (57), and prospective studies have shown

an association with asthma (133). However, studies on the association between obesity and atopy show conflicting results (135-137). Furthermore, cross-sectional studies have focused on the association between obesity and atopy, and existing longitudinal studies are mostly from registers; however, to the best of our knowledge, clinical studies have not been reported.

Obesity is possibly associated with asthma, and it may also be associated with altered lung function. Studies in adults suggest such an association (161), whereas those in children and adolescents show conflicting results (159). Studies indicate that at an early age, increasing BMI is associated with larger lung volumes and better lung function (139, 157). In comparison, at a later age in childhood, BMI is associated with a more obstructive lung function pattern; however, the age at which this transition occurs is not known (157).

The participants included in the thesis are from a nested case control study, called the Stavanger Study, of 614 children, of whom one-third were exposed to preeclampsia and two-thirds were unexposed (24). This thesis includes studies on the early-life risk factors; preeclampsia, growth and physical activity and the outcomes of allergy, allergic diseases and lung function in later childhood. The studies in this thesis are part to the lung-atopy branch of 'the Stavanger Study'.

As the cohort consisted of children exposed to preeclampsia and controls, any potential effect of preeclampsia exposure status on the outcomes of atopy and lung function via a possible effect on childhood growth might be of importance. However, during our work, we discovered that little is known about preeclampsia exposure and subsequent growth across childhood. Previous publications from the Stavanger Study showed that preeclampsia exposure was negatively associated with birthweight (25) and positively associated with BMI and waist circumference at puberty onset in girls (24). Seven other published studies on preeclampsia exposure and growth showed conflicting results (32, 75-80); however, no studies examined growth trajectories across childhood. To further explore this issue, the thesis also includes a study on the association between preeclampsia exposure and subsequent growth during childhood. This does not directly address the association between early life risk factors and

allergic disease, but may illuminate the associations between childhood growth and outcomes in our cohort.

2. Aims of the thesis

The overall aim of this thesis was to study early-life risk factors for atopy and lung function in a historical cohort. Specifically, the main early-life factors investigated were preeclampsia, weight-related anthropometrics and physical activity. We also aimed to study whether preeclampsia could have any effect on childhood growth from a longitudinal perspective.

The objectives of this study were as follows.

Preeclampsia as a risk factor for atopy and changed lung function by late childhood:

To study the associations between preeclampsia exposure according to severity and various outcomes including atopic sensitization, allergic rhinoconjunctivitis, atopic dermatitis asthma and lung function in late childhood.

Preeclampsia and childhood growth:

To study the associations of preeclampsia exposure according to severity with length/height, weight and BMI at several time-points from birth to late childhood and waist circumference and skinfolds in late childhood, and to analyse whether these associations are gender-dependent.

Weight-related anthropometrics and activity level as risk factors for atopy by late childhood:

To study the associations of birth weight, BMI at several time-points in childhood, changes in weight and BMI, late childhood waist circumference and skinfolds and physical activity level with various outcomes including atopic sensitization, allergic rhinoconjunctivitis, atopic dermatitis and asthma by late childhood.

Weight-related anthropometrics as risk factors for changed lung function in late childhood:

To study the associations of birth weight, BMI at several time-points in childhood, changes in weight and BMI, late childhood waist circumference and skinfolds with FVC, FEV_1, FEV_1/FVC ratio and $FEF_{25-75\%}$/FVC ratio in late childhood.

Based on these objectives, we hypothesized the following:

1. Preeclampsia exposure *in utero* is positively associated with atopic sensitization and atopic disease and negatively associated with lung function in late childhood
2. Preeclampsia exposure *in utero* affects linear growth. Preeclampsia exposure is positively associated with accelerated weight gain during childhood, especially in girls.
3. Childhood BMI and weight-related anthropometrics, accelerated weight gain and sedentary lifestyle are positively associated with atopic sensitization and atopic disease.
4. Childhood BMI and weight-related anthropometrics are negatively associated with lung function in late childhood.

3. Subjects and methods

3.1 Participants and study design

A population-based cohort including 12 804 deliveries during 1993-1995 at Stavanger University Hospital served as the basis of this study. The Medical Birth Registry of Norway was used to identify mothers from this cohort with preeclampsia (n = 366) and controls (n = 659) to conduct a nested case control study finished in 2002. The study design was as follows. For each case, two matched controls were selected: one was the next delivery in the hospital (i.e., a birth date match) and one was the next born matched on maternal age (i.e., a risk factor for preeclampsia) (25). This nested case control study was conducted to study maternal risk factors for preeclampsia and foetal growth in relation to preeclampsia. The Stavanger Study (24) was a follow-up of the nested case control study conducted to study anthropometry, blood pressure and reproductive development in children after preeclampsia exposure *in utero*. The 1025 children (366 cases and 659 controls) were invited to participate in late childhood in a first follow-up study at 10.8 years (girls) and 11.8 years (boys), and a second follow-up at 12.8 years (both genders) (24) (Paper I, Figure 1). The ages at follow-up were selected to coincide with the age of pubertal onset (first follow-up) and menarche (second follow-up) of the children (24, 32).

Invitations for follow-ups were sent to the mothers at addresses identified through public registries. Exposed non-responders received a written reminder, and if necessary, a telephone message or phone call. Unexposed non-responders did not receive a reminder.

The study was a part of the Stavanger Study, of which Papers I, III and IV are called the 'Lung-atopy arm of the Stavanger Study'. This study was conducted according to the original study design as a follow-up of the nested case control study described in Papers I and II. The study was conducted as a historical cohort in Papers III and IV and adjusted for preeclampsia as a potential confounder. The original matching of maternal age and birth date were ignored in the analyses owing to more missing participants in the unexposed group than in the exposed one, thus the analyses were

adjusted for maternal age. The analytic samples included all the children who participated in both follow-ups.

3.2 Questionnaires

Questionnaires were distributed to consenting parents and children at the first and second follow-ups of the Stavanger Study (Appendix to this thesis). The questionnaires included questions about diet, work, leisure time activities and health. The lung-atopy arm of the Stavanger Study included validated questions related to lung function and asthma (an ISAAC questionnaire) (101) at the second follow-up, and they were completed by the children. Questions and responses relevant for the studies of this thesis were extracted; these are explained further in Chapters 3.4.1 and 3.5.3. At the first follow-up, the mothers also answered questions about the health of their child, and at the second follow-up, the children answered questions about their own health. If the questionnaires were answered but specific yes/no questions had missing responses, the response was interpreted as 'no'.

3.3 Clinical examinations

Clinical examinations of participants were performed at birth and at the first and second follow-ups. The examinations relevant to the studies of this thesis are described below. Anthropometric measurements from well-baby visits during infancy and pre-school age were collected when the children attended the first follow-up. A second collection was performed for missing anthropometric data in 2014 after newly obtaining written consent from the participants.

3.4 Outcomes

Only the outcomes of the studies are described in this section. Anthropometric measurements were outcomes in Paper II, and predictors in Papers III and IV and are described in Chapter 3.5.2.

3.4.1 Atopy

Allergic rhinoconjunctivitis, atopic dermatitis and asthma ever were assessed at the first follow-up. Atopic sensitization and current asthma were assessed at the second follow-up.

Atopic sensitization

Definition: Blood specific IgE ≥ 0.35 *kU*/l for at least one common allergen. At the second follow-up, blood was drawn from the children, centrifuged and aliquoted, and the serum was stored at -80°C. Specific IgE antibodies were measured using Phadiatop® and fx5E® (ImmunoCAP® 250, Phadia AB, Uppsala, Sweden). If Phadiatop® was positive, the serum was further analysed for specific IgE against *Dermatophagoides pteronyssinus,* cat, horse, dog, timothy, common silver birch, mugwort and *Cladosporidum herbarum*. If fx5E® was positive, the serum was further analysed for specific IgE against egg white, milk, fish (cod), wheat, peanut and soya bean. The included allergens are shown in Paper III, Figure 1. The levels of specific IgE ≥ 0.35 *kU*/l were added, and high grade sensitization was defined as a sum > 3.9 *kU*/l: above the lower quartile of all children being sensitized. The ordinal outcome variable atopic sensitization was categorized as no, low-grade and high-grade sensitization.

Atopic disease: Asthma ever, allergic rhinoconjunctivitis or atopic dermatitis

At the first follow-up, questions about atopic diseases of the child were asked to the mothers: 'Has your child ever had doctor-diagnosed asthma or ever been diagnosed with allergy in nose/eyes (hay fever) or atopic dermatitis (childhood eczema)?' A 'yes' response was classified as having the respective diagnosis at any age up to and including 10.8/11.8 years (girls/boys).

Current asthma

At the second follow-up, the children answered a questionnaire on reported asthma symptoms and medication during the last year according to ISAAC (101) and asthma ever was recorded. Current asthma at 12.8 years of age was defined as a positive

answer to the question of doctor-diagnosed 'asthma ever', in addition to a positive answer to at least one of the two questions about asthma symptoms (wheezing/whistling/chest tightness) or the use of asthma medication during the last 12 months.

3.4.2 Lung function tests

At the second follow-up, lung function was measured by spirometry according to established guidelines (143) by using a Vmax Encore Spirometer (Sensor Medics Inc., Anaheim, USA), and FVC, FEV_1 and $FEF_{25-75\%}$ were recorded. In Paper I, reference values from 1995 were used (162). In Paper IV, measurements were compared to the values predicted by the more recent 2012 European Respiratory Society (ERS) Task Force standard reference equations from GLI relative to age, gender, height and ethnicity (145). The values for FVC, FEV_1 and FEV_1/FVC ratio were reported as percentages of predicted (%). The $FEF_{25-75\%}$/FVC ratio was given as a percentage as no predicted values were available.

3.5 Exposures and predictors

3.5.1 Preeclampsia

Preeclampsia was diagnosed according to the CLASP criteria (26), which define preeclampsia as a condition occurring after 20 weeks of gestation as a diastolic blood pressure increase of ≥25 mmHg to a persistent pressure of ≥90 mmHg and proteinuria with dipstick ≥+1 present in ≥1 urine sample. In the Stavanger Study, preeclampsia was further defined according to severity, and severe preeclampsia was defined as proteinuria with dipstick ≥+3 and diastolic blood pressure ≥110 mmHg; moderate preeclampsia, as proteinuria with dipstick ≥+2 and mild preeclampsia, as any other condition of preeclampsia.

3.5.2 Anthropometry

Anthropometry means the scientific study of the measurements and proportions of the human body (163).

These measurements are used as either predictors or outcomes in the papers depending on the research question. In Paper I, selected anthropometric measurements were used in descriptive analyses of the participants and as potential confounders in regression analyses. Anthropometric measurements were outcomes in Paper II and predictors in Papers III and IV.

Birth length and weight were abstracted from hospital records for consenting participants. In Norway, all children receive healthcare at well-child clinics with routine measurements of recumbent length before 2 years of age, standing height from 2 years of age, and weight from infancy to school age. At the first follow-up, length/height and weight measurements from the routine well-child visits at the target ages of 3, 6 and 12 months and 4 years were abstracted from clinical records. If a measurement was missing, the value from the closest visit in time was used, and the exact age was recorded for all visits. Three experienced and trained paediatric nurse researchers measured height, weight, triceps skinfold and waist circumference in the offspring two times at each follow-up and subscapular skinfold two times at the second follow-up, with the average used in the analyses. Skinfolds were measured using a Harpenden Skinfold Calliper ®. The consistency of the measurements was ensured by regular audits by a paediatrician (24). Body weight was measured using a Seca 770 electronic scale (Seca, Hamburg, Germany), and height was measured using a Holtain stadiometer (Holtain, Crosswell, Crymych, Wales, UK).

The waist-to-height ratio was calculated as the ratio of waist circumference (cm) to body height (cm).

In premature children, growth was corrected for prematurity in the first two years of life by evaluating the child as if it was born at the due date and not by chronological age.

3.5.3 Physical activity

The questionnaire distributed to mothers at the first follow-up included questions extracted from the 'Stanford Brief Activity Survey' (164), a questionnaire that has been validated for adults, and it requested responses about the child's physical

activity levels. Specifically, the answers to the following questions were extracted: 'How active was your child at 3–6 years?' and 'How active was your child at 6–10 years?' The response categories were passive, not so active, active and very active. The categories 'passive' and 'not so active' were combined and recoded as 'low activity', 'active' as 'normal' and 'very active' as 'high activity'.

3.6 Statistics

Due to the inclusion of children who were either exposed or unexposed to preeclampsia, there was a wide range of gestational ages at birth and a wide age range at later well-child visits. The actual anthropometric values would therefore not be appropriate for most analyses. For birth weight in Paper I, z-scores calculated from Scandinavian references were used when adjusting for birth weight (165). In the last three papers, SDS based on anthropometric values and actual ages and gender were computed from validated references (166-169). Conversions to SDS were performed using R version 2.6.2 (R Development Core Team, Vienna, Austria).

The results and demographic data were presented as numbers and percentages, means with standard deviations (SD) or 95% confidence intervals (CI) and medians with lower and upper quartiles (Q_1, Q_3). Categorical variables were compared using Pearson's chi-square exact test with Bonferroni-correction of P-values for multiple testing. Group comparisons for normally distributed continuous variables were performed using independent t-tests (Gosset's t-test, Student 1908) and one-way analysis of variance. The Kruskal-Wallis one way analysis of variance and Mann-Whitney U-test were used for continuous variables that were not normally distributed.

Multiple logistic and linear regression was used to analyse the associations between predictors and outcomes.

Generalized Estimating Equations (GEE) were used for multiple linear regression analyses of growth over time according to the severity of preeclampsia. Multiple Fractional Polynomial Regression (MFPR) was used to study possible non-straight-line associations between anthropometric measurements and outcomes of atopy and lung function, and MFPR in combination with GEE was used to identify possible

non-straight-line effects of preeclampsia on growth. The identified fractional polynomials in Paper II were plotted using R version 3.2.1 (R Development Core Team, Vienna, Austria).

Causal diagrams called directed acyclic graphs (DAGs) were used to select adjustment set variables for the regression analyses in Papers II, III and IV using the DAGitty program (170).

In the analyses in Papers I, II and III, a backward stepwise selection of confounders at $P < 0.05$ was performed: First, each variable was entered into simple regression models. Next, all potential confounders were included in fully adjusted models. Backward stepwise selections were performed to remove non-significant confounders. Ultimately, the final models included all remaining confounders and different variables forced into the final model.

Owing to missing values, the number of participants varied between the different analyses.

For each predictor, estimated coefficients (b) (linear regressions), odds ratios (OR) (logistic regressions) and 95% CIs were reported. For linear regression, P-values from the F-test (for variables of all types) or Wald's chi-square-test (for each b in the model and for GEE) were reported. For logistic regression, likelihood ratio (LR) test P-values were reported. Interactions between predictors and potential confounders were tested for all regression analyses for all Papers, and they were presented if significant.

All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant. The latest version of SPSS statistical package and STATA SE14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP) were used for the analyses.

3.7 Ethics

The study was approved by the Norwegian Data Inspectorate, the Regional Committee for Ethics in Medical Research Western Norway (Reference Numbers:

First: 078-03, Second: 2010/1375) and the Institutional Review Boards of the National Cancer Institute (Reference Number: LAB09-0139) and University of Texas at Austin, United States (Reference Number: 2013-04-0036). At follow-up, participating mothers and children signed an informed consent/assent form. When new research questions including outcomes of atopy and lung function were planned, The Regional Committee for Ethics in Medical Research Western Norway was applied to for approval, and it gave the second reference number.

3.8 Funding

The Stavanger Study was funded by an internal grant from the National Cancer Institute, National Institute of Health (RO3 grant number: 1R03CA137754), and it is a part of the MD Anderson Global Programme. The lung-atopy arm of the Stavanger Study was further funded by a PhD grant from the Western Norway Regional Health Authority for the first author (grant number: 911835).

The funders played no role in the study design, data collection and analysis, decision to publish or preparation of the papers.

4. Results

4.1 Participation

This chapter provides a complete overview of participation in the present studies in more detail than in each of the papers.

A complete flow-chart of participation is shown in Paper I, Figure 1. The number of participants who had information about preeclampsia severity and each outcome are shown in Paper I, Table 2. These were the children who were included in the statistical analyses in Paper I.

Of 1025 invited children, 614 assented to the first follow-up and 468 to the second follow-up.

An overview of information about preeclampsia severity for each follow-up is shown in Table 3. Only children with information about preeclampsia severity were included in the analyses in Papers I-IV, 603 children at the first follow-up and 459 children at the second follow-up.

Table 3. Participation in the two follow-ups according to preeclampsia severity

	Numbers of children				
			Preeclampsia severity		
	Total	Missing	No	Mild/moderate	Severe
First follow-up	614	11	385	164	54
Second follow-up	468	9	286	127	46

In Paper II, children with information about anthropometry and preeclampsia severity were included in the analyses, as shown in Table 4. In Paper II, GEE analyses were used. Therefore, the analytic sample included all children participating at each visit age, and it was not limited to the number of children at the follow-ups.

Table 4. Participation according to type of anthropometric measurement, and number of visiting children with information about preeclampsia severity in Paper II.

	Visit age (n)						
Variable	Birth	3 months	6 months	1 year	4 years	10.8/11.8 years[a)]	12.8 years
Length/height SDS	937	542	557	558	478	600	443
Weight SDS	942	553	558	559	477	595	443
BMI SDS		541	557	558	477	595	443
WC SDS						593	443
WHtR SDS						593	443
TSF SDS						589	442
SSF SDS							430

Abbreviations: n = number of participants; BMI = body mass index; WC = waist circumference; SDS= standard deviation score; WHtR = waist-to-height ratio; TSF = triceps skinfold; SSF = subscapular skinfold.
a) 10.8 years in girls, 11.8 years in boys

Paper III, Table 1 shows the number of participants available for the analysis for each predictor and outcome, irrespective of preeclampsia status information. The analytic sample in Paper III consisted of the children for whom we had information about preeclampsia severity. The number of children with information about anthropometry and physical activity, and the different outcomes in Paper III are shown in Table 5. The table includes only children with information about preeclampsia severity, because preeclampsia severity was included in the adjustment set of the regression analyses.

Table 5. Number of children with information about anthropometric measurements, physical activity and outcomes of atopy in Paper III, among those with information about preeclampsia severity in Paper III.

	Outcome (n)				
Predictor	Allergic rhino-conjunctivitis	Atopic dermatitis	Asthma ever	Current asthma	Atopic sensitization
Birthweight SDS	580	581	575	448	380
BMI SDS					
3 months	521	522	517	415	353
6 months	537	538	533	429	363
1 year	537	538	533	428	363
4 years	460	462	457	385	329
10.8/11.8 years[a)]	573	574	568	436	367
12.8 years				436	368
Physical activity					
3–6 years	575	576	570	434	367
6–10 years	569	570	564	431	363

Abbreviations: n = number of participants; SDS = standard deviation score.
a) 10.8 years in girls, 11.8 years in boys

The percentage of children sensitized to airborne allergens varied between 2% and 21%, and that to food allergens varied between 1% and 6%. Of these, 21% were

sensitized to timothy; 20% to house dust mite; and 14% to birch pollen (Paper III, Figure 1).

In total, 463 children performed lung function tests, and 456 also responded to the ISAAC questionnaire (Paper IV).

In all regression analyses, the response rate for each potential confounder varies owing to missing data from the questionnaires and antenatal visits.

In Paper IV, the clinical characteristics (anthropometry) are shown only for children who performed lung function tests, and thus, n is lower than that in Paper III, where clinical characteristics for all assenting children are shown.

In total, 468 children consented to participate at the second follow-up, but information about preeclampsia severity was available for only 459. The outcomes of lung function were measured at the second follow-up. Of the 459 children with information about preeclampsia severity, 453 performed lung function tests, and they constituted the analytic sample in Paper IV. Of these 453 children, 446 completed the ISAAC questionnaire.

In Paper IV, the extended International Obesity Task Force (IOTF) BMI classes of the participating children are shown, and the BMI of the participants was within the normal range when compared to other studies of Norwegian children (60).

The actual age of the participants at both follow-ups was the intended target age. At the first follow-up, the age of the girls was 10.8 (±0.22) years (mean, SD) and that for boys was 11.8 (±0.18) years. At the second follow-up, the age of the children was 12.8 (±0.19) years.

The average BMI for the girls who participated in the first follow-up but not the second follow-up was higher than that for the girls who participated in both follow-ups. There were more children with atopic dermatitis among those who assented only to the first follow-up than for those who assented to both follow-ups (Paper I).

Maternal age at delivery was higher in children who did than did not assent to the second follow-up (Paper II).

Otherwise, the baseline characteristics were similar between those who assented to the first follow-up only and those who assented to both follow-ups (Paper I). Furthermore, there were no significant differences in perinatal characteristics between children who did and did not assent to the first and the second follow-ups (Paper II).

4.2 Results from the four papers

The answers to the objectives are presented in this section. The relation between the four studies is illustrated in figure 16.

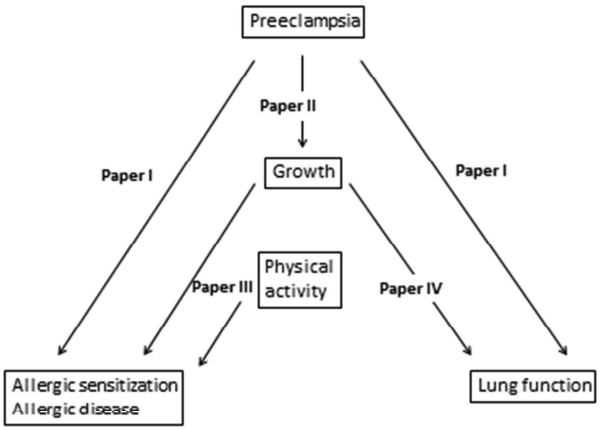


Figure 16: overview of studies

4.2.1 Preeclampsia and associations with atopy and lung function (Paper I)

Among children with any atopic sensitization, 50% had symptoms of allergic rhinoconjunctivitis. Atopic sensitization was found in 94.4% of children diagnosed with allergic rhinoconjunctivitis. Furthermore, 5.6% of children reported allergic rhinoconjunctivitis without being sensitized.

In adjusted regression analyses, severe preeclampsia was positively associated with high-level atopic sensitization (OR: 4.05; 95% CI: 1.62, 10.1) and allergic rhinoconjunctivitis (OR: 2.23; 95% CI: 1.20, 4.17).

We found that increasing severity of preeclampsia was associated with high-level atopic sensitization (OR. 1.88; 95 % CI: 1.23, 2.86; likelihood ratio (LR)-p = 0.003) and allergic rhinoconjunctivitis (OR: 1.42; 95 % CI: 1.07, 1.89; LR-p = 0.018).

We did not find any associations of preeclampsia with atopic dermatitis, asthma or changes in lung function.

4.2.2 Preeclampsia and childhood growth (Paper II)

Paper II shows the median gestational age in weeks (Q_1, Q_3) of children exposed to severe, mild/moderate and no preeclampsia: 36.1 (32.0, 38.6); 39.1 (37.6, 40.1); and 40.1 (39.3, 41.0), respectively.

The associations between preeclampsia and childhood growth yielded the predictive model shown in Paper II, Figures 1–2, and the equations for the predictive curves are shown in Paper II, Table 1.

In boys and girls, preeclampsia exposure was negatively associated with length/height SDS (linear growth). However, in boys, exposure to mild/moderate preeclampsia was positively associated with linear growth after 0.5 years of age.

In boys, exposure to severe preeclampsia was negatively associated with weight SDS and BMI SDS throughout childhood. Otherwise, preeclampsia exposure (for both genders and severity categories) was negatively associated with weight and BMI during infancy, but positively associated with weight and BMI thereafter.

Exposure to severe preeclampsia was positively associated with waist-to-height ratio SDS in late childhood in both genders. At the first follow-up: b = 0.47, 95% CI (0.15, 0.79). At second follow-up: b = 0.44, 95% CI (0.12, 0.75). Preeclampsia exposure was not associated with waist circumference or skinfolds (supplementary to Paper II).

4.2.3 Weight-related anthropometrics and activity level as risk factors for atopy by late childhood (Paper III)

BMI SDS at 1 year of age was positively associated with atopic sensitization at 12.8 years of age (OR: 1.22, 95 % CI: 1.00, 1.49).

Changes in BMI SDS at 1–4 years of age and BMI SDS at 4 years of age were positively associated with ever being diagnosed with atopic dermatitis by the time of the first follow-up (OR: 1.46, 95% CI: 1.11, 1.92 and OR: 1.32, 95% CI: 1.06, 1.65, respectively).

Low level of physical activity at 3–6 years of age was positively associated with atopic sensitization at 12.8 years of age (OR: 2.36, 95% CI 1.15, 4.81).

High level of physical activity at 6–10 years of age was positively associated with ever being diagnosed with atopic dermatitis by the time of the first follow-up (OR: 1.94, 95% CI: 1.16, 3.24).

Low levels of physical activity at both 3–6 and 6–10 years of age were positively associated with ever having doctor-diagnosed asthma by the first follow-up (OR: 3.61, 95% CI: 1.56, 8.36 and OR: 2.52, 95% CI: 1.24, 5.12, respectively).

We did not find associations of birthweight/BMI SDS and changes in weight or BMI SDS with allergic rhinoconjunctivitis (Paper III, Tables 2 and 3) or asthma (Paper III, Table 4 and Supplementary to Paper III). We did not find associations of waist circumference, waist-to-height ratio or skinfolds with atopic sensitization, allergic rhinoconjunctivitis, atopic dermatitis or asthma in late childhood (Supplementary to Paper III).

We did not find any non-straight-line associations between weight-related anthropometric measurements and atopy.

4.2.4 Weight-related anthropometrics as risk factors for changed lung function in late childhood (Paper IV)

Children with current asthma in late childhood had similar FVC % and FEV_1 % but lower $FEF_{25-75\%}$/FVC and a tendency for lower FEV_1/FVC %, than children without asthma.

Birthweight and BMI at different ages throughout childhood were positively associated with FVC % and FEV_1 % in late childhood. BMI, waist circumference, waist-to-height ratio and skinfolds at 12.8 years of age and the change in BMI from early to late childhood were positively associated with FVC % and FEV_1 % and negatively associated with FEV_1/FVC and $FEF_{25-75\%}$/FVC. Interaction analyses showed that positive associations between anthropometrics other than BMI and lung function were mostly present in girls (Paper IV, Tables 4 and 5). We found inverse U-shaped associations between BMI at the ages of 10.8/11.8 (girls/boys) and 12.8 years (both genders) and FVC % and FEV_1 % at 12.8 years of age (Paper IV, Figure 1). After gender stratification, these associations were not significant, except for girls at 10.8 years.

5. Discussion

5.1 Methodological considerations

5.1.1 Study design

As described in Chapter 3.1, the Stavanger Study was a follow-up of a nested case control study on preeclampsia. The design of the original study was also used in my first two studies (Paper I and II) to answer the research questions with preeclampsia as a predictor, and it showed associations with atopy, lung function and childhood growth. In Papers III and IV, childhood growth and physical activity were the predictors and atopy and lung function were the outcomes. Thus, Papers III and IV were not designed according to the original study but as a historical/retrospective cohort, and consequently, bias by preeclampsia might be an issue in these papers. However, preeclampsia was considered a confounder and adjusted for in the analyses in the last two studies. No confounding by preeclampsia was found. Therefore, bias by preeclampsia in Papers III and IV may not be very likely. This matter is discussed further in Chapter 5.1.4.

The sample population in Papers III and IV is biased because it consists of several children exposed to preeclampsia, and therefore, it consists of several prematurely born children. As Papers III and IV aim to show the associations between childhood growth/physical activity and atopy and lung function, a general population cohort would be better suited to answer the research questions.

The study population was homogeneous in terms of socio-economic status and ethnicity, which is an advantage of our study design, and these factors reduce the risk of bias.

The average BMI of the girls who assented to the first but not the second follow-up was higher than that of the girls who assented to both follow-ups; this might have caused a bias in the analyses in all the studies. We do not know why more girls with a higher BMI did not assent to the second follow-up; girls with the highest BMI might have disliked being weighed in the first follow-up and in anticipation of being

weighed, they did not assent to the second follow-up. Preeclampsia was, in general, positively associated with weight and BMI in girls. However, there is no reason to think that the girls with the higher BMI who were lost to the second follow-up were overrepresented in any particular exposure group. Therefore, the association between preeclampsia and growth would not be expected to be biased by the change in the BMI of the girls from the first to the second follow-up.

Other weight-related anthropometric measurements than BMI at both follow-ups were not related to atopy (Paper III) but they were associated with lung function (Paper IV). These two associations were similar in both follow-ups, although there was a difference in average BMI in the girls participating in the two follow-ups. Therefore, the bias may have only negligible consequences for the results.

Owing to the study design, atopic sensitization and atopic disease were assessed at two different follow-ups; however, this should not bias the independent associations found for the various outcomes of atopy.

There were fewer children ever diagnosed with atopic dermatitis in the second than in the first follow-up. The reason for this discrepancy is unknown, and it might bias the results in Papers I and III, in which atopy was an outcome. As atopic dermatitis was an outcome only at the first follow-up, the associations between the predictors of Papers I and III and atopic dermatitis may not be affected. However, atopic dermatitis is correlated with atopic sensitization. Thus, the number of sensitized children in the second follow-up that were ready for analyses of atopic sensitization may be lower than the number of sensitized children in the first follow-up. The results may therefore underestimate the associations of preeclampsia, anthropometry and physical activity with atopic sensitization.

The participation rate at the second follow-up was lower than at the first follow-up. Furthermore, there was a low response rate for the outcomes of asthma in the second follow-up. Together, these two issues decrease the power of the studies and increase the risk of false negative results.

The study was longitudinal with a long follow-up time, which is an advantage over cross-sectional studies. However, the outcomes (diagnoses of atopy and measures of

lung function) in Papers I, III and IV were assessed only at follow-ups; therefore, the age of onset is unknown. In Paper I, preeclampsia occurs before any of the outcomes of atopy and lung function. In Paper II, preeclampsia precedes childhood growth, and therefore, the models in these two studies are predictive, and the direction of the associations must be from preeclampsia to the outcomes.

Only the predictors and not the outcomes were assessed longitudinally in Papers III and IV; therefore, the potential causality and its direction must be interpreted with care. Furthermore, Papers III and IV had a retrospective design, which may be inferior to a prospective one.

Some outcomes of atopy and lung function were assessed at the first follow-up and others, at the second follow-up. Ideally, all variables should have been assessed at the second follow-up. The questionnaire completed by the mothers at the first follow-up included questions about all three atopic diseases in the offspring. The questionnaire completed by the children at the second follow-up included questions about asthma (ISAAC). Therefore, the outcome of asthma ever from the second follow-up could have been used in analyses. However, to assess asthma ever at the same time as atopic dermatitis ever and allergic rhinoconjunctivitis ever, we had to use the available information from the first follow-up. An advantage of using the diagnosis of asthma ever from the first and not the second follow-up was that several responses were missing from the second follow-up, and we had to use interpreted values which were possibly not as reliable as the maternal responses from the first follow-up. To assess current asthma in late childhood, however, the only available information was from the ISAAC questionnaire completed at the second follow-up.

5.1.2 Validity of diagnoses

Atopic sensitization

A specific IgE toward a particular allergen with a cut-off at 0.35 *kU*/l (also used in our studies) is normally used for the diagnosis of atopic sensitization, and it provided a good measure of atopic sensitization (171). However, low-grade sensitization just above the cut-off is less likely to be clinically relevant. Some authors define atopic

sensitization conservatively as a radio-allergo-sorbent test (RAST) class 2 or a specific IgE >0.7 *kU*/l (172, 173). The cut-off at 3.9 *kU*/l corresponds to the lower quartile of the sensitized children in our study. The cut-off was used in the present studies to include more clinically relevant atopic sensitizations, and it is supported by a previous study suggesting a positive predictive value of allergy to be 97% if specific IgE levels are ≥3.5 *kU*/l (171).

Allergic rhinoconjunctivitis, atopic dermatitis and asthma ever

These diagnoses were determined at the first follow-up and were based on maternal questionnaires. The conditions assessed by questionnaires could over- or underestimate the diagnoses owing to recall bias. The reported diagnoses may not be as accurate as those examined at follow-ups. Furthermore, two unknown issues regarding these diagnoses are the age of onset and continued symptoms at the first follow-up. However, the high proportion of allergic sensitization (94.4%) in children with rhinoconjunctivitis suggests a high degree of diagnostic accuracy. Although some children reported allergic rhinoconjunctivitis without having sensitization (5%), other studies have reported that allergic rhinoconjunctivitis could be due to local and not systemic sensitization (174), which supports our findings.

Atopic dermatitis was diagnosed at several primary care clinics without following any predefined criteria, so the diagnosis must be interpreted with care. Atopic dermatitis comprises both cases with IgE-associated mechanisms and around 20% of cases without (96, 175), and therefore, it may not always contribute to the 'atopic march'.

The diagnosis of asthma is not always based on objective measures. In particular, in children <5 years of age, the diagnosis is based on the evaluation of symptoms and associated factors such as atopy. During these years wheezing episodes may represent asthma or transient conditions, and the diagnosis of asthma may be used variously between physicians. 'Doctor-diagnosed asthma ever' may therefore be both over- and underdiagnosed (97).

Current asthma

This was assessed from an ISAAC form included in questionnaires completed by the children themselves at the second follow-up. Several children who answered the other questions in the questionnaire did not answer the ISAAC form. A missing response in the ISAAC form was therefore interpreted as a negative response. To what degree a positive answer in the ISAAC questionnaire was reliable is unknown, but the responses from the children may be less reliable than those of the mothers in the first follow-up.

Spirometry

Spirometry was performed under the guidance of experienced and trained paediatric nurses in the outpatient department of Stavanger University Hospital under the surveillance of a consultant paediatrician.

Seven of the 470 children who assented to the second follow-up were not able to perform a satisfactory spirometry, and they were excluded from the analyses in Paper IV. Owing to the personnel's expertise and the exclusion of unsatisfactory spirometries, the lung function testing in our study may be considered to have high quality and reliability. A recent study showed that the GLI-2012 reference values for lung function tests (which we used for the analyses in Paper IV) fit the Norwegian data, and therefore, they are recommended for use in Norway (176).

Preeclampsia

The diagnosis of preeclampsia was divided into none, mild, moderate and severe. Owing to pathophysiological similarities, the mild and moderate categories were combined (30). This classification affords the advantage of distinguishing the effects of preeclampsia from prematurity on offspring outcomes later in life.

Preeclampsia may also be classified as early or late onset, where early onset begins at <34–35 weeks of gestation (depending on country) and is often of the more severe type (29).

Because most cases of severe preeclampsia occur early (as also reported in Paper II) whereas mild/moderate preeclampsia occurs later during pregnancy and close to term,

the two types of classification do not differ substantially. One advantage of classifying preeclampsia according to severity might be that pathophysiological differences due to severity more likely affect the health of the offspring, whereas the classification based on gestational age may affect offspring health indirectly owing to gestational age or indirectly due to a correlation with severity.

The CLASP criteria are considered conservative, and the advantage of using such a classification is that all the cases are certain to have preeclampsia, and no cases will be falsely diagnosed with preeclampsia (26).

Anthropometric measurements

The anthropometric measurements used in our study may be considered to have high quality. Routine measurements at the well-child clinics are standardized. Trained paediatric nurses performed the measurements at the first and second follow-ups.

The repeatedly sampled measurements of length/height and weight yielded calculations of a predictive model of growth by preeclampsia exposure status; they may be advantageous in this study. The sampling of the growth variables as predictors enabled the window of time in childhood with the possibility of affecting the development of atopy and lung function to be examined. On the other hand, the measurements were not performed at every age during childhood. In the longitudinal analyses, only length/height, weight and BMI were available, and no other anthropometric measurements were. BMI may have a limited correlation with childhood adiposity (177). As both predictors and outcomes, waist circumference and skinfolds could have added valuable information to our studies, however, they were not measured at the well-child clinics, and therefore, they are impossible to collect retrospectively.

Physical activity

A validated questionnaire for adults was used for the Stavanger Study (164). A validated questionnaire for children would have been more appropriate. To the best of our knowledge, no validated recall questionnaire for physical activity for this age existed at the time the Stavanger Study was conducted. The response to this

questionnaire provided the only available data for physical activity in the age groups 3–6 and 6–10 years. Therefore, the associations between physical activity and atopy must be interpreted with care.

5.1.3 Sample size

The statistical analyses included several covariates, and owing to the complexity, it would have been difficult to estimate sample sizes. Power is the probability of rejecting the null hypothesis in a future study. Once the study has been conducted, this probability is either 1 or 0. Therefore, post hoc power calculations are not recommended (178). Instead, CIs and p-values are meaningful quantifications of uncertainty after the study has been conducted (179).

Because our studies were included in an established follow-up study, no power calculations targeted for our studies were performed to determine the necessary sample size. Instead, we had to interpret our results with care. Owing to the possibly of low power, we have to be aware of the possibility of false negative results. Therefore, the width of the CIs was of importance, especially when interpreting negative results. If the CIs included both no associations and clinically relevant effect measurements, the sample size may have been too small to detect these associations and to confirm that there are no associations between predictors and outcomes.

5.1.4 Statistical considerations

Information may be lost when grouping continuous variables into categorical variables, because similar data appear different if they happen to fall into different categories. Therefore, methods allowing the use of continuous variables are superior to those using categories, and the use of continuous variables should generally be attempted.

Atopic sensitization was analysed as an ordinal variable instead of as a continuous variable. Although specific IgE is a continuous variable, atopic sensitization is generally considered a dichotomous condition with a cut-off at 0.35 *kU*/l. We further introduced the term high-level atopic sensitization to differentiate between those who

merely had sensitization and those who were more likely to have a clinical allergy, thereby providing an ordinal variable for atopic sensitization which, in the context of our studies, was likely to be the most appropriate.

Anthropometric measurements were used as continuous variables and were not categorized. For BMI, there are specific IOTF categories for three underweight categories, and for normal weight, overweight and obesity (66). These could have been used in the analyses; however, IOTF classes are not available before 2 years of age. The age data of our participants consisted of five measurements before and only three after 2 years of age. Therefore, IOTF classes could not have been used in the GEE analyses (including all the ages of the participants from birth onwards). MFPR analyses were used to study non-straight-line associations between predictors and anthropometry or between anthropometry and outcomes. MFPR analyses have the advantage over simpler models of showing linear associations that may take any form or any equation, including U-shaped associations, while keeping continuous variables continuous.

A backward stepwise selection in logistic regression is not always reliable. The model might change simply because the number of variables is reduced, and not because there is confounding. We did check for confounding in backward stepwise selection by keeping the same analytic sample as in fully adjusted analyses; however, we could not rule out residual confounding.

Therefore, after the first paper, we began using DAGs. DAGs are causal diagrams, and by using the DAGitty software, we selected potential confounding variables. Using DAGs helps to avoid using variables that are intermediate on the causal pathway between the predictor and the outcome. Furthermore, using DAGs may help to avoid adjusting for variables that are common effects of both the predictor and the outcome either directly or indirectly (colliders). Adjusting for intermediate variables might falsely reduce the association between the predictor and the outcome (180). Adjusting for colliders might give rise to spurious associations between the predictor and the outcome (181, 182).

Therefore, for some of the models, especially with an adequate n in fully adjusted analyses, we chose not to use backward stepwise selections; instead, we obtained results through fully adjusted analyses containing variables as selected by using DAGitty (170), and we consider this as a strength of our analyses.

The variables gestational age and birthweight are intermediary on the pathway between preeclampsia and outcomes in the present studies. The group of participants exposed to severe preeclampsia showed lower gestational age and birthweight than the group of participants exposed to mild/moderate preeclampsia and the unexposed group. Therefore, gestational age and birthweight may confound the results in Papers I and II, in which preeclampsia was used as the predictor. As described above, in the section about intermediate variables and colliders, these could not be adjusted for. One method to reduce confounding from the variables gestational age and birthweight would be to match the participants on these variables, which was not done in the original study.

Wald-test P-values were used in Paper I. F-test and Wald-test P-values are identical for variables that are not represented by at least two indicator variables in the model. The Wald-test gives the P-values for each b in the model, whereas the F-test gives the P-values for all types of variables. In Papers II and IV F-test P-values were used, showing the overall significance level for ordinal explanatory variables as well. This is a better method, and it could also have been used in Paper I.

5.2 Discussion of results

In the studies, we found that exposure to severe preeclampsia *in utero* was positively associated with subsequent high-level atopic sensitization and allergic rhinoconjunctivitis in late childhood; however, preeclampsia was not associated with atopic dermatitis, asthma or lung function. Exposure to mild/moderate preeclampsia was positively associated with linear growth in boys, and with weight and BMI in both boys and girls. Exposure to preeclampsia was negatively associated with linear growth in girls. Exposure to severe preeclampsia was negatively associated with linear growth, weight and BMI in boys. Severe preeclampsia was positively

associated with waist-to-height ratio in late childhood. Preeclampsia exposure was not associated with waist circumference or skinfolds in late childhood.

BMI and accelerated weight gain in early childhood was positively associated with atopic sensitization and atopic dermatitis in late childhood. Low physical activity during childhood was positively associated with atopic sensitization and ever being diagnosed with asthma in late childhood. High physical activity during childhood was positively associated with atopic dermatitis in late childhood. BMI and physical activity were not associated with allergic rhinoconjunctivitis or current asthma in late childhood. Weight-related anthropometrics during childhood were positively associated with FVC % and FEV_1 % in late childhood; however, BMI, waist circumference and waist-to-height ratio in late childhood were negatively associated with FEV_1/FVC % and $FEF_{25-75\%}$/FVC. BMI in late childhood showed an inverse U-shaped association with FVC % and FEV_1 %.

5.2.1 Preeclampsia, atopy and lung function

A few studies on the associations of preeclampsia with atopy and lung function have been published after Paper I was published. A recent publication from Stokholm et al. (183) included two studies: one study of 411 Danish children born of mothers with asthma, where the children were examined at several occasions until 7 years of age and 5.6% were exposed to preeclampsia; and one registry-based cohort of 1.7 million children of which 3.7% were exposed to preeclampsia. Preeclampsia exposure was associated with atopic sensitization and allergic rhinoconjunctivitis in both cohorts, in accordance with our results. The authors also found positive associations of preeclampsia exposure with asthma treatment and bronchial responsiveness in the cohort of 411 children, which we did not study. Preeclampsia was associated with asthma and eczema in the registry-based cohort with adjusted Incidence Risk Ratio of 1.09 (1.05, 1.12) (183). The discrepancy of the registry-based cohort with our study and the cohort of 411 Danish children may be due to false negative results in smaller studies. In a study of 115 222 children, all of who were diagnosed with asthma, preeclampsia was positively associated with asthma (184). In a recent publication from the Avon Longitudinal Study of Parents and Children including more than 5000

children, hypertension before pregnancy was positively associated with asthma in children at 7 years of age with OR 1.34 (1.00, 1.79) and preeclampsia was negatively associated with FEV_1 at 8 years of age with an adjusted mean difference in SDS of -0.14 (-0.33, 0.06) (185). The difference from our results may arise from a tendency of false negative results in studies with fewer participants. In a recent Norwegian publication of two studies, a registry-based study of 406 907 children showed an association between preeclampsia and asthma at 7 years of age, whereas in a subsample of children participating in the Norwegian Mother and Child Cohort Study (n = 45 028), preeclampsia was not associated with asthma. Adjustments for prematurity yielded significant associations between preeclampsia and asthma, which may, as the authors noted, be due to collider bias. Furthermore, when a sibling comparison was performed, no association remained between preeclampsia and asthma (186).

Most children exposed to severe preeclampsia were born prematurely. Adjustment for prematurity in the statistical analyses was not appropriate because prematurity is an intermediate variable on the causal pathway between preeclampsia and the outcomes of atopy and lung function. A Swedish national cohort study showed a negative association between prematurity and allergic rhinitis, possibly owing to the protective effect of earlier exposure to pathogens (187). In a Norwegian register study of 9349 children with severe asthma and 6930 children with severe atopic dermatitis, preterm birth was positively associated with severe asthma and negatively associated with severe atopic dermatitis (188). As preeclampsia is positively associated with both prematurity and allergic rhinitis, our results may underline the importance of preeclampsia as a possible risk factor for allergic rhinitis independent of the effect of prematurity.

Antibiotics are frequently prescribed to prematurely born infants during the neonatal period; this may cause a delay in intestinal bacterial colonization, and therefore, it may pose a risk of developing allergic disorders (189). As preeclampsia is associated with allergy and prematurity, antibiotic use may contribute to the development of allergy in this group. However, we were not able to adjust our analyses for

intermediate variables on the causal pathway between preeclampsia and allergy, such as antibiotics.

Preeclampsia is a condition involving several pro-inflammatory cytokines in maternal circulation, which may initiate the development of immunological conditions such as atopy in the foetus. The cytokines of maternal circulation are reflected in those of the offspring until the age of 1 year (17, 190-192).

In the registry-based cohort study in the above-mentioned publication from Stokholm et al., the associations between preeclampsia and atopy were especially pronounced with longer duration of preeclampsia, suggesting a mechanism of *in utero* inflammation causing lasting immune dysregulation in the offspring (183). The possible impact on the foetus may be facilitated by foetal immune cell maturation. Immune tolerance is partly mediated by thymus-derived Tregs, and the foetal thymus is smaller in foetuses exposed to preeclampsia (193).

During normal pregnancy, but not in preeclampsia, there are increased levels of Th2 and Tregs, this, in turn, promotes maternal immune responses to avoid the rejection of the foetus (194). The levels of Th2 cells and Tregs are lower in blood from women with preeclampsia (195) and in cord blood in new-borns exposed to preeclampsia (196). Studies have shown the transplacental regulation of cellular immunity between the mother and the foetus (197), underlining the possibility of maternal immunity affecting that of the foetus. The proliferative responses of T-cells derived from cord-blood in children who later become allergic are reduced (198) and atopy has been associated with altered cytokine profile in neonates (199).

In a recent study, Herzog et al. reported that early-onset preeclampsia was associated with a derangement in foetal haematopoiesis (200). This underlines the importance of how preeclampsia may give rise to epigenetic changes in the offspring, especially immunological ones.

5.2.2 Preeclampsia and childhood growth

As described in Chapter 1.3.5, apart from one publication from the original nested case control study (25) and one publication from the Stavanger Study (24), six other

studies on childhood growth after preeclampsia exposure exist. In these studies, preeclampsia was examined as one entity rather than by severity, although in the smallest study, preeclampsia was differentiated by gestational age of onset (32, 75-77, 79, 80). These studies show conflicting results of weight and BMI development after preeclampsia exposure, and two of these studies found no association between preeclampsia and linear growth. The discrepancies across studies are possibly attributable to different designs including age and gender at participation.

In our study, severe preeclampsia was negatively associated with linear growth in boys but not in girls, in contrast to studies on foetal growth retardation showing a postnatal catch-up in linear growth (201, 202). Studies on very premature children born SGA show results similar to ours, as very premature children are less likely to show catch-up growth, or catch-up growth only after the age of 6 years (203). IGF-1 is lower in placental tissues and cord blood in pregnancies with severe, but not mild, preeclampsia (204). IGF-1 is one of the most important regulators of postnatal growth (205). Poor linear growth in children exposed to severe preeclampsia might therefore be due to effects on the growth hormone IGF-1 axis (206-208). Preeclampsia is a condition characterized by inflammation, especially severe preeclampsia, and the cytokines of pregnancy correlate with those in the offspring until 1 year of age (190, 191). This inflammatory status may induce apoptosis of the growth plate cartilage both prenatally and during infancy, thus explaining poor linear growth in children exposed to severe preeclampsia *in utero* (209).

In the current study, weight and BMI were initially lower in children exposed to mild/moderate preeclampsia and in girls exposed to severe preeclampsia; however, it was increased and was higher from preschool age and onwards compared to the unexposed children. Children born small for their gestational age and prematurely born children show similar development of weight and BMI (201, 210, 211). Preeclampsia, especially in the severe form, may cause starvation in the foetus; this, in turn, may lead to epigenetic changes causing a tendency for energy conservation throughout life and therefore cause overweight or obesity (212, 213). Children with catch-up growth postnatally show increased insulin sensitivity, and they show

favourable linear growth and weight development (214). Children born SGA frequently show catch-up in weight and length before the age of 1 year (203). However, in our study, catch-up growth, and only in weight, occurred at a later age. This difference suggests that preeclampsia affects weight and BMI independently whether the children were born SGA. In the current study, boys exposed to severe preeclampsia had a low weight and BMI throughout childhood, as opposed to children born SGA. Low levels of IGF-1 mediated through prematurity and inflammation may be a common pathophysiology of linear growth and weight development in boys exposed to severe preeclampsia (215).

The result of high waist-to-height ratio in children exposed to severe preeclampsia is in accordance with studies showing that children born SGA continue to gain excess body fat even after catch-up in weight is completed (203). As a high waist-to-height ratio is a risk factor for insulin resistance and metabolic syndrome (211), severe preeclampsia is an inflammatory condition (14, 216) and an association between inflammatory disorders in adults and metabolic syndrome has been suggested (217), severe preeclampsia may indirectly and/or via inflammation be a risk factor for metabolic syndrome in offspring.

The current study showed different effects of mild/moderate and severe preeclampsia, and as explained in Chapter 1.2.3, these may be considered two distinct pathophysiological entities with implications for child growth (14, 30).

There were different effects of preeclampsia exposure on childhood growth depending on the gender of the child. Generally, severe preeclampsia exposure was negatively associated with linear growth, weight and BMI development in boys throughout childhood. Mild/moderate preeclampsia was positively associated with linear growth in boys, negatively in girls, and it was positively associated with weight and BMI development in both boys and girls. Severe preeclampsia was positively associated with weight and BMI development in girls, but negatively associated in boys. Although previous publications have reported inconsistent results about gender differences in growth after preeclampsia exposure (32, 79, 80), boys are generally

more prone to neonatal complications (218). Boys are more likely to be affected by extreme prematurity or being born SGA than girls; even when born to term and being of adequate birthweight, boys are more prone to neonatal complications than girls (219, 220).

5.2.3 Preeclampsia as a marker of placental dysfunction and inflammation

Preeclampsia may be regarded as a syndrome rather than as one entity, with many pathways leading to the symptoms that are defined as preeclampsia. The cause of preeclampsia seems to be the placenta, and poor placentation means that poor uteroplacental circulation occurs secondary to inadequate remodelling of the spiral arteries between weeks 8 and 18 during pregnancy (221). Preeclampsia may only be one of several related causes of disease in the offspring. The international Human Placenta Project aims to study these issues (222).

Preeclampsia is only one of several causes of placental dysfunction. Placental abruption and placenta previa are two conditions with placental dysfunction that may be caused by preeclampsia as well as by high maternal age, multiparity, cigarette smoking, drug abuse, rapid uterine decompression, short umbilical cord, prolonged premature rupture of membranes, chorioamnionitis, folate deficiency, chronic hypertension, preeclampsia, and previous placental abruption or placenta previa (223-225).

One Norwegian study suggested that placental dysfunction may be represented as a range of clinical expressions such as pregnancy-induced hypertension, intrauterine growth retardation, preterm delivery and placental abruption and they may all share an etiological factor such as lesions in the utero-placental arteries (226).

Preeclampsia is characterized by inflammation which may be the common pathway to both altered growth and atopy development. However, the inflammatory status of preeclampsia may not affect childhood growth after the first few years. Microchimerism is increased during preeclampsia (38), and it may give rise to several inflammatory conditions in the offspring (37). Furthermore, inflammatory conditions

may affect normal growth (209), and therefore, it is possible to speculate over the possibility that maternal microchimerism after preeclampsia exposure, especially after long-lasting or severe preeclampsia, plays a role in the association between preeclampsia and childhood growth beyond infancy and early childhood and into puberty.

Preeclampsia may be a trigger for prenatal stress. In a recent metaanalysis by van de Loo et al., 10 studies showed that prenatal stress was positively associated with respiratory morbidity in the children. General stress components released by preeclampsia and other triggers may be direct causes of asthma (227), and therefore, preeclampsia as well as all other triggers of prenatal stress may have similar effects.

5.2.4 Weight-related anthropometrics and physical activity and associations with atopy

Weight-related anthropometrics and atopy

Previous studies on the association between BMI and atopic sensitization have shown conflicting results; furthermore, studies showing an association have mainly been cross-sectional, and therefore, they cannot be used to assess whether obesity precedes sensitization (140). BMI at 1 year was positively associated with atopic sensitization at 12.8 years in our cohort, and most children were sensitized to airborne allergens. Sensitization to airborne allergens is uncommon in Scandinavian children before the age of 1 year (228); therefore, the high BMI at 1 year probably preceded airborne sensitization. However, we did not assess sensitization during the first year of life, and therefore, we cannot exclude sensitization to food allergens during this period. An animal study showed that obesity in mice lowered the threshold for atopic sensitization, suggesting that obesity causes atopy (229). High BMI is associated with higher body fat and altered adipokines and, in turn, inflammatory changes; these, in turn, might predispose one to atopic sensitization (230). Our results indicate that BMI at 1 year of age is of importance.

On the other hand, animal studies have shown that allergen exposure induces adipose tissue inflammation and insulin resistance, indicating that allergen exposure may be a common cause of both allergy and overweight/obesity (231).

A change in BMI SDS from 1 to 4 years and BMI at 4 years of age was positively associated with ever being diagnosed with atopic dermatitis by the age of 10.8/11.8 years (girls/boys), which confirms previous results (135, 232). If the association is causal, reverse causality may be possible. Atopic dermatitis frequently begins during the first year of life and therefore precedes the age of any potential overweight or obesity (233). However, overweight/obesity may cause atopic dermatitis. First, obesity is associated with an increased risk of dry skin, thereby aggravating underlying skin defects (234). Second, a positive association of BMI increase and high BMI during preschool years with atopic dermatitis could be explained by immunological changes due to increased body fat, and an association between adipokines and atopic dermatitis has been reported (235). Third, not all atopic dermatitis begins in infancy. As shown in Chapter 1.5.2, 17% of 2-year-old children and 21%–33% of 9-to11-year-old children in Norway have atopic dermatitis (Norwegian Institute of Public Health, 2014 report). We did not find any association between weight-related anthropometrics and asthma, unlike previous large studies (138, 236). Our results do not contradict the fact that an association may be present, as we may have too few participants to show a significant association of a low magnitude, as reflected in the CIs that include effect measures similar to those in larger studies (138).

Physical activity and atopy

Low physical activity at 3–6 years in our cohort was positively associated with atopic sensitization at 12.8 years. To the best of our knowledge, this is the first publication showing such an association. A cross-sectional study of 2000 Spanish adolescents using questionnaires showed no association between physical activity and allergy at 13–17 years of age (237).

In our analyses, we adjusted for BMI; however, BMI may underestimate the relative amount of fat tissue in the body composition of children (68). The association between low activity and atopic sensitization may therefore be due to relatively more body fat in children with a low activity level independent of weight status, with subsequent changes in adipokines and, in turn, development of sensitization (230).

We found that a high activity level at 6–10 years of age was positively associated with atopic dermatitis at 10.8/11.8 years (girls/boys), in accordance with ISAAC 3; it showed that vigorous physical activity at 13–14 years was positively associated with atopic dermatitis at the same age, which was possibly attributable to sweat-induced itch (135). Natural killer cell cytotoxicity could be increased after long-lasting physical activity (92), and a positive association between natural killer cell cytotoxicity and atopic dermatitis has been suggested (238).

Low activity levels at 3–6 and 6–10 years of age were positively associated with ever being diagnosed with asthma by 10.8/11.8 years (girls/boys) in our cohort. There was no association with current asthma at 12.8 years of age. In ISAAC 3, Mitchell et al. found that several hours of TV viewing was positively associated with current asthma in adolescents (135). Other studies have indicated a protective effect of physical activity against asthma development (141).

We found no significant association between physical activity and allergic rhinoconjunctivitis; however, the CIs did include clinically relevant values. Therefore, our results did not contradict those of the ISAAC 3 study, where both vigorous physical activity and a sedentary lifestyle at 13 years of age were positively associated with allergic rhinoconjunctivitis with ORs of 1.25 and 1.17, respectively (135).

5.2.5 Weight-related anthropometrics and associations with lung function

The positive associations between weight-related anthropometrics and lung function are consistent with results from other studies in children (139, 152-155, 157, 239).

A negative association between BMI and FEV_1/FVC has been interpreted as flow limitation (153, 240). However, there is a positive association between BMI and FEV_1 and a stronger association between BMI and FVC within the normal range of BMI (139, 152). A disproportionate growth between lung size and airway calibre during childhood has been called 'dysanapsis', by many considered a physiological phenomenon and without clinical relevance for airflow limitation in individuals (241). Recently, the results of studies suggest that dysanapsis (defined as a normal FVC and FEV_1 and a low FEV_1/FVC ratio) is associated with respiratory symptoms and disease severity in obese children with asthma, suggesting that dysanapsis is not normal (242, 243).

As mentioned in Chapter 5.2.4, we found no association between weight-related anthropometrics and asthma. Together with a negative association with the FEV_1/FVC ratio, our results are similar to those of a cross-sectional study of 2393 children at the ages of 10–17 years, where a negative association between weight and FEV_1/FVC ratio was independent of respiratory disease or symptoms (152). However, as discussed in Chapter 5.1.6, larger studies have shown positive associations of rapid weight gain (138, 139) and overweight/obesity with childhood asthma (134, 236).

As mentioned above, our and other studies of children show positive associations of weight-related anthropometrics with FEV_1 and FVC, whereas studies of adults show negative associations (161, 244). A longitudinal study interpreted that an initial positive association between childhood BMI and FEV_1 and FVC was likely attributable to greater childhood lean body mass and not adiposity (161). BMI in normal-weight children may be a surrogate marker of relatively more lean body mass than fat mass, suggesting that the increase in muscle mass in parallel with BMI could explain the different results in children and adults (245). Skinfolds and waist circumference may be better markers of body fat mass than BMI in children (168, 169, 246). However, we found similar associations between BMI and waist circumference and skinfolds with lung function, suggesting that BMI also partly

reflects body fat in these children, and may contradict that the association between childhood BMI and lung volumes is only a result of lean body mass.

Inverse U-shaped associations were found between BMI SDS and FEV_1 % and FVC % in late childhood, and the breakpoint toward a negative association is around the BMI SDS corresponding to overweight. This is in accordance with other studies suggesting that BMI beyond a threshold is associated with reduced lung function (153, 157, 247). In the large PIAMA study including measurements at 8 and 12 years of age, perseverance of high BMI or large waist circumference was positively associated with FEV_1 at 12 years of age and showed a small inverse U-shaped association with lung function only in obese boys (153). The authors suggested that the transition from childhood association (i.e., BMI positively associated with lung volumes) to adult association (i.e., BMI negatively associated with lung volumes) occurs at a later age (153). In a cross-sectional study of 6784 students of age 8–20 years, BMI showed an inverse U-shaped association with FEV_1 only in children older than 12 years of age (247). Our results indicate that the transition from a positive to a negative association between BMI and lung function may appear some years earlier. Together, these results support that the negative impact of overweight/obesity depends on the duration of the overweight, where late childhood is of importance (159).

It is important to consider the composition of excess weight when studying the associations between weight-related anthropometrics and lung function (159). We found an inverse U-shaped association between subscapular skinfold and FEV_1 %, indicating that the inverse U-shaped associations may be due to fat and not lean mass. However, this should be interpreted with caution owing to the lack of similar findings for triceps skinfolds.

Internal fat deposition may reduce chest wall compliance and impede diaphragmatic descent, thus explaining the association between obesity and lung volumes as a mechanical effect (248). A negative association of leptin or leptin/adiponectin ratio with lung function suggests an effect mediated by a low-grade systemic inflammation

(159); this is supported by studies showing an association between adiposity and asthma in children (159) and adults (236).

We found positive straight-line associations, but no U-shaped associations for birthweight and change in BMI from 1–4 and 4 years to first follow-up and lung function at 12.8 years of age in accordance with another study reporting a positive association between rapid weight gain from 3–7 years of age and FEV_1 and FVC at 15 years of age (139). However, in a study of 1740 children followed from birth to 21 years of age, catch-up growth until 5 years of age was positively associated with lung function at 21 years of age but negatively associated with lung function in men if the weight gain or obesity started after 5 years of age (157), in contrast to our results.

Finally, results from our and from other studies indicate that the association between anthropometrics and lung function may differ between boys and girls. We found that the associations between anthropometrics other than BMI and FVC % and FEV_1 % were mainly found in girls, which is consistent with other studies (154, 249). When stratifying by gender, the inverse U-shaped associations persisted only for girls at 10.8 years of age, but this may possibly be owing to loss of power. Gender specific differences could be owing to differences in fat accumulation during and after puberty, with a peripheral fat deposition in girls and an abdominal fat deposition in boys, leading to reduction in lung function in boys (154).

5.3 Clinical implications

We found a positive association of severe preeclampsia with allergic rhinoconjunctivitis and high-level atopic sensitization, which emphasizes the possible early origin of atopic disease.

The trajectories of growth after preeclampsia exposure were partly of a large enough magnitude to be clinically relevant. Our predictive model of growth after preeclampsia exposure may have implications for targeted approaches for healthy growth and development.

The positive associations (1) of BMI with atopic sensitization and atopic dermatitis, (2) of low physical activity with atopic sensitization and asthma and (3) of high physical activity with atopic dermatitis were of both high and low effect measures; thus, some of the results could be clinically relevant.

We found positive associations between weight-related anthropometrics and FVC % and FEV_1 %, but negative associations between weight-related anthropometrics and FEV_1/FVC % and $FEF_{25-75\%}$/FVC. Whereas these could be physiological phenomena, increasing weight might also influence the diameter of the airways, thereby contributing to airflow limitation. The inverse U-shaped association of BMI in late childhood with lung function suggests that the impact of body composition on lung function is higher in obese children. The positive and negative regression coefficients between the weight-related anthropometrics and lung function in the present study were small, varying from approximately one to three. Therefore, if the predictors increase by one unit, the predicted lung function values increase or decrease by 1%–3%, making the clinical relevance of the results less substantial. However, the inverse U-shaped associations between weight-related anthropometrics and lung function at 10.8–12.8 years of age could suggest that the greater impact of airway obstruction occurs in children with the highest body fat mass.

Our studies do not have direct clinical implications and do not identify new preventive measures. Our studies mainly contribute to understanding associations and possible early risk factors for atopy, lung function and growth, thereby providing an opportunity to prevent atopic disease and unfavourable lung function, and promote healthy growth.

6. Conclusion

Based on the results of the studies in this thesis and considering the methodological limitations, the following answers can be provided for the study objectives.

Preeclampsia exposure *in utero* by increasing severity was (positively) associated with allergic rhinoconjunctivitis and high-level atopic sensitization in late childhood. We did not find any associations of preeclampsia with atopic dermatitis, asthma or lung function.

From birth to adolescence, linear growth, weight and BMI trajectories differed among children exposed to preeclampsia by severity of preeclampsia, age and gender compared with unexposed children. Exposure to mild/moderate preeclampsia was positively associated with linear growth in boys, and it was positively associated with weight and BMI in both genders. Exposure to severe preeclampsia was negatively associated with linear growth in both genders, and it was negatively associated with weight and BMI trajectories in boys, but in girls, it was positively associated with weight and BMI after preschool age. Exposure to severe preeclampsia was positively associated with waist-to-height ratio in late childhood; however, we did not find any associations with waist circumference, triceps skinfolds or subscapular skinfolds.

BMI and increase in BMI were positively associated with atopic sensitization and atopic dermatitis; however, we did not find any association with asthma or allergic rhinoconjunctivitis. Furthermore, low physical activity was associated with atopic sensitization and asthma ever. High physical activity was associated with atopic dermatitis. We did not find any association between physical activity and allergic rhinoconjunctivitis.

Different weight-related anthropometric measurements from birth throughout childhood were positively associated with FVC % and FEV_1 % and negatively associated with FEV_1/FVC % and $FEF_{25-75\%}$/FVC in late childhood. BMI in late childhood showed an inverse U-shaped association with FVC % and FEV_1 %.

7. Future perspectives

Larger studies are needed to further explore the role of preeclampsia in the development of atopic disease.

Our study was the first to provide a predictive model for growth after preeclampsia exposure. Similar studies will be needed to confirm our results. Larger studies on a population-based cohort with anthropometric measurements every third month until 2 years of age, and thereafter, every year until adulthood (167), would be necessary to further explore this issue.

The overall aim was to study early-life determinants of atopic diseases. To further clarify this topic, large prospective studies would need to be conducted to confirm the results of the studies included in this thesis and to identify other risk factors for atopic diseases. Such a cohort should be population-based instead of being a preeclampsia cohort.

8. References

1. Akinbami L, Centers for Disease C, Prevention National Center for Health S. The state of childhood asthma, United States, 1980-2005. Adv Data. 2006(381):1-24.
2. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. NCHS data brief. 2013(121):1-8.
3. Pawankar R CG, Holgate ST, Lockey RF, editors. World Allergy Organization (WAO) white book on allergy. Milwaukee (WI): World Allergy Organization; 2011.
4. Bakken HN, Nafstad P, Bolle R, Nystad W. Skin sensitization in school children in northern and southern Norway. J Asthma. 2007;44(1):23-7.
5. Ring J. History of allergy in antiquity. Chemical immunology and allergy. 2014;100:2-14.
6. Johansson SG. The discovery of IgE. J Allergy Clin Immunol. 2016;137(6):1671-3.
7. Ishizaka T, Ishizaka K, Johansson SGO, Bennich H. Histamine Release from Human Leukocytes by Anti-λE Antibodies. The Journal of Immunology. 1969;102(4):884-92.
8. Stanworth DR. The discovery of IgE. Allergy. 1993;48(2):67-71.
9. Gould HJ, Sutton BJ, Beavil AJ, Beavil RL, McCloskey N, Coker HA, et al. The biology of IGE and the basis of allergic disease. Annu Rev Immunol. 2003;21:579-628.
10. Ring J. Terminology of allergic phenomena. Chemical immunology and allergy. 2014;100:46-52.
11. De Luca G, Olivieri F, Melotti G, Aiello G, Lubrano L, Boner AL. Fetal and early postnatal life roots of asthma. J Matern Fetal Neonatal Med. 2010;23 Suppl 3:80-3.
12. Anderson EL, Fraser A, Martin RM, Kramer MS, Oken E, Patel R, et al. Associations of postnatal growth with asthma and atopy: the PROBIT Study. Pediatr Allergy Immunol. 2013;24(2):122-30.
13. Diesner SC, Forster-Waldl E, Olivera A, Pollak A, Jensen-Jarolim E, Untersmayr E. Perspectives on immunomodulation early in life. Pediatr Allergy Immunol. 2012;23(3):210-23.
14. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005;365(9461):785-99.
15. Nafstad P, Magnus P, Jaakkola JJ. Risk of childhood asthma and allergic rhinitis in relation to pregnancy complications. J Allergy Clin Immunol. 2000;106(5):867-73.
16. Nafstad P, Samuelsen SO, Irgens LM, Bjerkedal T. Pregnancy complications and the risk of asthma among Norwegians born between 1967 and 1993. Eur J Epidemiol. 2003;18(8):755-61.
17. Keski-Nisula L, Heinonen S, Remes S, Pekkanen J. Pre-eclampsia, placental abruption and increased risk of atopic sensitization in male adolescent offspring. Am J Reprod Immunol. 2009;62(5):293-300.
18. de Boo HA, Harding JE. The developmental origins of adult disease (Barker) hypothesis. Aust N Z J Obstet Gynaecol. 2006;46(1):4-14.
19. Hersoug LG, Linneberg A. The link between the epidemics of obesity and allergic diseases: does obesity induce decreased immune tolerance? Allergy. 2007;62(10):1205-13.
20. Wang R, Custovic A, Simpson A, Belgrave DC, Lowe LA, Murray CS. Differing associations of bmi and body fat with asthma and lung function in children. Pediatr Pulmonol. 2014;49(11):1049-57.
21. Chinn S. Obesity and asthma: evidence for and against a causal relation. J Asthma. 2003;40(1):1-16.

22. Murray CS, Canoy D, Buchan I, Woodcock A, Simpson A, Custovic A. Body mass index in young children and allergic disease: gender differences in a longitudinal study. Clin Exp Allergy. 2011;41(1):78-85.
23. von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. Thorax. 2001;56(11):835-8.
24. Ogland B, Vatten LJ, Romundstad PR, Nilsen ST, Forman MR. Pubertal anthropometry in sons and daughters of women with preeclamptic or normotensive pregnancies. Arch Dis Child. 2009;94(11):855-9.
25. Odegard RA, Vatten LJ, Nilsen ST, Salvesen KA, Austgulen R. Preeclampsia and fetal growth. Obstet Gynecol. 2000;96(6):950-5.
26. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. Lancet. 1994;343(8898):619-29.
27. Auger N, Luo ZC, Nuyt AM, Kaufman JS, Naimi AI, Platt RW, et al. Secular Trends in Preeclampsia Incidence and Outcomes in a Large Canada Database: A Longitudinal Study Over 24 Years. Can J Cardiol. 2016;32(8):987 e15-23.
28. Lam C, Lim KH, Karumanchi SA. Circulating angiogenic factors in the pathogenesis and prediction of preeclampsia. Hypertension. 2005;46(5):1077-85.
29. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010;376(9741):631-44.
30. Alsnes IV, Janszky I, Forman MR, Vatten LJ, Okland I. A population-based study of associations between preeclampsia and later cardiovascular risk factors. Am J Obstet Gynecol. 2014;211(6):657 e1-7.
31. Ananth CV, Vintzileos AM. Maternal-fetal conditions necessitating a medical intervention resulting in preterm birth. Am J Obstet Gynecol. 2006;195(6):1557-63.
32. Vatten LJ, Romundstad PR, Holmen TL, Hsieh CC, Trichopoulos D, Stuver SO. Intrauterine exposure to preeclampsia and adolescent blood pressure, body size, and age at menarche in female offspring. Obstet Gynecol. 2003;101(3):529-33.
33. Oglaend B, Forman MR, Romundstad PR, Nilsen ST, Vatten LJ. Blood pressure in early adolescence in the offspring of preeclamptic and normotensive pregnancies. J Hypertens. 2009;27(10):2051-4.
34. Ogland B, Nilsen ST, Forman MR, Vatten LJ. Pubertal development in daughters of women with pre-eclampsia. Arch Dis Child. 2011;96(8):740-3.
35. Pinheiro TV, Brunetto S, Ramos JGL, Bernardi JR, Goldani MZ. Hypertensive disorders during pregnancy and health outcomes in the offspring: a systematic review. Journal of Developmental Origins of Health and Disease. 2016;7(4):391-407
36. Gammill HS, Nelson JL. Naturally acquired microchimerism. Int J Dev Biol. 2010;54(2-3):531-43.
37. Stevens AM. Maternal microchimerism in health and disease. Best Pract Res Clin Obstet Gynaecol. 2016;31:121-30
38. Gammill HS, Aydelotte TM, Guthrie KA, Nkwopara EC, Nelson JL. Cellular fetal microchimerism in preeclampsia. Hypertension. 2013;62(6):1062-7.
39. Thompson EE, Myers RA, Du G, Aydelotte TM, Tisler CJ, Stern DA, et al. Maternal microchimerism protects against the development of asthma. J Allergy Clin Immunol. 2013;132(1):39-44.
40. Ekbom A, Hsieh CC, Lipworth L, Adami HQ, Trichopoulos D. Intrauterine environment and breast cancer risk in women: a population-based study. J Natl Cancer Inst. 1997;89(1):71-6.

41. Pettersson A, Richiardi L, Cnattingius S, Kaijser M, Akre O. Gestational hypertension, preeclampsia, and risk of testicular cancer. Cancer Res. 2008;68(21):8832-6.
42. Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. Behav Genet. 1997;27(4):325-51.
43. Carlson JJ, Eisenmann JC, Norman GJ, Ortiz KA, Young PC. Dietary fiber and nutrient density are inversely associated with the metabolic syndrome in US adolescents. J Am Diet Assoc. 2011;111(11):1688-95.
44. Zheng T, Zhang J, Sommer K, Bassig BA, Zhang X, Braun J, et al. Effects of Environmental Exposures on Fetal and Childhood Growth Trajectories. Annals of global health. 2016;82(1):41-99.
45. Tanner JM. Growth as a mirror of the condition of society: secular trends and class distinctions. Acta Paediatr Jpn. 1987;29(1):96-103.
46. Juliusson PB, Roelants M, Eide GE, Moster D, Juul A, Hauspie R, et al. [Growth references for Norwegian children]. Tidsskr Nor Laegeforen. 2009;129(4):281-6.
47. Yaghootkar H, Freathy RM. Genetic origins of low birth weight. Curr Opin Clin Nutr Metab Care. 2012;15(3):258-64.
48. Roland MC, Friis CM, Godang K, Bollerslev J, Haugen G, Henriksen T. Maternal factors associated with fetal growth and birthweight are independent determinants of placental weight and exhibit differential effects by fetal sex. PloS one. 2014;9(2):e87303.
49. Scifres CM, Nelson DM. Intrauterine growth restriction, human placental development and trophoblast cell death. The Journal of physiology. 2009;587(Pt 14):3453-8.
50. Lewis RM, Demmelmair H, Gaillard R, Godfrey KM, Hauguel-de Mouzon S, Huppertz B, et al. The placental exposome: placental determinants of fetal adiposity and postnatal body composition. Ann Nutr Metab. 2013;63(3):208-15.
51. Karlberg J. A biologically-oriented mathematical model (ICP) for human growth. Acta Paediatr Scand Suppl. 1989;350:70-94.
52. Mei Z, Grummer-Strawn LM, Thompson D, Dietz WH. Shifts in percentiles of growth during early childhood: analysis of longitudinal data from the California Child Health and Development Study. Pediatrics. 2004;113(6):e617-27.
53. Wit JM, Boersma B. Catch-up growth: definition, mechanisms, and models. J Pediatr Endocrinol Metab. 2002;15 Suppl 5:1229-41.
54. Karlberg J, Albertsson-Wikland K. Growth in full-term small-for-gestational-age infants: from birth to final height. Pediatr Res. 1995;38(5):733-9.
55. van der Steen M, Hokken-Koelega AC. Growth and Metabolism in Children Born Small for Gestational Age. Endocrinol Metab Clin North Am. 2016;45(2):283-94.
56. Cho WK, Suh BK. Catch-up growth and catch-up fat in children born small for gestational age. Korean J Pediatr. 2016;59(1):1-7.
57. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. Int J Pediatr Obes. 2006;1(1):11-25.
58. Jackson-Leach R, Lobstein T. Estimated burden of paediatric obesity and co-morbidities in Europe. Part 1. The increase in the prevalence of child obesity in Europe is itself increasing. Int J Pediatr Obes. 2006;1(1):26-32.
59. Juliusson PB, Roelants M, Eide GE, Hauspie R, Waaler PE, Bjerknes R. Overweight and obesity in Norwegian children: secular trends in weight-for-height and skinfolds. Acta Paediatr. 2007;96(9):1333-7.

60. Juliusson PB, Eide GE, Roelants M, Waaler PE, Hauspie R, Bjerknes R. Overweight and obesity in Norwegian children: prevalence and socio-demographic risk factors. Acta Paediatr. 2010;99(6):900-5.
61. Gungor NK. Overweight and obesity in children and adolescents. J Clin Res Pediatr Endocrinol. 2014;6(3):129-43.
62. Horne J. Obesity and short sleep: unlikely bedfellows? Obes Rev. 2011;12(5):e84-94.
63. Campbell MK. Biological, environmental, and social influences on childhood obesity. Pediatr Res. 2016;79(1-2):205-11.
64. Zhang YJ, Li S, Gan RY, Zhou T, Xu DP, Li HB. Impacts of gut bacteria on human health and diseases. Int J Mol Sci. 2015;16(4):7493-519.
65. Simonyte Sjodin K, Vidman L, Ryden P, West CE. Emerging evidence of the role of gut microbiota in the development of allergic diseases. Curr Opin Allergy Clin Immunol. 2016;16(4):390-5.
66. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatric obesity. 2012;7(4):284-94.
67. McCarthy HD, Ashwell M. A study of central fatness using waist-to-height ratios in UK children and adolescents over two decades supports the simple message--'keep your waist circumference to less than half your height'. Int J Obes (Lond). 2006;30(6):988-92.
68. Brannsether B, Eide GE, Roelants M, Bjerknes R, Juliusson PB. Interrelationships between anthropometric variables and overweight in childhood and adolescence. Am J Hum Biol. 2014;26(4):502-10.
69. Barker DJ. The fetal and infant origins of adult disease. Bmj. 1990;301(6761):1111.
70. Campbell CP, Raubenheimer D, Badaloo AV, Gluckman PD, Martinez C, Gosby A, et al. Developmental contributions to macronutrient selection: a randomized controlled trial in adult survivors of malnutrition. Evol Med Public Health. 2016;2016(1):158-69.
71. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008;359(1):61-73.
72. Portella AK, Kajantie E, Hovi P, Desai M, Ross MG, Goldani MZ, et al. Effects of in utero conditions on adult feeding preferences. J Dev Orig Health Dis. 2012;3(3):140-52.
73. Turner JA. Diagnosis and management of pre-eclampsia: an update. Int J Womens Health. 2010;2:327-37.
74. Jim B, Sharma S, Kebede T, Acharya A. Hypertension in pregnancy: a comprehensive update. Cardiol Rev. 2010;18(4):178-89.
75. Lazdam M, de la Horra A, Diesch J, Kenworthy Y, Davis E, Lewandowski AJ, et al. Unique blood pressure characteristics in mother and offspring after early onset preeclampsia. Hypertension. 2012;60(5):1338-45.
76. Miettola S, Hartikainen AL, Vaarasmaki M, Bloigu A, Ruokonen A, Jarvelin MR, et al. Offspring's blood pressure and metabolic phenotype after exposure to gestational hypertension in utero. Eur J Epidemiol. 2013;28(1):87-98.
77. Miettola S, Hovi P, Andersson S, Strang-Karlsson S, Pouta A, Laivuori H, et al. Maternal preeclampsia and bone mineral density of the adult offspring. Am J Obstet Gynecol. 2013;209(5).
78. Kvehaugen AS, Andersen LF, Staff AC. Anthropometry and cardiovascular risk factors in women and offspring after pregnancies complicated by preeclampsia or diabetes mellitus. Acta Obstet Gynecol Scand. 2010;89(11):1478-85.

79. Pizzi C, Cole TJ, Richiardi L, Dos-Santos-Silva I, Corvalan C, De Stavola B. Prenatal influences on size, velocity and tempo of infant growth: findings from three contemporary cohorts. PloS one. 2014;9(2):e90291.
80. Seidman DS, Laor A, Gale R, Stevenson DK, Mashiach S, Danon YL. Pre-eclampsia and offspring's blood pressure, cognitive ability and physical development at 17-years-of-age. Br J Obstet Gynaecol. 1991;98(10):1009-14.
81. Tremblay MS, LeBlanc AG, Kho ME, Saunders TJ, Larouche R, Colley RC, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth. Int J Behav Nutr Phys Act. 2011;8:98.
82. Norwegian Directorate of Health 2012. Physical activity among 6-, 9- and 15-year-olds in Norway: IS-2002.
83. Norwegian Directorate of Health 2008. Physical activity among children and adolescents in Norway: IS-1533.
84. Gatford KL, Kaur G, Falcao-Tebas F, Wadley GD, Wlodek ME, Laker RC, et al. Exercise as an intervention to improve metabolic outcomes after intrauterine growth restriction. Am J Physiol Endocrinol Metab. 2014;306(9):E999-1012.
85. Martinez-Gomez D, Eisenmann JC, Gomez-Martinez S, Veses A, Romeo J, Veiga OL, et al. Associations of physical activity and fitness with adipocytokines in adolescents: the AFINOS Study. Nutr Metab Cardiovasc Dis. 2012;22(3):252-9.
86. Vickers MH, Breier BH, McCarthy D, Gluckman PD. Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. Am J Physiol Regul Integr Comp Physiol. 2003;285(1):R271-3.
87. Richmond E, Rogol AD. Endocrine Responses to Exercise in the Developing Child and Adolescent. Front Horm Res. 2016;47:58-67.
88. Bai Y, Chen S, Laurson KR, Kim Y, Saint-Maurice PF, Welk GJ. The Associations of Youth Physical Activity and Screen Time with Fatness and Fitness: The 2012 NHANES National Youth Fitness Survey. PloS one. 2016;11(1):e0148038.
89. Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. Physiol Rev. 2000;80(3):1055-81.
90. Weinstock C, Konig D, Harnischmacher R, Keul J, Berg A, Northoff H. Effect of exhaustive exercise stress on the cytokine response. Med Sci Sports Exerc. 1997;29(3):345-54.
91. Lee YW, Shin KW, Paik IY, Jung WM, Cho SY, Choi ST, et al. Immunological impact of Taekwondo competitions. Int J Sports Med. 2012;33(1):58-66.
92. Del Giacco SR, Scorcu M, Argiolas F, Firinu D, Del Giacco GS. Exercise training, lymphocyte subsets and their cytokines production: experience of an Italian professional football team and their impact on allergy. BioMed research international. 2014;2014:429248.
93. Franca-Pinto A, Mendes FA, de Carvalho-Pinto RM, Agondi RC, Cukier A, Stelmach R, et al. Aerobic training decreases bronchial hyperresponsiveness and systemic inflammation in patients with moderate or severe asthma: a randomised controlled trial. Thorax. 2015;70(8):732-9.
94. Aldred S, Love JA, Tonks LA, Stephens E, Jones DS, Blannin AK. The effect of steady state exercise on circulating human IgE and IgG in young healthy volunteers with known allergy. J Sci Med Sport. 2010;13(1):16-9.
95. Morici G, Gruttad'Auria CI, Baiamonte P, Mazzuca E, Castrogiovanni A, Bonsignore MR. Endurance training: is it bad for you? Breathe (Sheffield, England). 2016;12(2):140-7.

96. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy. 2001;56(9):813-24.
97. Reddel HK, Bateman ED, Becker A, Boulet LP, Cruz AA, Drazen JM, et al. A summary of the new GINA strategy: a roadmap to asthma control. Eur Respir J. 2015;46(3):622-39.
98. Salo PM, Arbes SJ, Jr., Jaramillo R, Calatroni A, Weir CH, Sever ML, et al. Prevalence of allergic sensitization in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol. 2014;134(2):350-9.
99. Gergen PJ, Turkeltaub PC. The association of individual allergen reactivity with respiratory disease in a national sample: data from the second National Health and Nutrition Examination Survey, 1976-80 (NHANES II). J Allergy Clin Immunol. 1992;90(4 Pt 1):579-88.
100. Ronmark E, Bjerg A, Perzanowski M, Platts-Mills T, Lundback B. Major increase in allergic sensitization in schoolchildren from 1996 to 2006 in northern Sweden. J Allergy Clin Immunol. 2009;124(2):357-63, 63.e1-15.
101. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet. 1998;351(9111):1225-32.
102. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. 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(9537):733-43.
103. Pols DH, Wartna JB, van Alphen EI, Moed H, Rasenberg N, Bindels PJ, et al. Interrelationships between Atopic Disorders in Children: A Meta-Analysis Based on ISAAC Questionnaires. PloS one. 2015;10(7):e0131869.
104. Chawla J, Seear M, Zhang T, Smith A, Carleton B. Fifty years of pediatric asthma in developed countries: how reliable are the basic data sources? Pediatr Pulmonol. 2012;47(3):211-9.
105. Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2007;62(9):758-66.
106. Hansen TE, Evjenth B, Holt J. Increasing prevalence of asthma, allergic rhinoconjunctivitis and eczema among schoolchildren: three surveys during the period 1985-2008. Acta Paediatr. 2013;102(1):47-52.
107. Selnes A, Nystad W, Bolle R, Lund E. Diverging prevalence trends of atopic disorders in Norwegian children. Results from three cross-sectional studies. Allergy. 2005;60(7):894-9.
108. World Health Organization Fact sheet No 307, Updated November 2013. http://www.who.int/mediacentre/factsheets/fs307/en/.
109. Smidesang I, Saunes M, Storro O, Oien T, Holmen TL, Johnsen R, et al. Allergy related disorders among 2-yrs olds in a general population. The PACT Study. Pediatr Allergy Immunol. 2010;21(2 Pt 1):315-20.
110. Almqvist C, Worm M, Leynaert B. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. Allergy. 2008;63(1):47-57.
111. Chen W, Mempel M, Schober W, Behrendt H, Ring J. Gender difference, sex hormones, and immediate type hypersensitivity reactions. Allergy. 2008;63(11):1418-27.

112. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63 Suppl 86:8-160.
113. Bantz SK, Zhu Z, Zheng T. The Atopic March: Progression from Atopic Dermatitis to Allergic Rhinitis and Asthma. J Clin Cell Immunol. 2014;5(2).
114. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. J Allergy Clin Immunol. 2003;112(6 Suppl):S118-27.
115. Sly PD, Boner AL, Bjorksten B, Bush A, Custovic A, Eigenmann PA, et al. Early identification of atopy in the prediction of persistent asthma in children. Lancet. 2008;372(9643):1100-6.
116. Lack G. Update on risk factors for food allergy. J Allergy Clin Immunol. 2012;129(5):1187-97.
117. Maggi E. The TH1/TH2 paradigm in allergy. Immunotechnology. 1998;3(4):233-44.
118. Jutel M, Akdis CA. T-cell subset regulation in atopy. Curr Allergy Asthma Rep. 2011;11(2):139-45.
119. Vickery BP, Chin S, Burks AW. Pathophysiology of food allergy. Pediatr Clin North Am. 2011;58(2):363-76, ix-x.
120. Holgate ST. Pathogenesis of asthma. Clin Exp Allergy. 2008;38(6):872-97.
121. Gould HJ, Sutton BJ. IgE in allergy and asthma today. Nature reviews Immunology. 2008;8(3):205-17.
122. Prescott SL. Early-life environmental determinants of allergic diseases and the wider pandemic of inflammatory noncommunicable diseases. J Allergy Clin Immunol. 2013;131(1):23-30.
123. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989;299(6710):1259-60.
124. Schuijs MJ, Willart MA, Vergote K, Gras D, Deswarte K, Ege MJ, et al. Farm dust and endotoxin protect against allergy through A20 induction in lung epithelial cells. Science. 2015;349(6252):1106-10.
125. Lynch SV. Gut Microbiota and Allergic Disease. New Insights. Annals of the American Thoracic Society. 2016;13 Suppl 1:S51-4.
126. Nagel G, Weinmayr G, Kleiner A, Garcia-Marcos L, Strachan DP. Effect of diet on asthma and allergic sensitisation in the International Study on Allergies and Asthma in Childhood (ISAAC) Phase Two. Thorax. 2010;65(6):516-22.
127. Ellwood P, Asher MI, Garcia-Marcos L, Williams H, Keil U, Robertson C, et al. Do fast foods cause asthma, rhinoconjunctivitis and eczema? Global findings from the International Study of Asthma and Allergies in Childhood (ISAAC) phase three. Thorax. 2013;68(4):351-60.
128. Byberg K, Oymar K, Aksnes L. Fatty acids in cord blood plasma, the relation to soluble CD23 and subsequent atopy. Prostaglandins Leukot Essent Fatty Acids. 2008;78(1):61-5.
129. Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT, et al. Effect of Avoidance on Peanut Allergy after Early Peanut Consumption. N Engl J Med. 2016;374(15):1435-43.
130. Deng Q, Lu C, Li Y, Sundell J, Dan N. Exposure to outdoor air pollution during trimesters of pregnancy and childhood asthma, allergic rhinitis, and eczema. Environ Res. 2016;150:119-27.
131. Lin Z, Norback D, Wang T, Zhang X, Shi J, Kan H, et al. The first 2-year home environment in relation to the new onset and remission of asthmatic and allergic symptoms in 4246 preschool children. Sci Total Environ. 2016;553:204-10.

132. Gagliardi L, Rusconi F, Da Fre M, Mello G, Carnielli V, Di Lallo D, et al. Pregnancy disorders leading to very preterm birth influence neonatal outcomes: results of the population-based ACTION cohort study. Pediatr Res. 2013;73(6):794-801.
133. Egan KB, Ettinger AS, Bracken MB. Childhood body mass index and subsequent physician-diagnosed asthma: a systematic review and meta-analysis of prospective cohort studies. BMC Pediatr. 2013;13:121.
134. Mebrahtu TF, Feltbower RG, Greenwood DC, Parslow RC. Childhood body mass index and wheezing disorders: a systematic review and meta-analysis. Pediatr Allergy Immunol. 2015;26(1):62-72.
135. Mitchell EA, Beasley R, Bjorksten B, Crane J, Garcia-Marcos L, Keil U, et al. The association between BMI, vigorous physical activity and television viewing and the risk of symptoms of asthma, rhinoconjunctivitis and eczema in children and adolescents: ISAAC Phase Three. Clin Exp Allergy. 2013;43(1):73-84.
136. Magnusson JO, Kull I, Mai XM, Wickman M, Bergstrom A. Early childhood overweight and asthma and allergic sensitization at 8 years of age. Pediatrics. 2012;129(1):70-6.
137. Sidoroff V, Hyvarinen MK, Piippo-Savolainen E, Korppi M. Overweight does not increase asthma risk but may decrease allergy risk at school age after infantile bronchiolitis. Acta Paediatr. 2012 Jan;101(1):43-7
138. Magnus MC, Stigum H, Haberg SE, Nafstad P, London SJ, Nystad W. Peak weight and height velocity to age 36 months and asthma development: the Norwegian Mother and Child Cohort Study. PloS one. 2015;10(1):e0116362.
139. Sonnenschein-van der Voort AM, Howe LD, Granell R, Duijts L, Sterne JA, Tilling K, et al. Influence of childhood growth on asthma and lung function in adolescence. J Allergy Clin Immunol. 2015;135(6):1435-43 e7.
140. Boulet LP. Obesity and atopy. Clin Exp Allergy. 2015;45(1):75-86.
141. Eijkemans M, Mommers M, Draaisma JM, Thijs C, Prins MH. Physical activity and asthma: a systematic review and meta-analysis. PloS one. 2012;7(12):e50775.
142. Criee CP, Sorichter S, Smith HJ, Kardos P, Merget R, Heise D, et al. Body plethysmography--its principles and clinical use. Respir Med. 2011;105(7):959-71.
143. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med. 1995;152(3):1107-36.
144. Paton JY. A practical approach to the interpretation of lung function testing in children. Paediatric respiratory reviews. 2000;1(3):241-8.
145. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.
146. Sonnenschein-van der Voort AM, Gaillard R, de Jongste JC, Hofman A, Jaddoe VW, Duijts L. Foetal and infant growth patterns, airway resistance and school-age asthma. Respirology. 2016;21(4):674-82.
147. den Dekker HT, Sonnenschein-van der Voort AM, de Jongste JC, Anessi-Maesano I, Arshad SH, Barros H, et al. Early growth characteristics and the risk of reduced lung function and asthma: A meta-analysis of 25,000 children. J Allergy Clin Immunol. 2016;137(4):1026-35.
148. Lawlor DA, Ebrahim S, Davey Smith G. Association of birth weight with adult lung function: findings from the British Women's Heart and Health Study and a meta-analysis. Thorax. 2005;60(10):851-8.
149. Hancox RJ, Poulton R, Greene JM, McLachlan CR, Pearce MS, Sears MR. Associations between birth weight, early childhood weight gain and adult lung function. Thorax. 2009;64(3):228-32.

150. Kotecha SJ, Watkins WJ, Heron J, Henderson J, Dunstan FD, Kotecha S. Spirometric lung function in school-age children: effect of intrauterine growth retardation and catch-up growth. Am J Respir Crit Care Med. 2010;181(9):969-74.
151. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. BMJ. 1991;303(6804):671-5.
152. Cibella F, Bruno A, Cuttitta G, Bucchieri S, Melis MR, De Cantis S, et al. An elevated body mass index increases lung volume but reduces airflow in Italian schoolchildren. PloS one. 2015;10(5):e0127154.
153. Bekkers MB, Wijga AH, Gehring U, Koppelman GH, de Jongste JC, Smit HA, et al. BMI, waist circumference at 8 and 12 years of age and FVC and FEV at 12 years of age; the PIAMA birth cohort study. BMC pulmonary medicine. 2015;15(1):39.
154. Khan S, Little J, Chen Y. Relationship Between Adiposity and Pulmonary Function in School-Aged Canadian Children. Pediatr Allergy Immunol Pulmonol. 2014;27(3):126-32.
155. Chen Y, Rennie D, Cormier Y, Dosman JA. Waist circumference associated with pulmonary function in children. Pediatr Pulmonol. 2009;44(3):216-21.
156. van der Gugten AC, Koopman M, Evelein AM, Verheij TJ, Uiterwaal CS, van der Ent CK. Rapid early weight gain is associated with wheeze and reduced lung function in childhood. Eur Respir J. 2012;39(2):403-10.
157. Suresh S, O'Callaghan M, Sly PD, Mamun AA. Impact of childhood anthropometry trends on adult lung function. Chest. 2015;147(4):1118-26.
158. Li AM, Chan D, Wong E, Yin J, Nelson EA, Fok TF. The effects of obesity on pulmonary function. Arch Dis Child. 2003;88(4):361-3.
159. Jensen ME, Wood LG, Gibson PG. Obesity and childhood asthma - mechanisms and manifestations. Current opinion in allergy and clinical immunology. 2012;12(2):186-92.
160. Wang A, Holston AM, Yu KF, Zhang J, Toporsian M, Karumanchi SA, et al. Circulating anti-angiogenic factors during hypertensive pregnancy and increased risk of respiratory distress syndrome in preterm neonates. J Matern Fetal Neonatal Med. 2012;25(8):1447-52.
161. Curry BA, Blizzard CL, Schmidt MD, Walters EH, Dwyer T, Venn AJ. Longitudinal associations of adiposity with adult lung function in the Childhood Determinants of Adult Health (CDAH) study. Obesity (Silver Spring). 2011;19(10):2069-75.
162. Quanjer PH, Borsboom GJ, Brunekreef B, Zach M, Forche G, Cotes JE, et al. Spirometric reference values for white European children and adolescents: Polgar revisited. Pediatr Pulmonol. 1995;19(2):135-42.
163. English Oxford Living Dictionaries. https://en.oxforddictionaries.com/definition/anthropometry.
164. Taylor-Piliae RE, Fair JM, Haskell WL, Varady AN, Iribarren C, Hlatky MA, et al. Validation of the Stanford Brief Activity Survey: examining psychological factors and physical activity levels in older adults. J Phys Act Health 2010;7(1):87-94.
165. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr. 1996;85(7):843-8.
166. Niklasson A, Albertsson-Wikland K. Continuous growth reference from 24th week of gestation to 24 months by gender. BMC Pediatr. 2008;8:8.
167. Juliusson PB, Roelants M, Nordal E, Furevik L, Eide GE, Moster D, et al. Growth references for 0-19 year-old Norwegian children for length/height, weight, body mass index and head circumference. Ann Hum Biol. 2013;40(3):220-7.

168. Brannsether B, Roelants M, Bjerknes R, Juliusson PB. Waist circumference and waist-to-height ratio in Norwegian children 4-18 years of age: reference values and cut-off levels. Acta Paediatr. 2011;100(12):1576-82.
169. Brannsether B, Roelants M, Bjerknes R, Juliusson PB. References and cutoffs for triceps and subscapular skinfolds in Norwegian children 4-16 years of age. Eur J Clin Nutr. 2013;67(9):928-33.
170. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology. 2011;22(5):745.
171. Wickman M, Ahlstedt S, Lilja G, van Hage Hamsten M. Quantification of IgE antibodies simplifies the classification of allergic diseases in 4-year-old children. A report from the prospective birth cohort study--BAMSE. Pediatr Allergy Immunol. 2003;14(6):441-7.
172. Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. J Allergy Clin Immunol. 1999;103(6):1173-9.
173. Gustafsson D, Sjoberg O, Foucard T. Sensitization to food and airborne allergens in children with atopic dermatitis followed up to 7 years of age. Pediatr Allergy Immunol. 2003;14(6):448-52.
174. Rondon C, Campo P, Galindo L, Blanca-Lopez N, Cassinello MS, Rodriguez-Bada JL, et al. Prevalence and clinical relevance of local allergic rhinitis. Allergy. 2012;67(10):1282-8.
175. Wollenberg A, Bieber T. Atopic dermatitis: from the genes to skin lesions. Allergy. 2000;55(3):205-13.
176. Langhammer A, Johannessen A, Holmen TL, Melbye H, Stanojevic S, Lund MB, et al. Global Lung Function Initiative 2012 reference equations for spirometry in the Norwegian population. Eur Respir J. 2016 Dec;48(6):1602-1611.
177. Guibas GV, Manios Y, Xepapadaki P, Moschonis G, Douladiris N, Mavrogianni C, et al. The obesity-asthma link in different ages and the role of body mass index in its investigation: findings from the Genesis and Healthy Growth Studies. Allergy. 2013;68(10):1298-305.
178. Hoenig JM, Heisey DM. The Abuse of Power. The American Statistician. 2001;55(1):19-24.
179. Bacchetti P. Peer review of statistics in medical research: the other problem. BMJ. 2002;324(7348):1271-3.
180. Williamson EJ, Aitken Z, Lawrie J, Dharmage SC, Burgess JA, Forbes AB. Introduction to causal diagrams for confounder selection. Respirology. 2014;19(3):303-11.
181. Cole SR, Platt RW, Schisterman EF, Chu H, Westreich D, Richardson D, et al. Illustrating bias due to conditioning on a collider. Int J Epidemiol. 2010;39(2):417-20.
182. Wilcox AJ, Weinberg CR, Basso O. On the pitfalls of adjusting for gestational age at birth. Am J Epidemiol. 2011;174(9):1062-8.
183. Stokholm J, Sevelsted A, Anderson UD, Bisgaard H. Preeclampsia Associates with Asthma, Allergy and Eczema in Childhood. Am J Respir Crit Care Med. 2017;195(5):614-621.
184. Liu X, Olsen J, Agerbo E, Yuan W, Wu CS, Li J. Maternal preeclampsia and childhood asthma in the offspring. Pediatr Allergy Immunol. 2015;26(2):181-5.
185. Shaheen SO, Macdonald-Wallis C, Lawlor DA, Henderson AJ. Hypertensive disorders of pregnancy, respiratory outcomes and atopy in childhood. Eur Respir J. 2016;47(1):156-65.

186. Magnus MC, Haberg SE, Magnus P, Engeland A, Nafstad P, Karlstad O, et al. Pre-eclampsia and childhood asthma. Eur Respir J. 2016 Dec;48(6):1622-1630.
187. Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and risk of allergic rhinitis in young adulthood. J Allergy Clin Immunol. 2011;127(5):1173-9.
188. Tronnes H, Wilcox AJ, Lie RT, Markestad T, Moster D. The association of preterm birth with severe asthma and atopic dermatitis: a national cohort study. Pediatr Allergy Immunol. 2013;24(8):782-7.
189. Carstens LE, Westerbeek EA, van Zwol A, van Elburg RM. Neonatal antibiotics in preterm infants and allergic disorders later in life. Pediatr Allergy Immunol. 2016;27(7):759-64.
190. Herberth G, Hinz D, Roder S, Schlink U, Sack U, Diez U, et al. Maternal immune status in pregnancy is related to offspring's immune responses and atopy risk. Allergy. 2011;66(8):1065-74.
191. Szarka A, Rigo J, Jr., Lazar L, Beko G, Molvarec A. Circulating cytokines, chemokines and adhesion molecules in normal pregnancy and preeclampsia determined by multiplex suspension array. BMC Immunol. 2010;11:59.
192. van Gool CJ, Thijs C, Dagnelie PC, Henquet CJ, van Houwelingen AC, Schrander J, et al. Determinants of neonatal IgE level: parity, maternal age, birth season and perinatal essential fatty acid status in infants of atopic mothers. Allergy. 2004;59(9):961-8.
193. Eviston DP, Quinton AE, Benzie RJ, Peek MJ, Martin A, Nanan RK. Impaired fetal thymic growth precedes clinical preeclampsia: a case-control study. J Reprod Immunol. 2012;94(2):183-9.
194. Saito S, Shiozaki A, Nakashima A, Sakai M, Sasaki Y. The role of the immune system in preeclampsia. Mol Aspects Med. 2007;28(2):192-209.
195. Santner-Nanan B, Peek MJ, Khanam R, Richarts L, Zhu E, Fazekas de St Groth B, et al. Systemic increase in the ratio between Foxp3+ and IL-17-producing CD4+ T cells in healthy pregnancy but not in preeclampsia. J Immunol. 2009;183(11):7023-30.
196. Vargas-Rojas MI, Solleiro-Villavicencio H, Soto-Vega E. Th1, Th2, Th17 and Treg levels in umbilical cord blood in preeclampsia. J Matern Fetal Neonatal Med. 2016;29(10):1642-5.
197. Santner-Nanan B, Straubinger K, Hsu P, Parnell G, Tang B, Xu B, et al. Fetal-maternal alignment of regulatory T cells correlates with IL-10 and Bcl-2 upregulation in pregnancy. J Immunol. 2013;191(1):145-53.
198. Martino DJ, Bosco A, McKenna KL, Hollams E, Mok D, Holt PG, et al. T-cell activation genes differentially expressed at birth in CD4+ T-cells from children who develop IgE food allergy. Allergy. 2012;67(2):191-200.
199. Prescott SL, Macaubas C, Smallacombe T, Holt BJ, Sly PD, Holt PG. Development of allergen-specific T-cell memory in atopic and normal children. Lancet. 1999;353(9148):196-200.
200. Herzog EM, Eggink AJ, van der Zee M, Lagendijk J, Willemsen SP, de Jonge R, et al. The impact of early- and late-onset preeclampsia on umbilical cord blood cell populations. J Reprod Immunol. 2016;116:81-5.
201. Westerberg AC, Henriksen C, Ellingvag A, Veierod MB, Juliusson PB, Nakstad B, et al. First year growth among very low birth weight infants. Acta Paediatr. 2010;99(4):556-62.
202. Ong KK, Preece MA, Emmett PM, Ahmed ML, Dunger DB, Team AS. Size at birth and early childhood growth in relation to maternal smoking, parity and infant breast-feeding: longitudinal birth cohort study and analysis. Pediatr Res. 2002;52(6):863-7.

203. Druet C, Ong KK. Early childhood predictors of adult body composition. Best Pract Res Clin Endocrinol Metab. 2008;22(3):489-502.
204. Vatten LJ, Odegard RA, Nilsen ST, Salvesen KA, Austgulen R. Relationship of insulin-like growth factor-I and insulin-like growth factor binding proteins in umbilical cord plasma to preeclampsia and infant birth weight. Obstet Gynecol. 2002;99(1):85-90.
205. Dubova EA, Pavlov KA, Lyapin VM, Kulikova GV, Shchyogolev AI, Sukhikh GT. Expression of insulin-like growth factors in the placenta in preeclampsia. Bull Exp Biol Med. 2014;157(1):103-7.
206. Beardsall K, Vanhaesebrouck S, Frystyk J, Ogilvy-Stuart AL, Vanhole C, van Weissenbruch M, et al. Relationship between insulin-like growth factor I levels, early insulin treatment, and clinical outcomes of very low birth weight infants. J Pediatr. 2014;164(5):1038-44 e1.
207. Lanes R, Nieto C, Bruguera C, Moncada G, Moret LA, Lifshitz F. Growth hormone release in response to growth hormone-releasing hormone in term and preterm neonates. Biol Neonate. 1989;56(5):252-6.
208. Guasti L, Silvennoinen S, Bulstrode NW, Ferretti P, Sankilampi U, Dunkel L. Elevated FGF21 leads to attenuated postnatal linear growth in preterm infants through GH resistance in chondrocytes. J Clin Endocrinol Metab. 2014;99(11):E2198-206.
209. Sederquist B, Fernandez-Vojvodich P, Zaman F, Savendahl L. Recent research on the growth plate: Impact of inflammatory cytokines on longitudinal bone growth. J Mol Endocrinol. 2014;53(1):T35-44.
210. Ong KK, Kennedy K, Castaneda-Gutierrez E, Forsyth S, Godfrey KM, Koletzko B, et al. Postnatal growth in preterm infants and later health outcomes: a systematic review. Acta Paediatr. 2015;104(10):974-86.
211. Yadav S, Rustogi D. Small for gestational age: growth and puberty issues. Indian Pediatr. 2015;52(2):135-40.
212. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A. 2008;105(44):17046-9.
213. Jain V, Singhal A. Catch up growth in low birth weight infants: striking a healthy balance. Rev Endocr Metab Disord. 2012;13(2):141-7.
214. Jensen RB, Thankamony A, Day F, Scott RA, Langenberg C, Kirk J, et al. Genetic markers of insulin sensitivity and insulin secretion are associated with spontaneous postnatal growth and response to growth hormone treatment in short SGA children: the North European SGA Study (NESGAS). J Clin Endocrinol Metab. 2015;100(3):E503-7.
215. Hellstrom A, Ley D, Hansen-Pupp I, Hallberg B, Lofqvist C, van Marter L, et al. Insulin-like growth factor 1 has multisystem effects on foetal and preterm infant development. Acta Paediatr. 2016;105(6):576-86.
216. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension. 2008;52(5):873-80.
217. Davidovici BB, Sattar N, Prinz J, Puig L, Emery P, Barker JN, et al. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. J Invest Dermatol. 2010;130(7):1785-96.
218. Aibar L, Puertas A, Valverde M, Carrillo MP, Montoya F. Fetal sex and perinatal outcomes. J Perinat Med. 2012;40(3):271-6.

219. Simchen MJ, Weisz B, Zilberberg E, Morag I, Weissmann-Brenner A, Sivan E, et al. Male disadvantage for neonatal complications of term infants, especially in small-for-gestational age neonates. J Matern Fetal Neonatal Med. 2014;27(8):839-43.
220. Mansson J, Fellman V, Stjernqvist K, Group ES. Extremely preterm birth affects boys more and socio-economic and neonatal variables pose sex-specific risks. Acta Paediatr. 2015;104(5):514-21.
221. Redman C. Pre-eclampsia: A complex and variable disease. Pregnancy hypertens. 2014;4(3):241-2.
222. Guttmacher AE, Maddox YT, Spong CY. The Human Placenta Project: placental structure, development, and function in real time. Placenta. 2014;35(5):303-4.
223. Kramer MS, Usher RH, Pollack R, Boyd M, Usher S. Etiologic determinants of abruptio placentae. Obstet Gynecol. 1997;89(2):221-6.
224. Ananth CV, Oyelese Y, Srinivas N, Yeo L, Vintzileos AM. Preterm premature rupture of membranes, intrauterine infection, and oligohydramnios: risk factors for placental abruption. Obstet Gynecol. 2004;104(1):71-7.
225. Baron F, Hill WC. Placenta previa, placenta abruptio. Clin Obstet Gynecol. 1998;41(3):527-32.
226. Rasmussen S, Irgens LM, Dalaker K. A history of placental dysfunction and risk of placental abruption. Paediatr Perinat Epidemiol. 1999;13(1):9-21.
227. van de Loo KF, van Gelder MM, Roukema J, Roeleveld N, Merkus PJ, Verhaak CM. Prenatal maternal psychological stress and childhood asthma and wheezing: a meta-analysis. Eur Respir J. 2016;47(1):133-46.
228. Nissen SP, Kjaer HF, Host A, Nielsen J, Halken S. The natural course of sensitization and allergic diseases from childhood to adulthood. Pediatr Allergy Immunol. 2013;24(6):549-55.
229. Dietze J, Bocking C, Heverhagen JT, Voelker MN, Renz H. Obesity lowers the threshold of allergic sensitization and augments airway eosinophilia in a mouse model of asthma. Allergy. 2012;67(12):1519-29.
230. Nagel G, Koenig W, Rapp K, Wabitsch M, Zoellner I, Weiland SK. Associations of adipokines with asthma, rhinoconjunctivitis, and eczema in German schoolchildren. Pediatr Allergy Immunol. 2009;20(1):81-8.
231. Jung CC, Tsai YS, Chang CC, Cheng TJ, Chang CW, Liu PY, et al. Allergen exposure induces adipose tissue inflammation and insulin resistance. Int immunopharmacol. 2014;23(1):104-12.
232. Zhang A, Silverberg JI. Association of atopic dermatitis with being overweight and obese: a systematic review and metaanalysis. J Am Acad Dermatol. 2015;72(4):606-16 e4.
233. Eller E, Kjaer HF, Host A, Andersen KE, Bindslev-Jensen C. Development of atopic dermatitis in the DARC birth cohort. Pediatr Allergy Immunol. 2010;21(2 Pt 1):307-14.
234. Nino M, Franzese A, Ruggiero Perrino N, Balato N. The effect of obesity on skin disease and epidermal permeability barrier status in children. Pediatr Dermatol. 2012;29(5):567-70.
235. Machura E, Szczepanska M, Ziora K, Ziora D, Swietochowska E, Barc-Czarnecka M, et al. Evaluation of adipokines: apelin, visfatin, and resistin in children with atopic dermatitis. Mediators Inflamm. 2013;2013:760691.
236. Boulet LP. Asthma and obesity. Clin Exp Allergy. 2013;43(1):8-21.
237. Nova E, Martinez-Gomez D, Gomez-Martinez S, Veses AM, Calle ME, Veiga OL, et al. Influence of health behaviours on the incidence of infection and allergy in adolescents: the AFINOS cross-sectional study. BMC Public Health. 2014;14:19.

238. Luci C, Gaudy-Marqueste C, Rouzaire P, Audonnet S, Cognet C, Hennino A, et al. Peripheral natural killer cells exhibit qualitative and quantitative changes in patients with psoriasis and atopic dermatitis. Br J Dermatol. 2012;166(4):789-96.
239. Kotecha SJ, Watkins WJ, Henderson AJ, Kotecha S. The effect of birth weight on lung spirometry in white, school-aged children and adolescents born at term: a longitudinal population based observational cohort study. J Pediatr. 2015;166(5):1163-7.
240. Feng K, Chen L, Han SM, Zhu GJ. Ratio of waist circumference to chest circumference is inversely associated with lung function in Chinese children and adolescents. Respirology. 2012;17(7):1114-8.
241. ad hoc Statement Committee ATS. Mechanisms and limits of induced postnatal lung growth. Am J Respir Crit Care Med. 2004;170(3):319-43.
242. Thompson BR. Dysanapsis-Once Believed to be a Physiological Curiosity-Is Now Clinically Important. Am J Respir Crit Care Med. 2017;195(3):277-8.
243. Forno E, Weiner DJ, Mullen J, Sawicki G, Kurland G, Han YY, et al. Obesity and Airway Dysanapsis in Children with and without Asthma. Am J Respir Crit Care Med. 2017;195(3):314-23.
244. Ochs-Balcom HM, Grant BJ, Muti P, Sempos CT, Freudenheim JL, Trevisan M, et al. Pulmonary function and abdominal adiposity in the general population. Chest. 2006;129(4):853-62.
245. Maiolo C, Mohamed EI, Carbonelli MG. Body composition and respiratory function. Acta Diabetol. 2003;40 Suppl 1:S32-8.
246. Sweeting HN. Measurement and definitions of obesity in childhood and adolescence: a field guide for the uninitiated. Nutr J. 2007;6:32.
247. Perez-Padilla R, Rojas R, Torres V, Borja-Aburto V, Olaiz G, The Empece Working G. Obesity among children residing in Mexico City and its impact on lung function: a comparison with Mexican-Americans. Arch Med Res. 2006;37(1):165-71.
248. Lazarus R, Colditz G, Berkey CS, Speizer FE. Effects of body fat on ventilatory function in children and adolescents: cross-sectional findings from a random population sample of school children. Pediatr Pulmonol. 1997;24(3):187-94.
249. Wang R, Custovic A, Simpson A, Belgrave DC, Lowe LA, Murray CS. Differing associations of BMI and body fat with asthma and lung function in children. Pediatr Pulmonol. 2014;49(11):1049-57.

9. Errata

9.1 Paper I

9.1.1 Abstract

Severe maternal preeclampsia was associated with high level allergic sensitization (sum of specific IgE in serum ≥ 3.9 kU/l; the 25 percentile for all children being sensitized); odds ratio (OR): 3.79; 95 % confidence interval (CI): (1.54, 9.32); LR-p: 0.015 and with allergic rhinoconjunctivitis offspring; OR: 2.22; 95 % CI: (1.19, 4.14); LR-p: 0.047; should be:
Severe maternal preeclampsia was associated with high-level allergic sensitization (sum of specific IgE in serum ≥3.9 kU/l; the 25th percentile for all children being sensitized); odds ratio (OR): *4.05*; 95% confidence interval (CI): (*1.62, 10.1*); LR-p: *0.010* and with allergic rhinoconjunctivitis offspring; OR: *2.23*; 95% CI: (*1.20, 4.17*); LR-p: *0.046.*

9.1.2 Table 1 and Figure 1

n was not correct; however, the results did not change significantly when n was corrected as shown in Paper II, Table 1. Owing to the wrong merging of files, three participants were coded two times in the data file used for Paper I; however, this was corrected in Paper II. Therefore, it appeared to be 617in the first follow-up and 470 participants in the second follow-up, but the correct numbers should be 614 and 468, respectively.

10. Appendix

10.1.1 Questionnaire from the first follow-up administered to the mothers

Spørreskjema til mor

Del 1: Om svangerskapet ditt (Fyll inn eller kryss av for rett svar)

1. Hva var barnets fødselsvekt?

☐☐☐☐ gram ☐ Husker ikke

2 Hva var barnets fødselslengde?

☐☐ Centimeter ☐ Husker ikke

3. a) Hva var datoen for termin til dette barnet?

☐☐ Dag ☐☐ Måned 1 9 ☐☐ År

b) Dersom du ikke husker nøyaktig dato for termin, ble barnet født
(Kryss av bare en gang)

- ☐ Mer enn 8 uker for tidlig?
- ☐ 4 - 8 uker for tidlig?
- ☐ 2 – 4 uker for tidlig?
- ☐ Mindre enn 2 uker før termin?
- ☐ Ved termin
- ☐ Mindre enn to uker over tiden
- ☐ Mer enn to uker over tiden?
- ☐ Husker ikke når jeg hadde termin

4. Hva var din vanlige vekt før du ble gravid med dette barnet?
(Vær snill å gi et anslag dersom du er usikker.)

☐☐☐ Kg

5. Omtrent hvor mye la du på deg i løpet av svangerskapet? *(Kryss av en gang)*

- ☐ Mindre enn 5 kg
- ☐ 5 – 7 kg
- ☐ 7 – 10 kg
- ☐ 10 – 15 kg
- ☐ 15 – 20 kg
- ☐ Mer enn 20 kg
- ☐ Husker ikke

6. a) Gikk du til svangerskapsundersøkelser hos lege / jordmor?

☐ Ja ☐ Nei *(gå til spørsmål 7)*

→ b) Når gikk du til svangerskapsundersøkelse første gang? *(Kryss en gang)*

- ☐ I løpet av de første tre månedene av svangerskapet
- ☐ Etter de tre første, men før jeg var seks måneder på vei
- ☐ I løpet av de siste tre månedene av svangerskapet

c) Ble barnet forløst på vanlig måte eller med keisersnitt? *(Kryss en gang)*

☐ På vanlig måte ☐ Keisersnitt

7. Ble det brukt tang eller vakuum da du fødte dette barnet?

☐ Ja ☐ Nei ☐ Vet ikke

8. Hadde du morgenkvalme i dette svangerskapet?

☐ Ja ☐ Nei *(Gå til spørsmål 9)*

→ a) Hvordan vil du beskrive kvalmen? *(Sett ett kryss)*

- ☐ Mild (ikke oppkast)
- ☐ Moderat (noe oppkast)
- ☐ Alvorlig (mye oppkast)

b) Når i svangerskapet hadde du morgenkvalme? *(Ett eller flere kryss)*

- ☐ I de første tre månedene
- ☐ I de neste tre månedene
- ☐ I de siste tre månedene

c) Oppsøkte du lege eller jordmor på grunn av kvalmen?

☐ Ja ☐ Nei

9. I løpet av dette svangerskapet, fikk du noen av følgende typer medikamenter av din lege? *(Kryss ja eller nei for hver linje)*

a) Sovemedisin?	☐ Ja	☐ Nei
b) Medisin mot kvalme?	☐ Ja	☐ Nei
c) Kortison i tablettform (f.eks. Prednisolon tabletter)	☐ Ja	☐ Nei

10. Ble noen av diagnosene nedenfor stilt av din lege eller din jordmor i løpet av dette svangerskapet? *(Kryss ja eller nei på hver linje)*

a) Anemi (jernmangel).....	☐ Ja	☐ Nei
Tok du jerntilskudd i dette svangerskapet?...	☐ Ja	☐ Nei
b) Diabetes.....	☐ Ja	☐ Nei
Hvis ja, tok du insulin?.....	☐ Ja	☐ Nei
c) Høyt blodtrykk.....	☐ Ja	☐ Nei
d) Svangerskapsforgiftning (preeklampsi).....	☐ Ja	☐ Nei
e) Protein i urinen.....	☐ Ja	☐ Nei
f) Infeksjon (nyrene, luftveiene).....	☐ Ja	☐ Nei

11. a) Tok du vitamintilskudd I løpet av dette svangerskapet?

☐ Ja ☐ Nei

→ b) Tok du vitaminer regelmessig (hver dag)?

☐ Ja ☐ Nei

12. a) Var du noen gang innlagt på sykehus I løpet av svangerskapet – unntatt når du skulle føde?

☐ Ja ☐ Nei

→ b) Når i svangerskapet? *(Kryss av der det passer)*

☐ Første tre måneder
☐ Neste tre måneder
☐ Tre siste måneder

c) Hva var hovedgrunnen til innleggelsen?

- ☐ Sykdom som hadde med svangerskapet å gjøre
- ☐ Sykdom som ikke hadde noe med svangerskapet å gjøre
  (Vær snill å spesifisere)

  _____
- ☐ Skade (for eks. bilulykke)

13. Hvordan vil du beskrive din fysiske aktivitet utenom hjemmet (på arbeid) i løpet av dette svangerskapet? *(Kryss en gang)*

- ☐ Mest sitting og ståing
- ☐ Mest gåing, og noe sitting og ståing
- ☐ Mest tungt arbeid med en del gåing og ståing, men lite sitting
- ☐ *Spørsmålet passer ikke for min situasjon*

14. Hvordan vil du beskrive din fysiske aktivitet hjemme i dette svangerskapet? *(Sett ett kryss)*

- ☐ Mest sitting
- ☐ Mest gåing og ståing, og noe sitting
- ☐ For det meste aktivt husarbeid med lite sitting
- ☐ Tungt kroppsarbeid hjemme

15. Hvordan vil du beskrive din fysiske aktivitet i dette svangerskapet når du verken var hjemme eller på arbeid? *(Sett ett kryss)*

- ☐ Svært aktiv (tilsvarer å gå minst 5 kilometer hver dag)
- ☐ Nokså aktiv (tilsvarer å gå opptil 3 kilometer hver dag)
- ☐ Aktiv (tilsvarer å gå mellom 1 og 2 kilometer hver dag)
- ☐ For det meste lite aktiv (tilsvarer å gå mindre enn 1 kilometer hver dag)
- ☐ Lite aktiv (ikke regelmessig gåing eller fysisk trening)

16. Hvordan vil du beskrive din fysiske aktivitet i andre halvdel av svangerskapet? *(Kryss en gang)*

- ☐ Omtrent som i første halvdel
- ☐ Betydelig økt
- ☐ Betydelig redusert

17. Røykte du noen gang i dette svangerskapet?

☐ Ja ☐ Nei *(Gå til spørsmål 18)*

→ a) Vær snill å krysse av antallet sigaretter som du røykte daglig.
[1 pakke = 20 sigaretter] *(Sett ett kryss)*

☐ 1-4 sigaretter daglig
☐ 5-9 sigaretter daglig
☐ 10-14 sigaretter daglig
☐ 15-24 sigaretter daglig
☐ 25 eller flere sigaretter daglig

b) Sluttet du å røyke i dette svangerskapet?

☐ Ja ☐ Nei *(Gå til spørsmål 18)*

→ d) Når i svangerskapet sluttet du? *(Sett ett kryss)*

☐ I løpet av de tre første månedene
☐ I løpet av de neste tre månedene
☐ I løpet av de siste tre månedene

18. Hvor mange års utdanning hadde du da dette barnet ble født?
(Sett ett kryss)

☐ Mindre enn 9 års skolegang
☐ 9 års skolegang
☐ 1 – 2 år videregående
☐ Videregående (3 år)
☐ 1 - 3 år etter videregående
☐ 4 år eller mer etter videregående

19. Eide du/dere et sted å bo da barnet ble født?

☐ Ja ☐ Nei

20. a) Vi vil gjerne vite hva slags arbeid du hadde i dette svangerskapet. Kryss av det som passer best.

☐ lærer, bibliotekar, lege, advokat
☐ sykepleier
☐ daglig leder, administrator
☐ ekspeditør I butikk, sekretær
☐ fagarbeider
☐ maskinoperatør, sjåfør
☐ husholder, vaktmester, kelner, renholdsarbeider

- ☐ ufaglært arbeider
- ☐ bonde, landbruksarbeider
- ☐ husmor
- ☐ student/skoleelev
- ☐ hadde ikke arbeid

b) Vi vil også vite om du hadde noe arbeid i småbarnsperioden. Vær snill å krysse av det som passer best.

- ☐ lærer, bibliotekar, lege, advokat
- ☐ sykepleier
- ☐ daglig leder, administrator
- ☐ ekspeditør I butikk, sekretær
- ☐ fagarbeider
- ☐ maskinoperatør, sjåfør
- ☐ husholder, vaktmester, kelner, renholdsarbeider
- ☐ ufaglært arbeider
- ☐ bonde, landbruksarbeider
- ☐ husmor
- ☐ hadde ikke arbeid

21. a) Bodde du sammen med barnets biologiske far da barnet ble født ?

☐ Ja ☐ Nei *(Gå til spørsmål 22)*

→ b) Hvor mange års skolegang hadde barnets far da barnet ble født? *(Kryss ett sted)*

- ☐ Mindre enn 9 års skolegang
- ☐ 9 år
- ☐ 1 – 2 års videregående
- ☐ 3 års videregående
- ☐ 1 - 3 år etter videregående
- ☐ 4 år eller mer etter videregående

c) Hva slags arbeid hadde barnets far de første årene etter fødselen. Kryss av for det alternativet som passer best. ved fødselen og de første årene etter fødselen. Kryss av det alternativet som passer best.

- ☐ lærer, bibliotekar, lege, advokat
- ☐ sykepleier
- ☐ daglig leder, administrator
- ☐ ekspeditør I butikk, sekretær
- ☐ fagarbeider

- ☐ maskinoperatør, sjåfør
- ☐ husholder, vaktmester, kelner, renholdsarbeider
- ☐ ufaglært arbeider
- ☐ bonde, landbruksarbeider
- ☐ husmor
- ☐ hadde ikke arbeid

22. a) Pleide barnets far å røyke da du var gravid – eller da barnet var nyfødt?

☐ Ja ☐ Nei *(Gå til 22d)*

→ b) Spesifiser når han røykte. *(Kryss ett sted)*

- ☐ Da du var gravid
- ☐ Da barnet var nyfødt
- ☐ Begge deler

c) Omtrent hvor mye røykte han daglig?.
(Kryss ett sted)

- ☐ 1-14 sigaretter daglig
- ☐ 15-24 sigaretter daglig
- ☐ 25-34 sigaretter daglig
- ☐ 35 sigaretter eller mer daglig

d) Pleide barnets far/din samboer å røyke pipe eller sigar daglig?

☐ Ja ☐ Nei

Del 2: Ditt kosthold i svangerskapet

I denne delen spør vi hva du pleide å drikke da du var gravid. For hvert spørsmål vil vi be deg å krysse av hvor mye du drakk av de følgende drikkevarene. Prøv å gi et gjennomsnitt for hele svangerskapet.

23. Hvor mye kaffe drakk du daglig i dette svangerskapet? *(Ikke ta med koffeinfri kaffe)*

- ☐ Drakk ikke kaffe
- ☐ Mindre enn en kopp daglig
- ☐ 1 – 2 kopper daglig
- ☐ 3 – 4 kopper daglig

☐ 5 kopper eller mer daglig

☐ Husker ikke

24. Hvor mye te drakk du daglig i dette svangerskapet? *(Ikke ta med urtete eller te uten koffein)*

☐ Drakk ikke te

☐ Mindre enn en kopp daglig

☐ 1 – 2 kopper daglig

☐ 3 – 4 kopper daglig

☐ 5 kopper eller mer daglig

☐ Husker ikke

25. Hvor ofte drakk du alkoholholdige drikkevarer i dette svangerskapet?

For å sammenligne ulike typer alkohol spør vi etter det vi kaller alkoholenheter. En alkoholenhet tilsvarer:
1 flaske rusbrus/cider,
1 glass (1/3 liter) øl,
1 vinglass rød eller hvitvin,
1 hetvinsglass sherry eller annen hetvin,
1 drammeglass brennevin eller likør

☐ Drakk ikke alkohol da jeg var gravid

☐ Mindre enn en alkoholenhet i uken

☐ 1 – 2 alkoholenheter i uken

☐ 3 – 6 alkoholenheter i uken

☐ 1 alkoholenhet daglig

☐ 2 –3 alkoholenheter daglig

☐ 4 alkoholenheter eller mer daglig

☐ Husker ikke

Del 3: Om barnet i spedbarnsperioden

I denne delen spør vi om barnet i spedbarnsperioden – dvs i første leveår.

26. Dersom du fikk en jente, la du noen gang merke til om det var friskt blod i bleien ("spedbarns-mens") de første levedagene?

☐ Ja ☐ Nei ☐ Jeg fikk en gutt

27. Hos mange babyer kommer det hvit væske fra brystvortene de første dagene etter fødselen. La du merke til om det kom hvit væske ut av brystvortene til barnet omtrent en måned etter fødselen?

☐ Ja ☐ Nei

28. a) Hadde barnet noen gang betennelse i brystet (rød hevelse) tidlig i spedbarnsperioden?

☐ Ja ☐ Nei *(Gå til spørsmål 29)*

→ b) Måtte betennelsen fjernes kirurgisk? ☐ Ja ☐ Nei

29. La du merke til om barnets bryster var unormalt store før to års alder?

☐ Ja ☐ Nei

30. a) Ammet du barnet?

☐ Ja ☐ Nei *(Gå til spørsmål 31)*

→ b) **Hvis ja**, hvor lenge ammet du? *(Kryss ett sted)*

☐ Mindre enn en uke
☐ 1 uke – 3 måneder
☐ 3 – 6 måneder
☐ 6 – 9 måneder
☐ 9 – 12 måneder
☐ Ett år eller mer

31. a) Fikk barnet fabrikkfremstilt morsmelkerstatning (f.eks. Nan, Collett e.l.) daglig?

☐ Ja ☐ Nei *(Gå til spørsmål 33)*

→ b) Når begynte du å gi barnet dette?

☐ Før 3 måneders alder
☐ 3 – 6 måneders alder
☐ 6 – 9 måneder
☐ 9 måneder eller eldre

c) Når sluttet du? *(Kryss ett sted)*

☐ Før barnet var en uke
☐ 1 uke – 3 måneder
☐ 3 – 6 måneder
☐ 6 – 9 måneder
☐ 9 – 12 måneder
☐ Ett år eller mer

32. a) Fikk barnet soya-melk (Soya-semp) daglig?

☐ Ja ☐ Nei *(Gå til spørsmål 34)*

→ a) Når begynte du å gi barnet dette? *(Kryss ett sted)*

☐ Før 3 måneders alder
☐ 3 – 6 måneders alder
☐ 6 – 9 måneder
☐ 9 måneder eller eldre

b) Når sluttet du? *(Kryss ett sted)*

☐ Før barnet var en uke
☐ 1 uke – 3 måneder
☐ 3 – 6 måneder
☐ 6 – 9 måneder
☐ 9 – 12 måneder
☐ Ett år eller mer

33. Fikk barnet Nutramigen daglig?

a)

☐ Ja ☐ Nei

→ b) Når begynte du å gi dette til barnet Nutramigen? *(Kryss ett sted)*

☐ Før 3 måneders alder
☐ 3 – 6 måneder
☐ 6 – 9 måneder
☐ 9 måneder eller eldre

c) Når sluttet du å gi dette til barnet ? *(Kryss ett sted)*

☐ Før barnet var en uke
☐ 1 uke – 3 måneders alder
☐ 3 – 6 måneder
☐ 6 – 9 måneder
☐ 9 – 12 måneder
☐ Ett år eller mer

34. Når begynte du å gi barnet vanlig kumelk? *(Kryss ett sted)*

☐ Fikk ikke kumelk
☐ Før 3 måneders alder
☐ 3 – 6 måneder
☐ 6 – 9 måneder
☐ 9 måneder eller eldre

35. Når begynte du å gi barnet fast føde? *(Kryss ett sted)*

☐ Før 3 måneders alder
☐ 3 – 6 måneder
☐ 6 - 9 måneder
☐ 9 måneder elle eldre

36. Hva var den første faste maten du begynte med? *(Kryss ett sted)*

☐ Grøt
☐ Frukt
☐ Grønnsaker / potet

☐ Brød, kjeks

Del 4: Kostholdet til barnet før skolealder

I denne delen spør vi om maten barnet spiste i førskolealder (3-6 år). Prøv å tenke godt etter, og kryss av hvor ofte barnet spiste følgende matvarer. Det er ikke meningen å spørre om alt barnet spiste.

37. a) Hva slags melk drakk barnet for det meste ?
[Kryss ett sted]

☐ Helmelk
☐ Lettmelk
☐ Skummet melk
☐ annen melk (soyamelk, geitemelk)

b) Hvor ofte drakk barnet melk ? *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 glass i måneden
☐ 1 – 4 glass i uken
☐ 5 – 6 glass i uken
☐ 1 glass daglig
☐ 2 – 3 glass daglig
☐ minst 4 glass daglig

38. **Iskrem** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ 1 gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

39. **Ost** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 skiver i måneden
☐ 1 skive i uken
☐ 2 – 4 skiver i uken
☐ 5 – 6 skiver i uken
☐ 1 skive om dagen
☐ 2 eller flere skiver daglig

40. **Margarin** (mengde som trengs til å smøre en brødskive) *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ 1 gang i uken
☐ 2 – 6 ganger i uken
☐ 1 gang daglig
☐ 2 – 4 ganger daglig
☐ 5 ganger eller mer daglig

41. **Smør** (mengde som trengs til å smøre en brødskive) *[Kryss ett sted]*

☐ Aldri
☐ 1 gang daglig

☐ 1 – 3 ganger i måneden
☐ 1 gang i uken
☐ 2 – 6 ganger i uken
☐ 2 – 4 ganger daglig
☐ 5 ganger eller mer daglig

42. **Peanøttsmør** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

43. **Majones** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

44. **Epler** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 i måneden
☐ Ett i uken
☐ 2 – 4 i uken
☐ 5 – 6 i uken
☐ Ett eller flere om dagen

45. **Bananer** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 i måneden
☐ En i uken
☐ 2 – 4 per uke
☐ 5 – 6 per uke
☐ En eller flere om dagen

46. **Rosiner** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ 1 gang i uken
☐ 2 – 4 ganger i uken
☐ 5 – 6 ganger i uken
☐ 1 ganger eller mer om dagen

47. **Appelsiner** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 i måneden
☐ En i uken
☐ 2 – 4 i uken
☐ 5 eller flere i uken
☐ En eller flere om dagen

48. **Appelsinjuice** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 glass i måneden
☐ 1 glass daglig
☐ 2 – 3 glass daglig

☐ 1 – 4 glass i uken
☐ 5 – 6 glass i uken
☐ 4 glass eller mer daglig

49. **Eplejuice** *[Sett ett kryss]*

☐ Aldri
☐ 1 – 3 glass i måneden
☐ 1 – 4 glass i uken
☐ 5 – 6 glass i uken
☐ 1 glass daglig
☐ 2 – 3 glass daglig
☐ 4 glass eller mer daglig

50. **Brokkoli** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

51. **Gulrøtter** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

52. **Brekkbønner** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

53. **Erter** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

54. **Mais** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

55. **Spinat** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

☐ En gang i uken

56. **Egg** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 egg i måneden
☐ 1 egg i uken
☐ 2 – 4 egg i uken
☐ 5 egg eller mer i uken

57. **Pølser** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

58. **Kjøttpålegg** (for eks. fårepølse, salami, servelat, bacon) *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

59. **Mat av kjøttdeig** (for eksempel kjøttkaker, hamburger, kjøttpudding) *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

60. **Kjøtt av storfe, svin, lam** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

61. **Kylling eller kalkun** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

62. **Fisk eller annen sjømat** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

☐ En gang i uken

63. **Lever** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

64. **Tomat- eller spagettisaus** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

65. **Pizza** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

66. **Pasta** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

67. **Brød** *[Kryss ett sted]*

☐ Aldri
☐ 1 skive eller mindre i uken
☐ 2 – 4 skiver i uken
☐ 5 – 7 skiver i uken
☐ 2 – 3 skiver daglig
☐ 4 skiver eller mer daglig

68. **Bakervarer** (for eks. småkaker, kjeks, boller, muffins, wienerbrød og liknende) *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

69. **Ris** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

☐ En gang i uken

70. **Frokostblanding** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 porsjoner i måneden
☐ 1 porsjon i uken
☐ 2 – 4 porsjoner per uke
☐ 5 – 7 porsjoner i uken
☐ 2 eller flere porsjoner daglig

71. **Kokte poteter** *[Kryss ett sted]*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

72. a) Spiste barnet stekte poteter eller pommes frites i førskolealder?

☐ Ja ☐ Nei *(gå til spørsmål 73)*

→ b) Hvor ofte spiste barnet pommes frites/stekte poteter? *(Kryss ett sted)*

☐ Noen få ganger
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 eller flere ganger i uken

c) Var potetene vanligvis stekt: *(Kryss ett sted)*

☐ Fra frossen tilstand i pannen eller i stekeovnen
☐ I gatekjøkken eller "fast food" kafe (for eks., McDonald's eller liknende)
☐ Laget og stekt hjemme ***(Hvis ja,** gå til spørsmål 72d)*

↓

d) Dersom du laget pommes frites hjemme, hva slags fett brukte du til stekingen? *(Kryss ett sted)*

☐ Smør
☐ Kyllingfett
☐ Planteolje
☐ Plantemargarin

73. Hvor ofte spiste barnet andre typer stekte poteter (f.eks. potetgull) enn pommes frites? *[Kryss ett sted]*

☐ Aldri
☐ 2 – 4 ganger i uken

☐ 1 – 3 ganger i måneden
☐ 5 ganger eller mer i uken
☐ En gang i uken

74. Hva slags fett brukte du vanligvis til å steke mat (for eks., stekt fisk, kjøtt, kylling)
[Sett kryss for det som passer]

☐ Smør
☐ Margarin
☐ Fast plantefett
☐ Dyrefett
☐ Kyllingfett
☐ Planteolje
☐ Olivenolje
☐ Maisolje
☐ Solsikkeolje
☐ Bruker ikke stekefett

75. Pleide barnet å få vitaminpiller i førskolealderen? *(Kryss ett sted)*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

76. Pleide barnet å ta tran i førskolealderen? *(Kryss ett sted)*

☐ Aldri
☐ 1 – 3 ganger i måneden
☐ En gang i uken
☐ 2 – 4 ganger i uken
☐ 5 ganger eller mer i uken

Del 5: Om barnets aktiviteter

77. Tenk gjennom hva slags aktiviteter barnet ditt drev med i 3-6 årsalderen. Hvordan vil du beskrive aktivitetsnivået sammenliknet med andre barn på samme alder? *(Kryss ett sted)*

☐ Svært fysisk aktiv (løp og lekte det meste av tiden)
☐ Aktiv
☐ Ikke så aktiv
☐ Lite aktiv (syslet med stillesittende ting for det meste)

78. I 3-6 årsalderen, hvor mange timer daglig brukte barnet å se på TV?
(Kryss ett sted)

☐ Så ikke TV
☐ Opp til ½ time daglig
☐ Omtrent 1 time daglig
☐ Omtrent 3 timer daglig
☐ 4 timer daglig
☐ 5 timer eller mer daglig

☐ Omtrent 2 timer daglig

79. Tenk over aktivitetene til dette barnet etter 6 års alder.
Hvordan vil du beskrive aktivitetsnivået sammenliknet med barn på samme alder?
(Kryss ett sted)

☐ Svært fysisk aktiv (løp og lekte det meste av tiden)
☐ Aktiv
☐ Ikke så aktiv
☐ Lite aktiv (leste og drev med andre stillesittende sysler det meste av tiden)

80. I 6-10 årsalder, hvor mange timer daglig brukte barnet å se på TV?
(Kryss ett sted)

☐ Så ikke på TV
☐ Opp til ½ time daglig
☐ Omtrent 1 time daglig
☐ Omtrent 2 timer daglig
☐ Omtrent 3 timer daglig
☐ 4 timer daglig
☐ 5 timer eller mer daglig

81. Har barnet noen gang hatt en av de følgende sykdommene?
(Kryss Ja eller Nei for hver sykdom)

a) Diabetes	☐ Ja	☐ Nei
b) Lungebetennelse	☐ Ja	☐ Nei
c) Urinveisinfeksjon/nyrebekkeninfeksjon	☐ Ja	☐ Nei
d) Astma (diagnose satt av lege)	☐ Ja	☐ Nei
e) Allergi i øyne / nese ("høysnue")	☐ Ja	☐ Nei
f) Atopisk eksem ("barne-eksem")	☐ Ja	☐ Nei
g) Innlagt sykehus, *spesifiser* _____	☐ Ja	☐ Nei
h) Kreft, *spesifiser* _____	☐ Ja	☐ Nei
i) Fjernet mandler	☐ Ja	☐ Nei
j) Annen bakterieinfeksjon, *spesifiser* _____	☐ Ja	☐ Nei

82. a) Bruker barnet noen form for medisiner nå?

☐ Ja ☐ Nei

└▸ b) *Hvis ja, vær snill å spesifiser hvilken medisin*

_____

Del 6: Noen spørsmål om deg

83. Når ble du født?

				1	9		

Dag Måned År

84. Hva var din fødselsvekt?

- ☐ Mindre enn 2.5 kg
- ☐ 2.5 – 3.9 kg
- ☐ 4 – 4.5 kg
- ☐ Over 4.5 kg
- ☐ Vet ikke

85. Ble du født i Norge?

- ☐ Ja
- ☐ Nei

86. Hva er din ekteskapelige status? *(Kryss ett sted)*

- ☐ Gift/samboer
- ☐ Separert
- ☐ Skilt
- ☐ Enke
- ☐ Aldri vært gift eller samboende

87. Hvor høy er du?

Centimeter

88. Dersom du legger på deg, hvor på kroppen vises det best? *(Kryss av det som passer)*

- ☐ Rundt brystet og skuldrene
- ☐ Rundt midjen/magen
- ☐ Rundt hoftene/lårene
- ☐ Omtrent likt over det hele
- ☐ Annet *(Spesifiser)* _____
- ☐ Legger aldri på meg

89. Hvilken rase tilhører du? *(Kryss av det som passer)*

- ☐ Europeisk/hvit
- ☐ Asiatisk
- ☐ Afrikansk/svart

☐ Latinamerikansk ☐ Annet (*Spesifiser):*_____

90. Hvor gammel var du da du fikk menstruasjon første gang? *(Kryss ett sted)*

☐ Yngre enn 11 år	☐ 14 år	☐ 18 år eller mer
☐ 11 år	☐ 15 år	☐ Husker ikke
☐ 12 år	☐ 16 år	
☐ 13 år	☐ 17 år	

91. Hva er som regel lengden på en vanlig menstruasjonssyklus for deg? (antall dager fra første blødningsdag til første blødningsdag i neste syklus) *[Kryss ett sted]*

☐ Mindre enn 21 dager	☐ 40 dager eller mer
☐ 21 – 25 dager	☐ Svært uregelmessig
☐ 26 – 31 dager	☐ Har sluttet å menstruere
☐ 32 – 39 dager	

92. a) Vi vil gjerne vite mer om alle dine svangerskap som har vart i minst 6 måneder. [G = Gutt; J = Jente]

Fødedato (dag/måned/år)		**Kjønn**
	☐ Dødfødt ☐ Levende født	☐ G ☐ J
	☐ Dødfødt ☐ Levende født	☐ G ☐ J
	☐ Dødfødt ☐ Levende født	☐ G ☐ J
	☐ Dødfødt ☐ Levende født	☐ G ☐ J
	☐ Dødfødt ☐ Levende født	☐ G ☐ J
	☐ Dødfødt ☐ Levende født	☐ G ☐ J

b) Har du noen gang opplevd å ha en spontanabort?

☐ Ja ☐ Nei *(Gå til spørsmål 93)*

→ Hvor mange ganger? ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 eller flere

93. Har du noen gang prøvd å bli gravid i mer enn ett år uten å lykkes?

☐ Ja ☐ Nei

94. Har du eller din partner brukt noen form for prevensjon de siste 12 månedene ?

☐ Ja *(Gå til spørsmål 95)*

☐ Nei

☐ Vil helst ikke svare

(gå til spørsmål 96)

95. Kryss av for de prevensjonsmetodene som dere har brukt de siste 12 månedene.

☐ P-pille
☐ P-ring
☐ Hormonsprøyte ("P-sprøyte")
☐ Hormonimplantat (Implanon®)
☐ Kondomer
☐ Sæddrepende salve, krem eller gele
☐ Pessar
☐ Kobberspiral
☐ Hormonspiral
☐ Sterilisering - kvinnen
☐ Sterilisering (vasektomi) - mannen
☐ "Sikre" perioder
☐ Avbrutt samleie
☐ Andre metoder *(Spesifiser)* _____

96. Er du gravid nå?

☐ Ja
☐ Nei

97. Har du fått fjernet livmoren ?

☐ Ja
☐ Nei

98. a) Har du noen gang hatt forhøyet blodtrykk (målt av lege) uten at du har vært gravid?

☐ Ja ☐ Nei *(Gå til spørsmål 99)*

→ b) Hvor gammel var du da du fikk diagnosen forhøyet blodtrykk?

_____år

99. a) Har du noen gang fått diagnosen endometriose?

☐ Ja ☐ Nei *(gå til spørsmål 100)*

→ c) Hvor gammel var du da du fikk diagnosen? _____år

100. a) Har du noen gang fått diagnosen polycystisk ovariesyndrom (PCO)?

☐ Ja ☐ Nei *(gå til spørsmål 101)*

→ d) Hvor gammel var du da du fikk diagnosen?_____år

101. a) Har du noen gang hatt brystkreft?

☐ Ja ☐ Nei *(gå til spørsmål 104)*

→ b) Hvor gammel var du da du fikk diagnosen?_____år

102. Har din biologiske mor hatt brystkreft?

☐ Ja ☐ Nei ☐ Vet ikke

103. a) Hadde din biologiske mor noen gang svangerskapsforgiftning (preeklampsi)?

☐ Ja ☐ Nei *(gå til spørsmål 104)* ☐ Vet ikke

→ b) Da hun var gravid med deg?

☐ Ja ☐ Nei

→ c) Da hun var gravid med

☐ en bror av deg

☐ en søster av deg

104. a) Har du noen biologiske søstre? (Ta med avdøde, men ikke ta med halvsøsken)

☐ Ja ☐ Nei *(gå til spørsmål 105)*

→ b) Hvor mange?

☐ 1 ☐ 3

☐ 2 ☐ 4 eller flere

c) Har noen av dem hatt brystkreft?

☐ Ja ☐ Nei *(gå til spørsmål 105)* ☐ Vet ikke

d) Hvor gammel var hun da hun fikk sykdommen?

Søsters alder	☐ Under 45	☐ 50 – 55
	☐ 45 – 49	☐ 56 og eldre
Søsters alder	☐ Under 45	☐ 50 – 55
	☐ 45 – 49	☐ 56 og eldre
Søsters alder	☐ Under 45	☐ 50 – 55
	☐ 45 – 49	☐ 56 og eldre

e) Vet du om noen av dem hadde preeklampsi (svangerskapsforgifning)?

☐ Ja ☐ Nei *(gå til spørsmål 105)*

f) Hvor mange ganger? ☐ 1 ☐ 2 ☐ 3 ☐ 4 eller flere

105. Har du noen gang hatt noen av disse sykdommene?
(Kryss Ja eller Nei for hver enkelt)

a)	Diabetes	☐ Ja	☐ Nei
b)	Polypper i livmoren eller livmorhalsen	☐ Ja	☐ Nei
c)	Fibrom i livmoren	☐ Ja	☐ Nei
d)	Hjerteinfarkt	☐ Ja	☐ Nei
e)	Astma (diagnosert av lege)	☐ Ja	☐ Nei
f)	Godartet cyste / knuter i brystet	☐ Ja	☐ Nei
g)	Livmorhalskreft	☐ Ja	☐ Nei
h)	Kreft i livmoren (endometrium)	☐ Ja	☐ Nei
i)	Eggstokkreft	☐ Ja	☐ Nei
j)	Tykktarm- eller endetarmskreft	☐ Ja	☐ Nei
k)	Brystkreft	☐ Ja	☐ Nei
l)	Lungekreft	☐ Ja	☐ Nei

m) Annen kreftsykdom..... ☐ Ja ☐ Nei

106. a) Bruker du noen form for medisin nå?

☐ Ja ☐ Nei

b) Hvis ja, kan du spesifisere

_____

106. Fylte du ut dette skjemaet ut fra hukommelsen, eller brukte du noen "hjelpemidler"?:
(Sett kryss for det som passer)

☐ På egen hånd ut fra hukommelsen

☐ Jeg måtte se etter i babybok, helsestasjonskort eller liknende

☐ Jeg måtte ha hjelp (av partner, slektning, venn)

_____

Takk for hjelpen!

10.1.2 ISAAC questionnaire

Om lungene dine:

15. Har du noen gang hatt tung pust eller piping/surkling/tetthet i brystet ?

☐ ja
☐ nei
Hvis du har svart nei, gå til spørsmål 20

16. Har du hatt tung pust eller piping/surkling/tetthet i brystet i løpet av de siste 12 måneder ?

☐ ja
☐ nei
Hvis du har svart nei, gå til spørsmål 20

17. Hvor mange anfall av tung pust eller piping/surkling/tetthet i brystet har du hatt i løpet av de siste 12 måneder ?

☐ ingen
☐ 1 til 3
☐ 4 til 12
☐ mer enn 12

18. Hvor ofte har din søvn i gjennomsnitt blitt forstyrret på grunn av tung pust eller piping/surkling/tetthet i brystet de siste 12 måneder ?

☐ aldri våknet
☐ mindre enn 1 natt pr. uke
☐ 1 eller flere netter pr. uke

19. Har piping/surkling/tetthet i brystet eller tung pust vært så alvorlig de siste 12 måneder at du har hatt problemer med å snakke slik at du bare kunne si ett eller to ord mellom hvert pust ?

☐ ja
☐ nei

20. Har du noen gang hatt astma ?

☐ ja
☐ nei

21. Har du i løpet av de siste 12 måneder hatt tung pust eller piping/surkling/tetthet i brystet under eller etter fysisk trening, aktiv lek eller mosjonering ?

☐ ja
☐ nei

22. Har du i løpet av de siste 12 måneder hatt tørr hoste om natten, utenom hoste i forbindelse med en forkjølelse eller andre luftveisinfeksjoner ?

☐ ja
☐ nei

23. Har du i løpet av de siste 12 måneder noen gang tatt en medisin for astma ?

☐ ja
☐ nei

11. Original publications

I

BMC Pediatrics

RESEARCH ARTICLE Open Access

Birth after preeclamptic pregnancies: association with allergic sensitization and allergic rhinoconjunctivitis in late childhood; a historically matched cohort study

Kristine Kjer Byberg[1*], Bjorn Ogland[1,2], Geir Egil Eide[3,4] and Knut Øymar[1,5]

Abstract

Background: The development of allergic sensitization and allergic disease may be related to factors during intrauterine life, but the role of maternal preeclampsia is not known.
We studied if maternal preeclampsia is associated with long-term allergic sensitization, allergic rhinoconjunctivitis, atopic dermatitis, asthma and with altered lung function in late childhood.

Methods: 617 children participated in a 1:2 matched and controlled historical cohort study; 230 born after preeclamptic pregnancies and 387 born after normotensive pregnancies. Specific IgE in serum and lung function were measured at the age of 12.8 years and questionnaires on maternal and adolescent data were completed at the ages of 10.8 years (girls) and 11.8 years (boys), and at 12.8 years (both genders). The association between birth after preeclampsia and the main outcome measures allergic sensitization, allergic rhinoconjunctivitis, atopic dermatitis, asthma and lung function in late childhood were analysed with multiple regression analyses, including possible confounders.

Results: Severe maternal preeclampsia was associated with high level allergic sensitization (sum of specific IgE in serum ≥ 3.9 kU/l; the 25 percentile for all children being sensitized); odds ratio (OR): 3.79; 95% confidence interval (CI): (1.54, 9.32); p = 0.015 and with allergic rhinoconjunctivitis in offspring; OR: 2.22, 95% CI: (1.19, 4.14), p = 0.047. Preeclampsia was not associated with atopic dermatitis, asthma or altered lung function in late childhood.

Conclusion: Maternal preeclampsia was associated with allergic sensitization and allergic rhinoconjunctivitis in offspring in late childhood, but not with other atopic diseases.

Keywords: Childhood, Allergy, Allergic rhinoconjunctivitis, Allergic sensitization, Asthma, Atopic dermatitis, Atopy, Child, Lung function, Preeclampsia

Background

The prevalence of allergy and asthma has been increasing in both adults and children during the last decades [1]. There is also increasing evidence that early life events including intrauterine factors are important for the development of atopic disease [2-4].

Atopic diseases are associated with an inhibition of the transition towards an increased T-helper cell type 1 (Th1)/Th2 balance after birth, resulting in Th2 cytokine predominance [4,5]. Maternal inflammatory cytokines during pregnancy have been shown to correlate with corresponding cytokines in offspring at the age of one [6], and an association between an altered maternal cytokine profile and subsequent atopic disease in offspring has been suggested [7].

Preeclampsia is a common and potentially serious complication of the second half of pregnancy affecting both mother and child, characterised by maternal hypertension and proteinuria, and occasionally foetal growth restriction [8,9]. Preeclampsia is associated with an increase in

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several circulating maternal cytokines, and a skewed maternal immune response towards an increased Th1/Th2 balance [10]. This could potentially skew the child's cytokine balance after birth in the same direction, and thereby protect against the development of atopic disease [6]. However, clinical studies have suggested that complications during pregnancy may rather increase the risk of childhood asthma and allergic rhinoconjunctivitis [11,12], and an association between maternal preeclampsia and subsequent allergic sensitization in offspring during adolescence has been suggested [13].

Preeclampsia has also been associated with an increased risk of RDS and BPD in preterm infants and to recurrent wheezing in a general population of preschool children [14]. This association might either be due to an increased soluble antiangiogenic factor [15], or a congenital reduction in airways calibre and compliance in particular in infants with intrauterine growth restriction [16]. However, no studies have evaluated a possible long-term association between maternal preeclampsia and asthma or lung function in offspring.

In a long–term follow-up of children of preeclamptic and normal pregnancies, the aim was to study if maternal preeclampsia is associated with allergic sensitization, allergic rhinoconjunctivitis, atopic dermatitis, asthma, and lung function in late childhood.

Methods

Study population and design

The study was a part of "the Stavanger study" described in detail elsewhere [17]. In short, cord blood was drawn from all newborns at Stavanger University Hospital during 1993–1995, during which 12 804 deliveries took place. The Medical Birth Registry of Norway was used to identify offspring exposed to maternal preeclampsia and unexposed offspring, and information was verified and supplemented with data from hospital records. All offspring of preeclamptic pregnancies were defined as exposed. For each exposed, two matched unexposed offspring were selected as follows: one was defined as the next delivery in the hospital and one as the next delivery matched on maternal age. Exposed and unexposed offspring were invited to participate in a follow-up (FU) study at the target ages of 10.8 years (girls) and 11.8 years (boys) (FU1), and a second follow-up at the target age of 12.8 years (FU2) (Figure 1). The target ages at FU1 were selected to also be able to collect puberty stage data at an age presumed to represent the start of puberty development in the children [17]. If unexposed offspring did not respond, no substitutes were invited. Consequently, the study design was a historically matched cohort with 1025 children; 366 in the preeclampsia cohort and 659 in the control cohort.

The study was approved by the Norwegian Data Inspectorate, the Regional Committee for Ethics in medical research and the Institutional Review Board of the National Cancer Institute of the United States. Written consent was obtained from all participating children and mothers at follow-up.

Data collection and definitions

Preeclampsia was defined as a diastolic blood pressure increased by ≥ 25 mmHg to a persistent pressure of ≥ 90 mmHg and proteinuria with dipstick ≥ +1 present in at least one urine sample after 20 weeks of gestation. Preeclampsia was further divided into mild, moderate and severe. Moderate preeclampsia was defined as proteinuria with dipstick ≥ +2. Severe preeclampsia was defined as

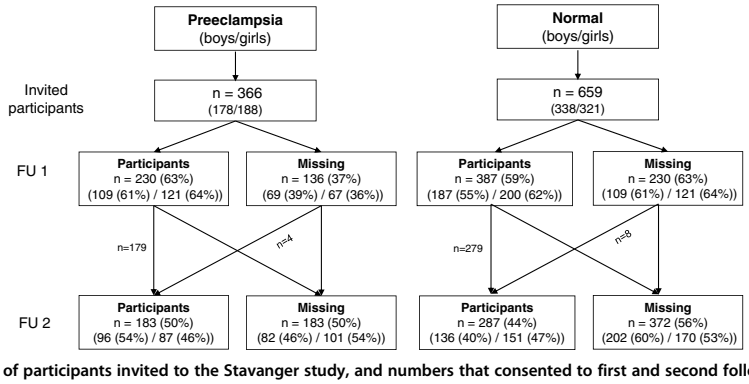

Figure 1 Number of participants invited to the Stavanger study, and numbers that consented to first and second follow-up. *Abbreviations:* FU1 = First follow-up at the ages of 10.8 years (girls) and 11.8 years (boys); FU2 = Second follow-up at the age of 12.8 years (both genders); Preeclampsia = children born after pregnancies with preeclampsia; Normal = children born after pregnancies without preeclampsia.

proteinuria with dipstick ≥ + 3 and diastolic blood pressure of ≥110 mmHg.

Maternal body mass index (BMI, kg/m^2) was calculated using weight measurement at the first antenatal visit at primary healthcare examination during the first trimester of pregnancy and height measurement from FU1. Maternal smoking in pregnancy was recorded at the same antenatal visit. Data on gestational age at birth and mode of delivery were extracted from hospital records. Birth weight for gestational age was calculated as z-scores based on Scandinavian normal standards [18]. Weight and height in offspring were recorded at FU1, and z-scores for BMI were calculated using the latest growth references for Norwegian children [19].

Questionnaires

At FU1, the questions included the birth order of the child, parental asthma, and atopic disease of the child. The mothers were asked as follows: Has your child ever had asthma (diagnosed by physician), allergy in nose/eyes (hay fever) or atopic dermatitis (childhood eczema)?

At FU2, the children answered a questionnaire from the International Study of Asthma and Allergies in Childhood (ISAAC) translated into Norwegian [20]. Reported asthma symptoms and asthma medication during the last year and asthma diagnosis ever were recorded. Missing answers were interpreted as negative. Current asthma at FU2 was defined as asthma ever, in addition to asthma symptoms or the use of asthma medication during the last 12 months.

Laboratory methods

At FU2 blood was drawn from the children, centrifuged and aliquoted, and serum stored at -80°C. Allergic sensitization was determined by serum specific immunoglobulin E (IgE) antibodies using Phadiatop® and fx5E® (ImmunoCAP® 250, Phadia AB, Uppsala, Sweden). If Phadiatop® was positive, serum was further analysed for specific IgE against *Dermatophagoides pteronyssinus*, cat, horse, dog, timothy, common silver birch, mugwort and *Cladosporium herbarum*. If fx5E® was positive, serum was further analysed for specific IgE against egg white, milk, fish (cod), wheat, peanut and soya bean. Allergic sensitization was defined as specific IgE ≥ 0.35 *kU/l* for at least one allergen. The levels of specific IgE ≥ 0.35 were added together, and high level allergic sensitization was defined as a sum > 3.9 *kU/l*; the 25 percentile for all children being sensitized.

At FU2, lung function measures were performed by spirometry according to standard quality criteria [21] with a Vmax Encore spirometer (Sensor Medics Inc., Anaheim, USA).

Statistics

Groups were compared with Pearson's chi-square exact test for the dichotomous outcomes and independent t-tests (Gosset's t-test) and one way analysis of variance for the continuous outcomes. Bonferroni-correction of p-values was applied to adjust for multiple testing.

Before analyses, the variable preeclampsia was categorised into none, mild/moderate (combined) and severe. Risk associations between preeclampsia and related pregnancy variables with outcomes in late childhood were analysed by multiple logistic and linear regression analyses, including the covariates gender, birthweight z-score for gestational age, being firstborn, maternal smoking during pregnancy, maternal age at birth, caesarean section, gestational age, maternal BMI and maternal asthma. Paternal asthma was not included as a covariate due to low response rate. Each variable was first entered separately into simple regression models. Covariates significant at the 10% level and those considered important were included in backward stepwise logistic and linear regression analyses. Final models included the remaining covariates significant at the 5% level and the covariates gender and maternal asthma, considered as biologically important. Analysing the ordinal variable preeclampsia as were it a continuous variable with scores 0, 1 and 2 for the three levels, ORs showing a trend have been calculated by multiple logistic regression analysis.

From logistic regression odds ratios (OR) with 95% confidence interval (CI) and likelihood ratio p-value (LR-p) for each exposure are reported. From linear regression the estimated coefficients (b), 95% CI and F-test p-value are reported. Interactions between preeclampsia and all other risk factors remaining in the final models were tested. Also interactions between preeclampsia and gender were tested.

All tests were 2-tailed and p-values ≤ 0.05 were considered statistically significant. Due to missing data, matching was not included in the analyses, but the matching variables were adjusted for. SPSS for Windows (version 18.0.0, Chicago, Ill., USA) was used for all analyses.

Results

Characteristics of the participants

The number of children invited and participating in FU1 and FU2 are shown in Figure 1. Table 1 shows the characteristics of children who consented to FU1, and those who did not consent. There were no significant differences in perinatal characteristics of children who consented and those who did not consent.

At FU1, the age of the girls was 10.8 (±0.22) years (mean, SD), and for boys 11.8 (±0.18) years. At FU2 the age for both genders was 12.8 (±0.19) years.

BMI z-score at FU1 was higher in children who only consented to FU1 than in children who consented to both

Table 1 Initial characteristics of 1025 Norwegian children born in 1993–1995 and invited to the Stavanger study according to consenting or not to the first follow-up 11–12 years later[a)]

	Consented (n = 617)			Did not consent (n = 409)			
Variable	**n**			**n**			**p**
Gender: boys, *n (%)*	617	296	(48.0)	408	220	(53.9)	0.065[b)]
Preeclampsia, *n (%)*	617	230	(37.3)	409	137	(33.5)	0.231[b)]
Maternal age, years, *mean, 95% CI*	610	28.0	(27.7, 28.4)	408	27.6	(27.2, 28.1)	0.194[c)]
Gestational age, weeks; *mean, 95% CI*	604	39.3	(39.1, 39.5)	343	39.2	(39.0, 39.5)	0.855[c)]
Birth weight z-score[d)]	590	−0.17	(−0.27, −0.07)	339	−0.06	(−0.18, 0.06)	0.169[c)]

Abbreviations: CI confidence interval.
[a)]Follow-up at the ages of 10.8 years (girls) and 11.8 years (boys);
[b)]Exact chi-square test;
[c)]Gosset's t-test;
[d)]Number of standard deviations from mean.

FU1 and FU2 (mean difference BMI z-score: 0.31 kg/m^2; 95% CI: 0.13 to 0.49; p = 0.001). When analysed separately for girls and boys, the difference persisted for girls only (mean difference BMI: 0.44 kg/m^2; 95% CI: 0.20 to 0.68; p < 0.001). More children had atopic dermatitis of those who only consented to FU1 (48/150; 32%), than those who consented to both FU1 and FU2 (100/445; 22.5%); p = 0.022. No other variables differed significantly between those who consented to FU1 only and those who consented to both FU1 and FU2.

Preeclampsia and outcomes

The outcome in children according to maternal preeclampsia status is shown in Table 2. A greater proportion of offspring from pregnancies with severe preeclampsia had allergic rhinoconjunctivitis and high level allergic sensitization than offspring from pregnancies with mild/moderate or no preeclampsia.

Among children with any allergic sensitization, 50% had symptoms of allergic rhinoconjunctivitis, whereas 5.6% of children with allergic rhinoconjunctivitis did not have any allergic sensitization.

Table 2 Atopy, asthma and lung function in late childhood in 586 Norwegian children according to mother's preeclampsia status

	Severe preeclampsia			Mild/moderate preeclampsia			No preeclampsia			Severe vs. no preeclampsia	Mild/moderate vs. no preeclampsia	Overall
Outcome variable	**n**			**n**			**n**			**p-value[a)]**	**p-value[a)]**	**p-value[b)]**
FU1 variables												
Allergic rhinoconjunctivitis, *n (%)*	54	19	(35.2)	161	36	(22.4)	371	71	(19.1)	0.018	0.822	0.015
Atopic dermatitis, *n (%)*	54	15	(27.8)	163	37	(22.7)	369	92	(24.9)	1.476	1.172	1.000
Asthma, *n (%)*	53	9	(17.0)	161	14	(8.7)	366	30	(8.2)	0.092	1.730	0.100
FU2 variables												
Allergic sensitization, *n (%)*	39	15	(38.5)	112	40	(36.3)	230	72	(31.3)	0.918	0.924	0.296
High level allergic sensitization, *n (%)*[c)]	39	15	(38.5)	112	28	(25.0)	230	50	(21.7)	0.056	1.166	0.042
Current asthma, *n (%)*	46	6	(13.0)	123	12	(9.8)	279	19	(6.8)	0.454	0.630	0.126
FEV_1%, *mean, 95% CI*	45	89.7	(87.0, 92.5)	126	91.0	(89.0, 93.0)	272	91.1	(90.0, 92.2)	1.000	1.000	0.682
FVC%, *mean, 95% CI*	45	99.2	(95.5, 102.8)	126	100.0	(97.7, 102.3)	272	101.1	(99.8, 102.4)	0.965	1.000	0.489
FEV_1/FVC, *mean, 95% CI*	45	84.6	(82.7, 86.5)	126	85.3	(83.9, 86.6)	272	84.9	(84.1, 85.7)	1.000	1.000	0.482
FEF_{25-75}%, *mean, 95% CI*	45	84.9	(79.4, 90.3)	126	89.6	(85.9, 93.4)	272	87.4	(85.1, 89.6)	1.000	0.827	0.317
FEF_{25-75}/FVC, *mean, 95% CI*	45	54.5	(50.0, 59.0)	126	57.3	(54.7, 59.9)	272	55.7	(54.1, 57.4)	1.000	0.906	0.429

Abbreviations: FU1 first follow-up at the ages of 10.8 years (girls) and 11.8 years (boys), *FU2* second follow-up at the age of 12.8 years (both genders), *FEV_1*% forced expiratory volume in first second predicted, *CI* Confidence interval, *FVC*% forced vital capacity predicted, *FEF_{25-75}*% forced expiratory flow between 25% and 75% of the forced vital capacity, predicted.
[a)]Pearson's exact chi-square test (dichotomous variable) and one way analysis of variance (continuous variable) with Bonferroni corrections;
[b)]Cochran-Armitage test for dichotomous outcomes and one way analysis of variance for continuous outcomes;
[c)]Sum of specific IgE > 3.9 *kU/l*.

In the unadjusted logistic regression analyses, severe preeclampsia was a risk factor for allergic rhinoconjunctivitis; OR: 2.29; 95% CI: 1.24 to 4.24; LR-p = 0.036. Table 3 shows the results of adjusted logistic regression analyses with different atopic diseases as outcomes according to maternal preeclampsia status. In fully adjusted analyses, severe preeclampsia was a significant risk factor for high level allergic sensitization, but not so for any other outcomes of atopic disease.

In the backward stepwise regression analysis of high level allergic sensitization the final model included preeclampsia as a significant risk factor, in addition to male gender, maternal smoking during pregnancy, gestational age in weeks and maternal asthma (Table 3). Specifically, birth after severe preeclampsia gave 4.05 times higher odds for high level allergic sensitization than birth after non-preeclampsia, adjusted for the other variables.

In a backward stepwise regression analysis of allergic rhinoconjunctivitis the final model included preeclampsia in addition to male gender and maternal asthma (Table 3). Specifically, severe preeclampsia gave 2.23 times higher odds for allergic rhinoconjunctivitis than no preeclampsia, adjusted for the other variables.

Adjusted for the same covariates as in final analysis, there was a trend of an increasing effect of preeclampsia (none, mild/moderate, severe) on both high level allergic sensitization (OR = 1.88; 95% CI: (1.23, 2.86); LR-p = 0.003) and on allergic rhinoconjunctivitis (OR = 1.42; 95% CI: (1.07, 1.89); LR-p = 0.018).

Preeclampsia was not a significant risk factor for other outcomes of atopic disease in the final models.

Preeclampsia was not a risk factor for any outcomes of lung function in unadjusted or fully adjusted linear regression analyses. Table 4 shows the results of linear regression analyses of lung function variables according to maternal preeclampsia status.

Discussion

In the present study we found positive associations between severe maternal preeclampsia and both high level allergic sensitization and allergic rhinoconjunctivitis in adolescent offspring. This is to our knowledge showed for the first time. Preeclampsia was not associated with subsequent atopic dermatitis, asthma or alterations in lung function.

Preeclampsia and atopic disease

Few other studies have evaluated preeclampsia as a possible risk factor for subsequent allergic sensitization or atopic disease in a long-term perspective. Keski-Nisula et al. found an association between maternal preeclampsia and severe atopy in children. However, in that study only women who underwent caesarean section were included, and a very high percentage of children were sensitized [13]. Nafstad et al. found a relation between uterus-related complications during pregnancy and allergic rhinoconjunctivitis and asthma, but not for children born after preeclamptic pregnancies [11]. To our knowledge, no other studies have evaluated the risk for allergic rhinoconjunctivitis after preeclamptic pregnancies.

A possible causal relation between preeclampsia and atopic disease in offspring could be linked to the

Table 3 Summary of logistic regression analyses of atopic diseases in late childhood in 586 Norwegian children according to mother's preeclampsia status

	Effects of maternal preeclampsia											
	Fully adjusted[a)]						Final analysis[b)]					
	n	Mild/moderate preeclampsia		Severe preeclampsia		Likelihood-ratio-p	n	Mild/moderate preeclampsia		Severe preeclampsia		Likelihood-ratio p
Outcome variable		OR	95% CI	OR	95% CI			OR	95% CI	OR	95% CI	
FU1 variables												
Allergic rhinoconjunctivitis	514	1.21	(0.70, 2.07)	2.10	(0.86, 5.11)	0.268	586	1.25	(0.79, 1.97)	2.23	(1.20, 4.17)	0.046
Atopic dermatitis	513	0.90	(0.54, 1.50)	0.97	(0.39, 2.39)	0.914						____
Asthma	506	0.87	(0.38, 1.97)	0.72	(0.19, 2.77)	0.878						____
FU2 variables												
Allergic sensitization	329	1.49	(0.84, 2.63)	2.44	(0.93, 6.42)	0.138						____
High level allergic sensitization[c)]	329	1.64	(0.87, 3.11)	4.42	(1.58, 12.3)	0.015	347	1.60	(0.88, 2.91)	4.05	(1.62, 10.1)	0.010[d)]
Current asthma	388	1.11	(0.45, 2.73)	0.69	(0.15, 3.18)	0.802						____

Abbreviations: OR Odds ratio, *CI* Confidence interval, *FU1* first follow-up at the ages of 10.8 years (girls) and 11.8 years (boys), *FU2* second follow-up at the age of 12.8 years (both genders); Likelihood-ratio-p refers to exposure only.

[a)]Adjusted for gender, birth weight z-score adjusted for gestational age, being firstborn, Caesarean section, maternal smoking during pregnancy, gestational age in weeks, maternal age, maternal body mass index (kg/m^2) and maternal asthma;

[b)]After backward stepwise selection from fully adjusted model with $p \leq 0.05$; all final analyses include the covariates gender and maternal asthma as default.

[c)]High level allergic sensitization = Sum of specific IgE > 3.9 *kU/l;* the 25 percentile of sensitized children.

[d)]Adjusted for gender, maternal smoking during pregnancy, gestational age in weeks and maternal asthma. No significant interaction effects were found in final analyses.

Table 4 Summary of linear regression analyses of lung function in late childhood in 395 Norwegian children according to mother's preeclampsia status

	Effects of maternal preeclampsia						
	Fully adjusted[a)]						
	n	Mild/moderate preeclampsia			Severe preeclampsia		
Outcome variable		b	95% CI	p	b	95% CI	p
FEV1%	381	0.57	(−1.86, 2.99)	0.647	1.27	(−2.95, 5.49)	0.555
FVC%	381	−1.47	(−4.36, 1.42)	0.317	−2.24	(−7.28, 2.79)	0.381
FEV1/FVC	381	1.28	(−0.35, 2.92)	0.124	2.79	(−0.06, 5.64)	0.055

Abbreviations: FEV1% forced expiratory volume in first second predicted, *FVC%* Forced vital capacity predicted, *FEV1/FVC* Ratio of actual FEV1 over FVC, *n* number of participants, *b* regression coefficient, *CI* confidence interval,
[a)]Adjusted for gender, birth weight z-score adjusted for gestational age, being firstborn, Caesarean section, maternal age, maternal smoking during pregnancy, gestational age in weeks, maternal body mass index (kg/m^2) and maternal asthma.

inflammatory changes observed during preeclampsia. If the tendency for preeclampsia to skew the cytokine profile of the mother towards an increased Th1/Th2 ratio is reflected in the cytokine pattern of the offspring during pregnancy and early life, it could potentially protect the child from the development of Th2 driven atopic disease [6,22]. However, preeclampsia is a complex inflammatory condition characterised by a variety of pro-inflammatory cytokines beyond the Th1 type of cytokines [10,23]. Pro-inflammatory cytokines, chemokines and adhesion molecules appear to be increased in maternal circulation during preeclampsia [13], and could potentially initiate the development of immunological conditions in the foetus, such as atopic sensitization or diseases [6].

The association between preeclampsia and atopy could be due to shared genetic or environmental factors in pregnancy. Preeclampsia is more common in nulliparous [24] and pregnancies with a male foetus [25], and atopic disease is more common in first-born-children [26] and boys up to adolescence [27]. According to the hygiene hypothesis, the birth order effect on atopy may be explained by a reduced tendency for Th2 deviation due to greater exposure to pathogens from older siblings [28]. However, recent studies have demonstrated a birth order effect on cord blood IgE and food allergy in very early life, suggesting a prenatal origin of this effect [29,30]. Our analyses were controlled for birth order, suggesting that preeclampsia may be a risk factor for atopy in the offspring unrelated to birth order. However, as this is an observational study, the possibility of residual confounding cannot be excluded.

Finally, maternal conditions prior to pregnancy could increase the risk for both preeclampsia and atopic disease in offspring. Maternal asthma has been shown as a risk factor for preeclampsia [31]. To our knowledge, no studies have shown any association between maternal allergy and preeclampsia.

There was a trend of an increased risk of atopic disease in the child by an increasing severity of the maternal preeclampsia. Moreover, preeclampsia was not associated with low level allergic sensitization, asthma or atopic dermatitis. Low level allergic sensitization may be unspecific and less related to clinical atopic disease compared to higher levels of sensitization [32]. The pathophysiology of asthma and atopic dermatitis is more multifactorial than the specific allergy driven pathophysiology of rhinoconjunctivitis. Our results may therefore suggest that the association between severe preeclampsia and atopic disease in offspring is related to specific Th2-mediated mechanisms [29].

Preeclampsia, asthma, wheezing and lung function

Some studies have shown an association between different complications of pregnancy and asthma in offspring, but preeclampsia was not shown to be a risk factor in these studies [12,33]. In a large population-based study using a questionnaire, an association between maternal preeclampsia and wheezing in the offspring was shown [34]. A possible explanation for this association could be that hypertension in pregnancy is related to fetal growth restriction and hence altered airway function [35]. Our results do not contradict this. Although we could not find any association between preeclampsia and asthma ever, current asthma or lung function in late childhood, we did not investigate wheezing disorders in the first years of life. However, the present study had a longer follow-up than in the studies mentioned above, and may therefore be better suited to study any long time effect of preeclampsia on asthma and lung function in late childhood.

One limitation of the study is the rather low rate of participation, especially in FU2. It is not known whether there was a difference in prevalence of asthma or atopy between those who consented and those who didn't consent to overall follow-up. Especially for the outcomes of asthma, there was a rather low response rate which increases the risk of a type 2 error. Furthermore, children who participated in FU1 but not in FU2 had a higher BMI and more atopic dermatitis. This may have biased our results, as both overweight and atopic dermatitis may be associated with allergic sensitization and other atopic disease.

Another limitation may be that that allergic rhinoconjunctivitis, asthma and atopic dermatitis were defined only by questionnaire. However, allergic sensitization was found in 94.4% of children diagnosed with rhinoconjunctivitis, suggesting a high degree of diagnostic accuracy. Some children reported allergic rhinoconjunctivitis

without having sensitization, but this is also seen in other studies and does not rule out allergic rhinoconjunctivitis [36]. Due to study design, allergic rhinoconjunctivitis and allergic sensitization were assessed at two different ages. However, this should not affect that independent associations were found between preeclampsia pregnancies and allergic rhinoconjunctivitis and allergic sensitization respectively.

In the multivariate analyses we included a set of variables possibly influencing the outcomes. The covariates gestational age, birthweight z-score and caesarean section could be considered as intermediate variables between preeclampsia and the outcomes, but may also be independent risk factors for subsequent allergy and atopic disease and were therefore included as covariates in the analyses. Given the lack of complete ascertainment of causal links, one cannot exclude the possibility of collider bias and therefore biased associations between exposures and outcomes [37].

The only data on family atopy available were on maternal and paternal asthma. Paternal asthma was not considered to be a possible confounder for the relationship between maternal preeclampsia and subsequent atopy, asthma or lung function in offspring and not included as a covariate.

Conclusion

The results of this study suggest that severe maternal preeclampsia may be associated with allergic sensitization and allergic rhinoconjunctivitis in late childhood. This emphasizes the possible early origin of atopic disease, but larger studies are needed to further explore the role of preeclampsia in the development of atopic disease. No other significant associations between maternal preeclampsia and atopic dermatitis, asthma or lung function were found.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

KKB performed the registration of data, controlled the database, arranged the blood samples for analyses, performed statistical analyses, wrote a draft and completed the manuscript. BO drafted the primary study, was the leader of the data collection, performed registration of data, and critically revised the manuscript. GEE contributed to the outline of the tables, supervised statistical analyses and critically revised the manuscript. KØ supervised all parts of the study, the drafting, registration of data, and analyses, and contributed significantly to the writing of the manuscript. All authors read and approved the final manuscript.

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References

1. Schernhammer ES, Vutuc C, Waldhor T, Haidinger G: **Time trends of the prevalence of asthma and allergic disease in Austrian children.** *Pediatr Allergy Immunol* 2008, **19**(2):125–131.
2. de Boo HA, Harding JE: **The developmental origins of adult disease (Barker) hypothesis.** *Aust N Z J Obstet Gynaecol* 2006, **46**(1):4–14.
3. De Luca G, Olivieri F, Melotti G, Aiello G, Lubrano L, Boner AL: **Fetal and early postnatal life roots of asthma.** *J Matern Fetal Neonatal Med* 2010, **23**(Suppl 3):80–83.
4. Diesner SC, Forster-Waldl E, Olivera A, Pollak A, Jensen-Jarolim E, Untersmayr E: **Perspectives on immunomodulation early in life.** *Pediatr Allergy Immunol* 2012, **23**(3):210–223.
5. Jutel M, Akdis CA: **T-cell subset regulation in atopy.** *Curr Allergy Asthma Rep* 2011, **11**(2):139–145.
6. Herberth G, Hinz D, Roder S, Schlink U, Sack U, Diez U, Borte M, Lehmann I: **Maternal immune status in pregnancy is related to offspring's immune responses and atopy risk.** *Allergy* 2011, **66**(8):1065–1074.
7. Pfefferle P, Bocking C, Renz H: **Maternal cytokine profiles during pregnancy - predictors for later allergy or just reading the tea leaves?** *Allergy* 2011, **66**(8):987–988.
8. Turner JA: **Diagnosis and management of pre-eclampsia: an update.** *Int J Womens Health* 2010, **2:**327–337.
9. Jim B, Sharma S, Kebede T, Acharya A: **Hypertension in pregnancy: a comprehensive update.** *Cardiol Rev* 2010, **18**(4):178–189.
10. Szarka A, Rigo J Jr, Lazar L, Beko G, Molvarec A: **Circulating cytokines, chemokines and adhesion molecules in normal pregnancy and preeclampsia determined by multiplex suspension array.** *BMC Immunol* 2010, **11:**59.
11. Nafstad P, Magnus P, Jaakkola JJ: **Risk of childhood asthma and allergic rhinitis in relation to pregnancy complications.** *J Allergy Clin Immunol* 2000, **106**(5):867–873.
12. Nafstad P, Samuelsen SO, Irgens LM, Bjerkedal T: **Pregnancy complications and the risk of asthma among Norwegians born between 1967 and 1993.** *Eur J Epidemiol* 2003, **18**(8):755–761.
13. Keski-Nisula L, Heinonen S, Remes S, Pekkanen J: **Pre-eclampsia, placental abruption and increased risk of atopic sensitization in male adolescent offspring.** *Am J Reprod Immunol* 2009, **62**(5):293–300.
14. Gagliardi L, Rusconi F, Da Fre M, Mello G, Carnielli V, Di Lallo D, Macagno F, Miniaci S, Corchia C, Cuttini M: **Pregnancy disorders leading to very preterm birth influence neonatal outcomes: results of the population-based ACTION cohort study.** *Pediatr Res* 2013, **73**(6):794–801.
15. Wang A, Holston AM, Yu KF, Zhang J, Toporsian M, Karumanchi SA, Levine RJ: **Circulating anti-angiogenic factors during hypertensive pregnancy and increased risk of respiratory distress syndrome in preterm neonates.** *J Matern Fetal Neonatal Med* 2011, **25**(8):1447–1452.
16. Kotecha SJ, Watkins WJ, Heron J, Henderson J, Dunstan FD, Kotecha S: **Spirometric lung function in school-age children: effect of intrauterine growth retardation and catch-up growth.** *Am J Respir Crit Care Med* 2010, **181**(9):969–974.
17. Ogland B, Vatten LJ, Romundstad PR, Nilsen ST, Forman MR: **Pubertal anthropometry in sons and daughters of women with preeclamptic or normotensive pregnancies.** *Arch Dis Child* 2009, **94**(11):855–859.
18. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B: **Intrauterine growth curves based on ultrasonically estimated foetal weights.** *Acta Paediatr* 1996, **85**(7):843–848.
19. Juliusson PB, Roelants M, Eide GE, Moster D, Juul A, Hauspie R, Waaler PE, Bjerknes R: **Growth references for Norwegian children.** *Tidsskr Nor Laegeforen* 2009, **129**(4):281–286.
20. **Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee.** *Lancet* 1998, **351**(9111):1225–1232.
21. Quanjer PH, Borsboom GJ, Brunekreef B, Zach M, Forche G, Cotes JE, Sanchis J, Paoletti P: **Spirometric reference values for white European**

children and adolescents: Polgar revisited. *Pediatr Pulmonol* 1995, **19**(2):135–142.
22. Jonsson Y, Ruber M, Matthiesen L, Berg G, Nieminen K, Sharma S, Ernerudh J, Ekerfelt C: **Cytokine mapping of sera from women with preeclampsia and normal pregnancies.** *J Reprod Immunol* 2006, **70**(1–2):83–91.
23. Molvarec A, Shiozaki A, Ito M, Toldi G, Stenczer B, Szarka A, Nakashima A, Vasarhelyi B, Rigo J Jr, Saito S: **Increased prevalence of peripheral blood granulysin-producing cytotoxic T lymphocytes in preeclampsia.** *J Reprod Immunol* 2011, **91**(1–2):56–63.
24. Myatt L, Miodovnik M: **Prediction of preeclampsia.** *Semin Perinatol* 1999, **23**(1):45–57.
25. Aliyu MH, Salihu HM, Lynch O, Alio AP, Marty PJ: **Fetal sex and differential survival in preeclampsia and eclampsia.** *Arch Gynecol Obstet* 2012, **285**(2):361–365.
26. van Gool CJ, Thijs C, Dagnelie PC, Henquet CJ, van Houwelingen AC, Schrander J, Menheere PP, van den Brandt PA: **Determinants of neonatal IgE level: parity, maternal age, birth season and perinatal essential fatty acid status in infants of atopic mothers.** *Allergy* 2004, **59**(9):961–968.
27. Alm B, Goksor E, Thengilsdottir H, Pettersson R, Mollborg P, Norvenius G, Erdes L, Aberg N, Wennergren G: **Early protective and risk factors for allergic rhinitis at age 4(1/2) yr.** *Pediatr Allergy Immunol* 2011, **22**(4):398–404.
28. Strachan DP: **Hay fever, hygiene, and household size.** *BMJ* 1989, **299**(6710):1259–1260.
29. Kusunoki T, Mukaida K, Morimoto T, Sakuma M, Yasumi T, Nishikomori R, Heike T: **Birth order effect on childhood food allergy.** *Pediatr Allergy Immunol* 2012, **23**(3):250–254.
30. Karmaus W, Arshad H, Mattes J: **Does the sibling effect have its origin in utero? Investigating birth order, cord blood immunoglobulin E concentration, and allergic sensitization at age 4 years.** *Am J Epidemiol* 2001, **154**(10):909–915.
31. Triche EW, Saftlas AF, Belanger K, Leaderer BP, Bracken MB: **Association of asthma diagnosis, severity, symptoms, and treatment with risk of preeclampsia.** *Obstet Gynecol* 2004, **104**(3):585–593.
32. Hattevig G, Kjellman B, Bjorksten B: **Appearance of IgE antibodies to ingested and inhaled allergens during the first 12 years of life in atopic and non-atopic children.** *Pediatr Allergy Immu : official publication of the European Society of Pediatric Allergy and Immunology* 1993, **4**(4):182–186.
33. Annesi-Maesano I, Moreau D, Strachan D: **In utero and perinatal complications preceding asthma.** *Allergy* 2001, **56**(6):491–497.
34. Rusconi F, Galassi C, Forastiere F, Bellasio M, De Sario M, Ciccone G, Brunetti L, Chellini E, Corbo G, La Grutta S, Lombardi E, Piffer S, Talassi F, Biggeri A, Pearce N: **Maternal complications and procedures in pregnancy and at birth and wheezing phenotypes in children.** *Am J Respir Crit Care Med* 2007, **175**(1):16–21.
35. Lum S, Hoo AF, Dezateux C, Goetz I, Wade A, DeRooy L, Costeloe K, Stocks J: **The association between birthweight, sex, and airway function in infants of nonsmoking mothers.** *Am J Respir Crit Care Med* 2001, **164**(11):2078–2084.
36. Rondon C, Campo P, Galindo L, Blanca-Lopez N, Cassinello MS, Rodriguez-Bada JL, Torres MJ, Blanca M: **Prevalence and clinical relevance of local allergic rhinitis.** *Allergy* 2012, **67**(10):1282–1288.
37. Robins JM, Greenland S: **Identifiability and exchangeability for direct and indirect effects.** *Epidemiology* 1992, **3**(2):143–155.

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II

PLOS ONE

RESEARCH ARTICLE

Exposure to preeclampsia *in utero* affects growth from birth to late childhood dependent on child's sex and severity of exposure: Follow-up of a nested case-control study

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Abstract

Background and objective

An adverse intrauterine environment may affect offspring growth and development. Our aim was to explore whether preeclampsia (PE) exposure *in utero* influences growth from birth to 13 years.

Methods

In a nested case-control study, 229 children were exposed to PE (mild/moderate: $n = 164$, severe: $n = 54$) and 385 were unexposed. Length/height and weight were abstracted from records at birth, 3 and 6 months, 1 and 4 years, and measured along with waist circumference and skinfolds at follow-up at 11/12 (girls/boys) and 13 years (both sexes). Associations between PE and z-scores for growth were analyzed by multiple linear and fractional polynomial regression with adjustment for potential confounders.

Results

In boys, exposure to mild/moderate PE was positively associated with linear growth after 0.5 years, but severe PE was negatively associated with linear growth in all ages. In girls, both exposure to mild/moderate and severe PE were negatively associated with linear growth. Exposure to PE was negatively associated with weight and body mass index (BMI) during infancy, but positively associated with weight and BMI thereafter, except that boys exposed to severe PE consistently had a lower weight and BMI compared to the unexposed.

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Exposure to severe PE only was positively associated with waist-to-height ratio at 11/12 (girls/boys) and 13 years (both sexes).

Conclusions

From birth to adolescence, linear growth, weight and BMI trajectories differed between the sexes by severity of exposure to PE. In general, PE exposure was negatively associated with linear growth, while in girls; positive associations with weight and BMI were observed. This underlines fetal life as a particularly sensitive period affecting subsequent growth and this may have implications for targeted approaches for healthy growth and development.

Introduction

Preeclampsia (PE) is diagnosed in 3–5% of pregnancies and may be a serious complication of the second half of pregnancy affecting both mother and child. It is characterized by maternal hypertension and proteinuria, and associated in its severe form with fetal growth restriction [1–3]. PE is classified by severity into mild, moderate and severe forms, with differences in pathophysiology, gestational age at diagnosis, fetal growth and outcomes [4].

According to the Barker hypothesis, a hostile intrauterine environment may be associated with low birth weight, with increased risk for having a shorter adult height, metabolic disorders, obesity, diabetes and cardiovascular diseases [5–7]. Children born small for gestational age frequently experience catch-up growth, although more catch-up in weight than in height [8].

PE has been associated with low birthweight, catch-up growth in infants and a high body mass index (BMI, kg/m^2) during adolescence [9, 10]. Delay of thelarche but accelerated pubarche and increased risk for obesity in late childhood with subsequent metabolic anomalies and altered risk for cancer in adulthood, have also been reported in offspring exposed to PE compared to the unexposed [10–12].

The present study is a part of "The Stavanger study", which has previously shown that exposure to PE is associated with a low birthweight, especially after severe PE [3], large waist circumference and a high BMI in girls at the onset of puberty [10]. However, there are limited data on longitudinal growth patterns of children exposed to PE from birth to late childhood. The aim of the present study was therefore to explore whether length/height, weight and BMI trajectories from birth to late childhood and waist circumference and skinfolds in late childhood vary by severity of PE and the child's sex and differ in comparison with the unexposed. We specifically hypothesized that exposure to severe PE *in utero*, a known risk factor for small for gestational age, contributes to compromised linear growth and accelerated weight gain during childhood and that the pathways to growth may differ by severity of PE and by child's sex.

Methods

Study population and design

From a population-based cohort including 12 804 deliveries during 1993–1995 at Stavanger University Hospital [3], the Medical Birth Registry of Norway was used to identify mothers with PE (n = 366) and controls (n = 659) to conduct a nested case control study: For each case, two matched controls were selected; one was the next delivery in the hospital (i.e. a birth date

match) and one was the next born matched on maternal age (i.e. a risk factor for PE). The present study, "The Stavanger Study" described in detail elsewhere [10], was a follow-up of the nested case control study, aiming to study anthropometry, blood pressure and pubertal development in children after PE exposure *in utero*. The cases and controls were invited to participate in a first follow-up study. The ages at follow-up were selected to coincide with the age of pubertal onset (first follow-up) and menarche (second follow-up) of the children [10, 12]. Thus the mean age was 10.8 years (girls) and 11.8 years (boys) at the first follow-up, and at the second follow-up it was 12.8 years (both sexes), as shown previously [13]. As there were more missing participants in the controls than the case group, the original matching on maternal age and birth date was compromised, and maternal age was included as a potential confounder in the analyses. The analyzed sample included all children who participated in both follow-ups.

The study was approved by the Norwegian Data Inspectorate, the Regional Committee for Ethics in Medical Research Western Norway (Reference Numbers: First: 078–03, Second: 2010/1375) and the Institutional Review Boards of the National Cancer Institute (Reference Number: LAB09-0139) and University of Texas at Austin, United States (Reference Number: 2013-04-0036). At follow-up, participating mothers and children signed an informed consent/assent form.

Exposures

PE was diagnosed based on blood pressure and proteinuria levels at gestational age (GA) 20 weeks on and further classified as mild, moderate or severe according to the Collaborative Low-dose Aspirin Study in Pregnancy (CLASP) criteria as specified previously [10, 14]. However, due to the pathophysiological similarity between mild and moderate PE, these two conditions were combined into one category for analyses [15].

Outcomes

Birth length and weight were abstracted from hospital records for consenting participants.

In Norway, all children receive healthcare at well baby clinics with routine measurements of recumbent length (or standing height from 2 years of age) and weight from infancy to school age. At first follow-up, length/height and weight measurements from routine visits at well baby clinics at the target ages of 3, 6 and 12 months and 4 years were abstracted from clinical records. If a measurement was missing, the value from the closest visit in time was used and the exact age was recorded for all visits. Height, weight, triceps skinfold and waist circumference in offspring were measured twice each at both follow-ups, and subscapular skinfold at second follow-up, with the average used in the analyses. The measurements at follow-ups were performed by three specially trained nurses, as described previously [10]. Standard deviation scores (SDS) for height, weight, BMI, skinfold and waist measurements including the waist-to-height ratio, relative to sex and age, were calculated in R version 2.6.2 (R Development Core Team, Vienna, Austria). Calculating SDS according to WHO standards could put the data into an international perspective. However, growth of Norwegian children has been shown to deviate significantly from the WHO standards [16]. We have therefore used SDS based on the Norwegian growth reference in our calculations [17–19].

Confounders

The potential confounders including categorical and continuous variables are presented below, and illustrated in a directed acyclic graph (S1 Fig):

Child's sex: From medical records.

Birth order (recoded to firstborn or not): From maternal questionnaire at first follow-up.

Maternal BMI: Calculated from pre-pregnancy weight measurement at the first antenatal visit at primary healthcare examination during the first trimester of pregnancy and height measurement from first follow-up.

Maternal smoking in pregnancy (yes/no): Recorded at first antenatal visit.

Maternal age at delivery: Design variable.

Maternal education at time of delivery (< 9 years, 9–12 years, > 12 years): From maternal questionnaire at first follow-up.

GA and puberty staging were not adjusted for, as these are intermediate variables between the exposures and outcomes.

The questionnaires used have been shown as supporting information in a recent publication by Alsnes et al [20].

Statistics

For descriptive statistics we used the mean and 95% confidence interval (CI) as well as median and lower and upper quartiles (Q_1, Q_3). For comparison between groups by severity of PE exposure Kruskal-Wallis one way analysis of variance and Mann-Whitney U-test were used for continuous variables that were not normally distributed, and compared by Gosset's unpaired t-tests (Student, 1908) for approximately normally distributed variables.

Multiple linear regression analysis of growth (SDS for length/height, weight and BMI) over time,.i.e. at birth, 3 and 6 months, 1 and 4 years, and both follow-ups was computed using generalized estimating equations (GEE) taking into account correlations between repeated measurements in each child. To identify potential non-straight line effects of PE on growth, we used multiple fractional polynomial regression (MFPR) [21] adjusted for repeated measurements in each child by use of the mfpr and xtgee procedures in GEE of Stata 14. The effect of maternal PE (no, mild/moderate, and severe) on growth was studied using regression models with adjustment for potential confounders. Interactions with sex and age were tested using the likelihood ratio test. Finally, the identified fractional polynomials were plotted using R (version 3.2.1)

Also, associations between the severity of PE and SDS for skinfolds, waist circumference and waist-to-height ratio were analyzed by separate multiple linear regression analyses (general linear model: GLM) including the covariates above. A backward stepwise selection of confounders at P-values of < 0.05 was performed, with child's sex and maternal smoking forced into the final model with adjustment for significant confounders.

The estimated coefficients (b), 95% CI and P-values from Wald's chi-square-test (GEE) and the *F*-test (GLM) are reported. All tests were 2-tailed and P-values ≤ 0.05 were considered statistically significant.

STATA SE14 (StataCorp. 2015. *Stata Statistical Software*: *Release 14*. College Station, TX: StataCorp LP.) was used for the GEE analyses, and IBM SPSS for Windows (version 22.0.0, Chicago, Ill., USA) was used for the GLM analyses.

Results

Characteristics of the participants

A detailed description of the cohort is previously published [13]. Briefly, out of 366 exposed and 659 unexposed invited children, 229 (63%) of the exposed (mild/moderate: n = 164, severe: n = 54) and 385 (59%) of the unexposed children assented to the first follow-up. 182 (50%) of the exposed (mild/moderate: n = 127, severe: n = 46) and 286 (43%) of the unexposed children assented to the second follow-up. Information about PE severity was missing for 11

Table 1. Comparison of invited children to the Stavanger Study (n = 1025) according to assenting status to follow-ups[a)].

Variable	First follow-up[a)]							Second follow-up[a)]						
	Assented (n = 617)			Did not assent (n = 408)				Assented (n = 470)			Did not assent (n = 555)			
	n			n			p	n			n			p
Gender: boys, *n (%)*	613	293	(47.8)	408	220	(53.4)	0.056[b)]	468	230	(49.1)	553	283	(51.2)	0.530[b)]
Preeclampsia, *n (%)*	614	229	(37.3)	438	165	(37.7)	0.676[b)]	469	182	(38.8)	583	212	(36.4)	0.184[b)]
Maternal age, years, *mean, 95% CI*	612	28.0	(27.7, 28.4)	408	27.6	(27.2, 28.1)	0.189[c)]	467	28.2	(27.8, 29.7)	553	27.6	(27.2, 28.0)	0.030[c)]
Gestational age, weeks; *median, Q_1, Q_3*[d)]	602	39.9	(38.6, 40.7)	372	39.9	(38.4, 40.9)	0.718[e)]	458	39.9	(38.6, 40.9)	516	39.9	(38.5, 40.7)	0.781[e)]
Birth weight SDS[f)]	601	-0.16	(-0.27, -0.08)	341	-0.07	(-0.19, 0.05)	0.185[c)]	457	-0.20	(-0.31, -0.09)	485	-0.08	(-0.18, 0.02)	0.123[c)]

Abbreviations: CI = confidence interval

[a)] First follow-up at the ages of 10.8 years (girls) and 11.8 years (boys); Second follow-up at 12.8 years;

[b)] Exact chi-square test;

[c)] Gosset's t-test;

[d)] Q_1, Q_3 = Lower and upper quartiles;

[e)] Mann-Whitney U Test;

[f)] SDS = standard deviation score

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children at the first follow-up, and for 9 children at the second follow-up. Maternal age at delivery was greater in children who did than did not assent to the second follow-up. Otherwise, there were no significant differences in perinatal characteristics between children who did and did not assent to the first and the second follow-ups (Table 1) [13]. GA at birth differed between the three PE exposure groups (Kruskal-Wallis test: $P < 0.001$). Pairwise comparisons showed that children exposed to severe PE had a lower GA at birth than those exposed to mild/moderate PE and the unexposed (Mann-Whitney U-test for both comparisons: $P < 0.001$) and that children exposed to mild/moderate PE had a lower GA at birth than the unexposed (Mann-Whitney U-test: $P < 0.001$). Median weeks (Q_1, Q_3) were, respectively; 36.1 (32.0, 38.6), 39.1 (37.6, 40.1) and 40.1 (39.3, 41.0). BMI SDS at the first follow-up was higher in girls who only assented to first follow-up than in those who assented to both follow-ups (mean difference BMI: 0.44 kg/m^2; 95% CI: 0.20 to 0.68; unpaired t-test $P < 0.001$).

PE and outcomes

The growth curves for height, weight and BMI by sex and severity of PE as developed by fractional polynomial regression are shown in Figs 1 and 2. The corresponding regression models appear in Table 2.

The results of fully adjusted analysis of the interaction between sex, age and PE and the effect on height, weight and BMI appear in Table 2 and are described below.

Length/Height SDS (Fig 1A–1D, Table 2)

In utero exposure to PE was associated with linear growth. Specifically, boys exposed to mild/moderate PE had an increased linear growth above 0.5 years compared to the unexposed. Boys exposed to severe PE had a decreased linear growth trajectory compared to the unexposed boys across all ages. As an example, boys exposed to severe PE were approximately 3 cm shorter than the unexposed boys at 2 years of age. Girls exposed to PE had a decreased linear growth trajectory until 12 years of age (non-significant difference between boys and girls;

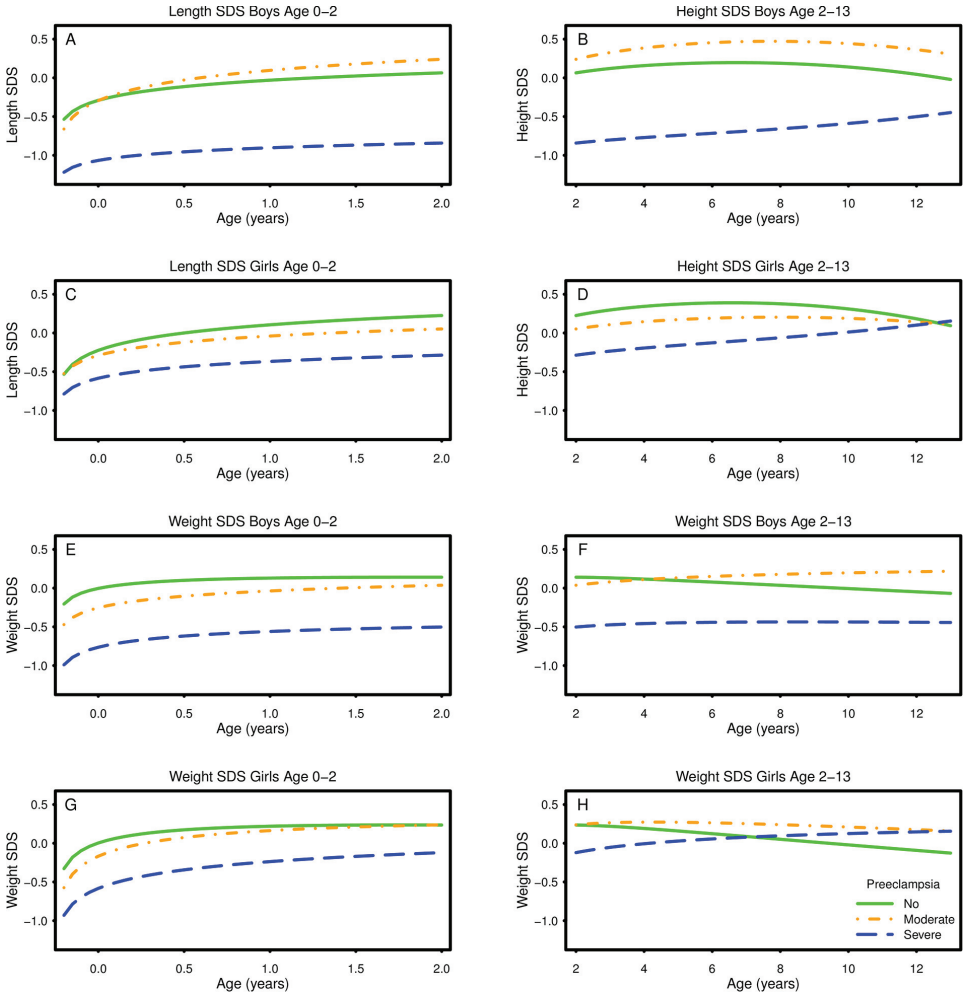

Fig 1. Plots of predicted length/height standard deviation score (SDS) (A-D) and weight SDS (E-H) vs. age according to sex and severity of preeclampsia. Key to figures: Solid line = Unexposed, Dash-dot line = mild/moderate preeclampsia, Dashed line = Severe preeclampsia. Each figure represents the fractional polynomial (FP) with the best fit for each measure (X), i.e. FP (0, 3) = $b_1\ln(X) + b_2X^3$; FP (0, 0.5) = $b_1\ln(X) + b_2\sqrt{X}$. The plots are adjusted for sex, age, birth order, maternal age, smoking, BMI, education and an interaction between preeclampsia and age. Details appear in Table 2.

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$P < 0.290$, Table 2). Girls exposed to severe PE were approximately 2 cm shorter than the unexposed girls at 2 years of age.

Weight SDS (Fig 1E–1H, Table 2)

Weight SDS in children exposed to mild/moderate PE, and in girls exposed to severe PE, was lower than in the unexposed from birth through preschool age and higher thereafter, but the

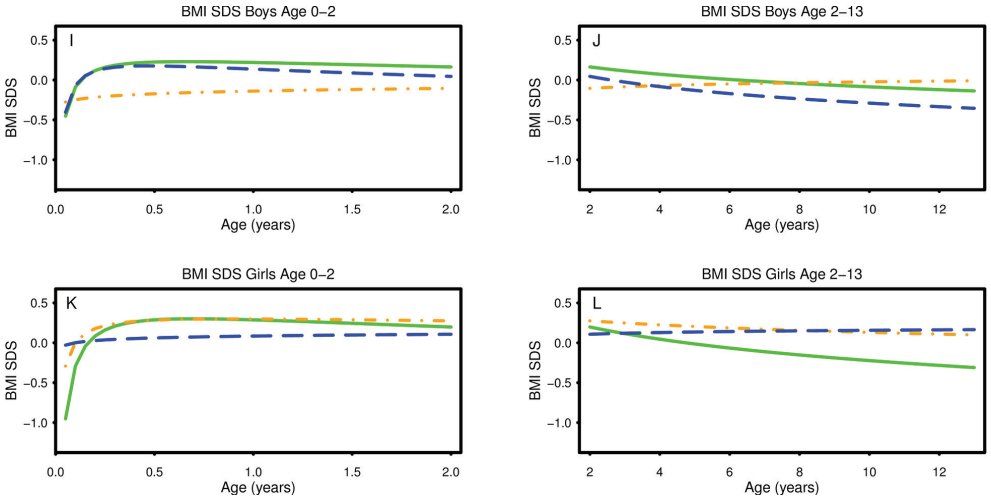

Fig 2. Continued from Fig 1. Plots of predicted BMI SDS (I-L) vs. age according to sex and severity of preeclampsia. Key to figures: Solid line = Unexposed, Dash-dot line = mild/moderate preeclampsia, Dashed line = Severe preeclampsia. Each figure represents the fractional polynomial (FP) with the best fit for each measure (X), i.e. FP (-0.5, 0) = $-b_1/\sqrt{X} + b_2 \ln(X)$.

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differences were maximally equivalent to 0.5 kg. Weight SDS in boys exposed to severe PE was lower than in the unexposed across all ages in childhood (non-significant difference between boys and girls; P = 0.299, Table 2). As an example, weight in boys exposed to severe PE was approximately on1 kg lower than in the unexposed boys at 2 years of age.

BMI SDS (Fig 2I–2L, Table 2)

BMI SDS in boys exposed to mild/moderate PE was lower than in the unexposed from infancy through 7 years, e.g. at 6 months of age, BMI in boys exposed to mild/moderate PE was approximately 0.8 kg/m^2 lower than in the unexposed boys. Boys exposed to severe PE experienced a lower BMI SDS than the unexposed boys across all ages, e.g. BMI in boys exposed to severe PE was approximately 0.1 kg/m^2 lower than in the unexposed boys at 12 years of age. BMI SDS in girls exposed to mild/moderate PE was higher than in the unexposed from 1 year of age. Girls exposed to severe PE experienced a lower BMI SDS than the unexposed from infancy, but higher after 4 years of age, with the maximum difference of 1.5 kg/m^2 at 12.8 years of age (significant difference between boys and girls; P = 0.020, Table 2).

Other measurements

At both 10.8/11.8 (girls/boys) and 12.8 years, severe PE was positively associated with waist-to-height ratio SDS (Table 3). Finally, in multiple linear regression analyses, there were no associations between PE (both categories) and waist circumference SDS, triceps or scapular skinfold SDS at any age (S1, S2 and S3 Tables).

Discussion

In the present study of children exposed and unexposed to PE *in utero*, absolute values for and trajectories in length/height, weight and BMI from birth to late childhood differed by sex and

Table 2. Multiple fractional polynomial regression of growth from birth to 13 years of age[a)] using generalized estimating equations analyses in Norwegian children born in 1993–1995 according to mother's preeclampsia status and interaction with age and sex.

Independent variables	Outcome variable								
	Length/height SDS *n* = 502			Weight SDS *n* = 502			BMI SDS *n* = 501		
	b	95% CI	*P*	b	95% CI	*P*	b	95% CI	*P*
Preeclampsia (No = reference)									
Mild/Moderate	-0.20	(-0.47, 0.08)		0.08	(-0.16, 0.33)		0.21	(-0.01, 0.44)	
Severe	**-0.54**	**(-0.99, -0.08)**		-0.19	(-0.59, 0.21)		0.14	(-0.24, 0.52)	
Age									
FP1	**0.21**	**(0.16, 0.26)**		**0.30**	**(0.15, 0.44)**		**-0.23**	**(-0.34, 0.13)**	
FP2	**-0.22**	**(-0.31, -0.12)**		**-1.32**	**(-1.87, -0.76)**		**-0.44**	**(-0.58, -0.30)**	
Sex (male)	**-0.19**	(-0.41, 0.04)		-0.07	(-0.27, 0.13)		0.05	(-0.14, 0.23)	
Preeclampsia × Age									
Mild/Moderate × FP1	-0.05	(-0.14, 0.04)		0.03	(-0.20, 0.26)		**0.13**	**(0.01, 0.26)**	
Mild/Moderate × FP2	0.12	(-0.04, 0.28)		0.34	(-0.57, 1.24)		**0.27**	**(0.09, 0.46)**	
Severe × FP1	-0.07	(-0.21, 0.07)		-0.05	(-0.39, 0.29)		**0.23**	**(0.01, 0.45)**	
Severe × FP2	**0.30**	**(0.03, 0.57)**		1.08	(-0.30, 2.44)		**0.47**	**(0.14, 0.80)**	
Preeclampsia × sex									
Mild/Moderate × sex	**0.43**	**(0.02, 0.84)**		-0.09	(-0.45, 0.27)		-0.32	(-0.65, 0.02)	
Severe × sex	-0.39	(-1.00, 0.22)		-0.38	(-0.91, 0.15)		-0.31	(-0.82, 0.20)	
Sex × Age									
Sex × FP1	-0.04	(-0.12, 0.04)		-0.12	(-0.33, 0.10)		0.10	(-0.05, 0.26)	
Sex × FP2	0.05	(-0.08, 0.19)		0.54	(-0.28, 1.35)		0.19	(-0.02, 0.39)	
Sex × Preeclampsia × Age			0.290			0.299			**0.020**
Sex × Mild/Moderate × FP1	0.13	(-0.01, 0.27)		-0.06	(-0.41, 0.30)		-0.001	(-0.23, 0.23)	
Sex × Mild/Moderate × FP2	-0.12	(-0.36, 0.12)		0.31	(-1.07, 1.68)		0.03	(-0.29, 0.35)	
Sex × Severe × FP1	0.01	(-0.17, 0.19)		0.04	(-0.35, 0.43)		-0.24	(-0.53, 0.07)	
Sex × Severe × FP2	-0.05	(-0.38, 0.29)		-0.66	(-2.27, 0.94)		**-0.52**	**(-0.97, -0.08)**	
Birth order (firstborn)	-0.03	(-0.20, 0.13)	0.698	-0.04	(-0.20, 0.11)	0.558	0.01	(-0.14, 0.17)	0.873
Maternal age at delivery (years)	0.01	(-0.01, 0.02)	0.486	-0.002	(-0.02, 0.01)	0.794	-0.002	(-0.02, 0.01)	0.819
Maternal smoking (yes)	**-0.24**	**(-0.41, -0.06)**	**0.007**	**-0.16**	**(-0.33, -0.002)**	**0.047**	0.03	(-0.13, 0.19)	0.719
Maternal BMI (kg/m^2)	**0.02**	**(0.002, 0.04)**	**0.029**	**0.05**	**(0.03, 0.07)**	**<0.001**	**0.05**	**(0.03, 0.07)**	**<0.001**
Maternal education[b)]	-0.05	(-0.15, 0.06)	0.364	-0.05	(-0.14, 0.05)	0.356	-0.01	(-0.10, 0.09)	0.920
Intercept	-0.22	(-0.97, 0.52)		-0.76	(-1.44, -0.07)		-1.21	(-1.90, -0.52)	

Abbreviations: *n* = number of participants; CI = confidence interval; BMI = body mass index; SDS = standard deviation score; *P* = Wald chi-square test for interaction between preeclampsia and age; FP = fractional polynomial. FP1 (length/height SDS) = ln(X) + 0.8368401723; FP2 (length/height SDS) = X^3 − 0.0812259488; where: X = (Age + 0.258516924726631)/10. FP1 (weight SDS) = ln(X) + 0.8404720262; FP2 (weight SDS) = $\sqrt{}$X−0.6568917665; where: X = (Age + 0.258516924726631)/10. FP1 (BMI) = 1/$\sqrt{}$X − 1.435656586; FP2 (BMI) = ln(X) + 0.7232445915; where: X = Age/10.

[a)] Calculated from measurements at birth and the target ages of 3, 6 months, 1, 4, 10.8 (girls)/11.8 (boys) and 12.8 years;

[b)] Maternal education at delivery: ≤9 years, 9–12 years, > 12 years.

For all the interactions involving preeclampsia, the category "no" preeclampsia is the reference.

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severity of PE. Mild/moderate PE was in general positively associated with the development of length/height in boys, and with weight and BMI for both sexes. Severe PE was in general negatively associated with the development of length/height, weight and BMI except in girls, where severe PE was positively associated with weight and BMI after preschool ages. Severe PE was also associated with a larger waist-to-height ratio in late childhood in both sexes.

Apart from the Stavanger Study [3, 10], three earlier studies examined the association between PE and childhood growth. In all of those three studies, PE was examined as one entity

Table 3. Multiple linear regression analysis of waist-to-height ratio SDS in 586 Norwegian children born in 1993–1995 according to mother's pre-eclampsia status.

Independent variables	10.8/11.8 years[a], *n* = 519			12.8 years, *n* = 390		
	b	95% CI	*F*-test *P*[b]	b	95% CI	*F*-test *P*[b]
Intercept	-1.57	(-2.15, -0.98)	< 0.001	-0.93	(-1.53, -0.33)	0.002
Preeclampsia			**0.011**			**0.019**
None	0.00	Reference		0.00	Reference	
Mild/moderate	0.16	(-0.06, 0.38)		-0.03	(-0.25, 0.20)	
Severe	**0.47**	**(0.15, 0.79)**		**0.44**	**(0.12, 0.75)**	
Sex (male)	-0.07	(-0.26, 0.11)	0.435	-0.15	(-0.35, 0.04)	0.124
Maternal BMI (kg/m^2)	**0.07**	**(0.04, 0.09)**	**< 0.001**	**0.06**	**(0.03, 0.08)**	**< 0.001**
Maternal smoking (yes)	**0.25**	**(0.03, 0.47)**	**0.024**	0.21	(-0.02, 0.45)	0.072

Abbreviations: *n* = number of participants; CI = Confidence interval; SDS = Standard deviation scores; *F*-test *P* refers to exposure only; BMI = body mass index (kg/m^2).

Bold numbers indicate statistical significance

[a] 10.8 years for girls, 11.8 years for boys

[b] After backward stepwise selection from fully adjusted model.

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rather than by severity. First, in a Norwegian study of 4096 girls aged 13–19 years PE was positively associated with BMI, and our results are in accord [12]. Second, in a large cohort of Israeli adolescents, exposure to PE (n = 428) was positively associated with weight and BMI at 17 years of age in boys but not girls [22]. This corresponds to our findings in boys exposed to mild/moderate preeclampsia, but not severe preeclampsia. Third, in a study of three cohorts with a total of 4622 children, those exposed to PE had low birthweight, but catch-up growth postnatally [9]. This corresponds to our results in children exposed to mild/moderate PE, and girls, but not boys, exposed to severe PE. The discrepancies across studies may be due to different designs namely different ages at assessment and because in the other three studies [9, 12, 22] PE was not differentiated by severity.

To our knowledge, no previous publications exist on the associations between PE exposure and linear growth. In our study, boys exposed to mild/moderate PE had a recumbent length at birth similar to that of unexposed, but exceeded linear growth during preschool age, while those exposed to severe PE had a decreased linear growth compared to unexposed at all ages. PE had less impact on linear growth in girls, however both mild/moderate and severe PE was negatively associated with linear growth in girls. The decreased linear growth after exposure to severe PE is in contrast with studies on fetal growth retardation where postnatal catch-up in linear growth is reported [23, 24]. However, studies on very premature children born small for gestational age have reported that they may be less likely to have catch-up in linear growth, or only after 6 years of age [25]. IGF-I is one of the most important regulators of postnatal growth and is known to be lower in placental tissues and cord blood in women with severe, but not mild, PE [26, 27]. Therefore, poor linear growth in children exposed to severe PE might be due to effects on the growth hormone- IGF-1 axis [28–30], an effect that might be mediated through inflammation or perhaps the result of fetal programming. PE is characterized by inflammation and the cytokines of pregnancy could correlate with those in offspring until the age of 1 year [31, 32]. Furthermore, a pro-inflammatory status might induce apoptosis of the growth plate cartilage both prenatally and during infancy [33].

Weight and BMI were lower in children exposed to mild/moderate PE, and girls exposed to severe PE, but weight and BMI in these children were higher from school age and onwards when compared to unexposed children. This effect is similar to what is found in other children

born small for gestational age [25, 34] and in prematurely born children [35]. Prenatal starvation is associated with epigenetic changes that could persist throughout life, causing a tendency for energy conservation and thus overweight [36, 37]. Children with catch-up growth postnatally have better insulin sensitivity than other children, so these children will have a favorable linear growth and weight development [38]. However, most children born small for gestational age catch up in weight and length before 12 months of age [25], but this was not the case in our study subjects who experienced catch-up at a later age. This difference suggests that PE affects weight and BMI independently of small for gestational age status. Boys exposed to severe PE had lower weight and BMI during infancy and childhood when compared to the unexposed. These results are different from children born prematurely or small for gestational age. The effects of severe PE on weight trajectories in boys could be influenced by some of the same mechanisms as those for linear growth, like low levels of IGF-1, mediated through prematurity and inflammation [39].

Children exposed to severe PE had a higher waist-to-height ratio than the unexposed children in late childhood. Similar results have been found in children born small for gestational age, who continue to gain excess body fat even after catch-up in weight [25]. A high waist-to-height ratio is a known risk factor for insulin resistance and metabolic syndrome [34]. As severe PE is characterized by inflammation [40, 41], and studies indicate an association between inflammatory disorders in adults and metabolic syndrome [42] one can speculate that exposure to severe PE might indirectly and via inflammation be a risk factor for metabolic syndrome.

The current study shows different effects of mild/moderate and severe PE on childhood growth. This might be explained by different pathophysiology of the two conditions. Mild/moderate PE more often appears late whereas severe PE appears early in pregnancy. Early and late-onset PE differ by maternal age, pre-pregnancy BMI, maternal cardiac output, vascular resistance and endothelial damage [15, 41, 43]. Further, only early onset PE is associated with fetal growth restriction, due to incomplete invasion of trophoblast into the maternal spiral arteries, and changes in blood flow in umbilical arteries [4, 41]. Mild/moderate PE is more common in overweight mothers with metabolic syndrome, while severe PE is more common in normal weight women, but possibly characterized by more inflammation; thereby reflecting different maternal phenotypes by severity of PE with implications for child growth [15, 40].

There were differences between the sexes regarding the effect of PE on length/height and weight, and significant differences between the sexes regarding the effect of PE on BMI. While PE exposure in girls had some negative effects on linear growth, in boys mild/moderate PE exposure was generally positively associated, and severe PE negatively associated with linear growth. PE was generally positively associated with weight and BMI in boys and girls, while in boys only, severe PE was generally negatively associated with weight and BMI. Although there are inconsistencies in the literature regarding sex differences in growth after exposure to PE [10, 12, 22], boys are generally more prone to neonatal complications [44]; whether born to term and of adequate birthweight, small for gestational age [45] and extreme prematurity affects boys more severely than it does to girls [46].

Statistical considerations

We did not adjust for gestational age or birthweight in the analyses because they are intermediary variables on the causal pathway from PE to growth in childhood, and adjusting for them could attenuate the association between PE and growth. Further, as gestational age and birthweight may be influenced by unknown factors, adjusting for them could give rise to spurious

associations between PE and growth. Therefore, modeling conditional growth (and thereby correcting for the regression to the mean) was not feasible.

Other strategies to compare growth between the three groups unexposed, exposed to mild/moderate and exposed to severe PE could have been pursued if we wanted to separate from the effects of gestational age and child's birth weight. Stratification is a statistically inferior method of adjusting, and as explained, adjustment for these variables cannot be done. Further, stratification would lead to a loss of power if used.

For the same reasons, we did not adjust for pubertal status. Some effects of PE could be indirect and mediated through prematurity and being born small for gestational age, but the distinct differences in growth between children exposed to PE from those who are otherwise born small for gestational age indicates that PE has effects on growth other than through pathways related to gestational age or birthweight.

The extremes of Figs 1 and 2 should be interpreted with caution. The mathematical model attempting to predict the best curve might be influenced by very few observations of length SDS and weight SDS before age 0.0 years, particularly in the group of mild/moderate PE and in the unexposed group.

Strengths and limitations

An advantage of the study population is its homogeneity of socio-economic status and ethnicity. Furthermore, the measurements of height and weight were sampled repeatedly during childhood, enabling the possibility of calculating a predictive model of growth, i.e., the length/height, weight or BMI of a child at a given age, by sex or PE exposure status.

The study also has some limitations. The original matching on maternal age and birth date in the analyses was compromised due to more missing participants in the unexposed than the exposed group, which may be a source of bias. However, we adjusted for maternal age in the statistical analyses to avoid confounding bias. We described above why the analyses could not be adjusted for gestational age or birthweight; therefore, the study might be biased. A matching of participants on gestational age and birthweight could have reduced bias. The anthropometric measurements from the well-baby clinics were not measured by the research team; however, routine measurements at well-baby clinics are standardized. Repeated measurements of waist circumference (a more accurate measurement of adiposity) and skinfolds were not performed at well-baby clinics [17]. Furthermore, we do not have consecutive anthropometric measurements across ages in childhood. There was a considerable attrition at the second follow-up of around 50%, which may be a source of selection bias. However, there were no known perinatal differences between those who assented to the first follow-up and those who did not assent, and most baseline characteristics between those who participated in the first and the second follow-ups did not differ. The average BMI of girls who participated in the first but not the second follow-up was higher than the BMI of girls who participated in both follow-ups. However, there is no reason to assume that the girls with the higher BMI who were lost to the second follow-up were overrepresented in any particular exposure group. Therefore, the association between PE and growth would not be expected to be biased by the change in BMI of the girls from the first to the second follow-up.

Conclusions

From birth to adolescence, linear growth, weight and BMI trajectories differed among the PE exposed children by severity of PE, age and sex compared with the unexposed. In general, PE exposure was negatively associated with linear growth, while in girls positive associations with weight and BMI were observed. The trajectories might differ from those found in studies of

children born small for gestational age. The present results underline that fetal life is a particularly sensitive period regarding growth, supporting the hypothesis that an adverse intrauterine environment may affect postnatal development, anthropometry throughout childhood and probably also the metabolic phenotype. Our results may have implications for targeted approaches for healthy growth and development.

Supporting information

S1 Fig. Directed acyclic graph of the association between preeclampsia and growth with confounders. Green with arrowhead = exposure, blue with black bar = outcome, red = ancestor of exposure and outcome, blue = ancestor of outcome. Green arrows = causal path, red arrows = biasing path.
(PDF)

S1 Table. Multiple linear regression analyses of waist circumference SDS at 10.8/11.8 and 12.8 years of age in 593 children according to mother's preeclampsia status.
(DOCX)

S2 Table. Multiple linear regression analyses of triceps skinfold SDS at 10.8/11.8 and 12.8 years of age in 589 children according to mother's preeclampsia status.
(DOCX)

S3 Table. Multiple linear regression analyses of waist circumference SDS at 12.8 years of age in 487 children according to mother's preeclampsia status.
(DOCX)

S1 Statistics File. SPSS dataset.
(SAV)

S2 Statistics File. STATA dataset.
(DTA)

S3 Statistics File. Text document with script for R.
(R)

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Author Contributions

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Formal analysis: KKB GEE.

Funding acquisition: KKB KØ.

Investigation: KKB KØ.

Methodology: KKB KØ GEE MRF PBJ.

Project administration: KØ.

Supervision: KØ PBJ.

Validation: KKB KØ GEE MRF PBJ.

Visualization: KKB KØ GEE MRF PBJ.

Writing – original draft: KKB.

Writing – review & editing: KKB KØ GEE MRF PBJ.

References

1. Turner JA. Diagnosis and management of pre-eclampsia: an update. International journal of women's health. 2010; 2:327–37. Epub 2010/12/15. https://doi.org/10.2147/IJWH.S8550 PMID: 21151680
2. Jim B, Sharma S, Kebede T, Acharya A. Hypertension in pregnancy: a comprehensive update. Cardiol Rev. 2010; 18(4):178–89. Epub 2010/06/12. https://doi.org/10.1097/CRD.0b013e3181c60ca6 PMID: 20539101
3. Odegard RA, Vatten LJ, Nilsen ST, Salvesen KA, Austgulen R. Preeclampsia and fetal growth. Obstet Gynecol. 2000; 96(6):950–5. PMID: 11084184
4. Huppertz B. Placental origins of preeclampsia: challenging the current hypothesis. Hypertension. 2008; 51(4):970–5. https://doi.org/10.1161/HYPERTENSIONAHA.107.107607 PMID: 18259009
5. Gillman MW. The first months of life: a critical period for development of obesity. Am J Clin Nutr. 2008; 87(6):1587–9. Epub 2008/06/11. PMID: 18541543
6. Taveras EM, Rifas-Shiman SL, Belfort MB, Kleinman KP, Oken E, Gillman MW. Weight status in the first 6 months of life and obesity at 3 years of age. Pediatrics. 2009; 123(4):1177–83. Epub 2009/04/02. https://doi.org/10.1542/peds.2008-1149 PMID: 19336378
7. de Boo HA, Harding JE. The developmental origins of adult disease (Barker) hypothesis. Aust N Z J Obstet Gynaecol. 2006; 46(1):4–14. Epub 2006/01/31. https://doi.org/10.1111/j.1479-828X.2006.00506.x PMID: 16441686
8. van der Steen M, Hokken-Koelega AC. Growth and Metabolism in Children Born Small for Gestational Age. Endocrinol Metab Clin North Am. 2016; 45(2):283–94. https://doi.org/10.1016/j.ecl.2016.01.008 PMID: 27241965
9. Pizzi C, Cole TJ, Richiardi L, Dos-Santos-Silva I, Corvalan C, De Stavola B. Prenatal influences on size, velocity and tempo of infant growth: findings from three contemporary cohorts. PloS one. 2014; 9(2):e90291. https://doi.org/10.1371/journal.pone.0090291 PMID: 24587314
10. Ogland B, Vatten LJ, Romundstad PR, Nilsen ST, Forman MR. Pubertal anthropometry in sons and daughters of women with preeclamptic or normotensive pregnancies. Arch Dis Child. 2009; 94(11):855–9. Epub 2009/07/04. https://doi.org/10.1136/adc.2008.150870 PMID: 19574235
11. Ogland B, Nilsen ST, Forman MR, Vatten LJ. Pubertal development in daughters of women with pre-eclampsia. Arch Dis Child. 2011; 96(8):740–3. Epub 2010/10/12. https://doi.org/10.1136/adc.2009.178434 PMID: 20930013
12. Vatten LJ, Romundstad PR, Holmen TL, Hsieh CC, Trichopoulos D, Stuver SO. Intrauterine exposure to preeclampsia and adolescent blood pressure, body size, and age at menarche in female offspring. Obstet Gynecol. 2003; 101(3):529–33. PMID: 12636958
13. Byberg KK, Ogland B, Eide GE, Oymar K. Birth after preeclamptic pregnancies: association with allergic sensitization and allergic rhinoconjunctivitis in late childhood; a historically matched cohort study. BMC Pediatr. 2014; 14(1):101.
14. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group. Lancet. 1994; 343(8898):619–29. Epub 1994/03/12. PMID: 7906809
15. Alsnes IV, Janszky I, Forman MR, Vatten LJ, Okland I. A population-based study of associations between preeclampsia and later cardiovascular risk factors. Am J Obstet Gynecol. 2014; 211(6):657 e1–7.
16. Juliusson PB, Roelants M, Hoppenbrouwers K, Hauspie R, Bjerknes R. Growth of Belgian and Norwegian children compared to the WHO growth standards: prevalence below -2 and above +2 SD and the

effect of breastfeeding. Arch Dis Child. 2011; 96(10):916–21. https://doi.org/10.1136/adc.2009.166157 PMID: 19948662

17. Brannsether B, Roelants M, Bjerknes R, Juliusson PB. Waist circumference and waist-to-height ratio in Norwegian children 4–18 years of age: reference values and cut-off levels. Acta Paediatr. 2011; 100 (12):1576–82. Epub 2011/06/02. https://doi.org/10.1111/j.1651-2227.2011.02370.x PMID: 21627692

18. Brannsether B, Roelants M, Bjerknes R, Juliusson PB. References and cutoffs for triceps and subscapular skinfolds in Norwegian children 4–16 years of age. Eur J Clin Nutr. 2013; 67(9):928–33. https://doi.org/10.1038/ejcn.2013.91 PMID: 23632751

19. Juliusson PB, Roelants M, Nordal E, Furevik L, Eide GE, Moster D, et al. Growth references for 0–19 year-old Norwegian children for length/height, weight, body mass index and head circumference. Ann Hum Biol. 2013; 40(3):220–7. https://doi.org/10.3109/03014460.2012.759276 PMID: 23414181

20. Alsnes IV, Janszky I, Asvold BO, Okland I, Forman MR, Vatten LJ. Maternal Preeclampsia and Androgens in the Offspring around Puberty: A Follow-Up Study. PloS one. 2016; 11(12):e0167714. https://doi.org/10.1371/journal.pone.0167714 PMID: 27992610

21. Royston P, Sauerbrei W. MFP: Multivariable Model-Building with Fractional Polynomials. Multivariable Model-Building: John Wiley & Sons, Ltd; 2008. p. 115–50.

22. Seidman DS, Laor A, Gale R, Stevenson DK, Mashiach S, Danon YL. Pre-eclampsia and offspring's blood pressure, cognitive ability and physical development at 17-years-of-age. Br J Obstet Gynaecol. 1991; 98(10):1009–14. PMID: 1751432

23. Westerberg AC, Henriksen C, Ellingvag A, Veierod MB, Juliusson PB, Nakstad B, et al. First year growth among very low birth weight infants. Acta Paediatr. 2010; 99(4):556–62. https://doi.org/10.1111/j.1651-2227.2009.01667.x PMID: 20096031

24. Ong KK, Preece MA, Emmett PM, Ahmed ML, Dunger DB, Team AS. Size at birth and early childhood growth in relation to maternal smoking, parity and infant breast-feeding: longitudinal birth cohort study and analysis. Pediatr Res. 2002; 52(6):863–7. https://doi.org/10.1203/00006450-200212000-00009 PMID: 12438662

25. Druet C, Ong KK. Early childhood predictors of adult body composition. Best practice & research Clinical endocrinology & metabolism. 2008; 22(3):489–502.

26. Dubova EA, Pavlov KA, Lyapin VM, Kulikova GV, Shchyogolev AI, Sukhikh GT. Expression of insulin-like growth factors in the placenta in preeclampsia. Bull Exp Biol Med. 2014; 157(1):103–7. https://doi.org/10.1007/s10517-014-2502-4 PMID: 24915949

27. Vatten LJ, Odegard RA, Nilsen ST, Salvesen KA, Austgulen R. Relationship of insulin-like growth factor-I and insulin-like growth factor binding proteins in umbilical cord plasma to preeclampsia and infant birth weight. Obstet Gynecol. 2002; 99(1):85–90. Epub 2002/01/05. PMID: 11777516

28. Beardsall K, Vanhaesebrouck S, Frystyk J, Ogilvy-Stuart AL, Vanhole C, van Weissenbruch M, et al. Relationship between insulin-like growth factor I levels, early insulin treatment, and clinical outcomes of very low birth weight infants. J Pediatr. 2014; 164(5):1038–44 e1. https://doi.org/10.1016/j.jpeds.2013.12.046 PMID: 24518169

29. Lanes R, Nieto C, Bruguera C, Moncada G, Moret LA, Lifshitz F. Growth hormone release in response to growth hormone-releasing hormone in term and preterm neonates. Biol Neonate. 1989; 56(5):252–6. PMID: 2513890

30. Guasti L, Silvennoinen S, Bulstrode NW, Ferretti P, Sankilampi U, Dunkel L. Elevated FGF21 leads to attenuated postnatal linear growth in preterm infants through GH resistance in chondrocytes. J Clin Endocrinol Metab. 2014; 99(11):E2198–206. https://doi.org/10.1210/jc.2014-1566 PMID: 25137423

31. Herberth G, Hinz D, Roder S, Schlink U, Sack U, Diez U, et al. Maternal immune status in pregnancy is related to offspring's immune responses and atopy risk. Allergy. 2011; 66(8):1065–74. Epub 2011/03/30. https://doi.org/10.1111/j.1398-9995.2011.02587.x PMID: 21443636

32. Szarka A, Rigo J Jr., Lazar L, Beko G, Molvarec A. Circulating cytokines, chemokines and adhesion molecules in normal pregnancy and preeclampsia determined by multiplex suspension array. BMC Immunol. 2010; 11:59. Epub 2010/12/04. https://doi.org/10.1186/1471-2172-11-59 PMID: 21126355

33. Sederquist B, Fernandez-Vojvodich P, Zaman F, Savendahl L. Recent research on the growth plate: Impact of inflammatory cytokines on longitudinal bone growth. J Mol Endocrinol. 2014; 53(1):T35–44. https://doi.org/10.1530/JME-14-0006 PMID: 24711646

34. Yadav S, Rustogi D. Small for gestational age: growth and puberty issues. Indian Pediatr. 2015; 52 (2):135–40. PMID: 25691182

35. Ong KK, Kennedy K, Castaneda-Gutierrez E, Forsyth S, Godfrey KM, Koletzko B, et al. Postnatal growth in preterm infants and later health outcomes: a systematic review. Acta Paediatr. 2015; 104 (10):974–86. https://doi.org/10.1111/apa.13128 PMID: 26179961

36. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, et al. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A. 2008; 105 (44):17046–9. https://doi.org/10.1073/pnas.0806560105 PMID: 18955703

37. Jain V, Singhal A. Catch up growth in low birth weight infants: striking a healthy balance. Reviews in endocrine & metabolic disorders. 2012; 13(2):141–7.

38. Jensen RB, Thankamony A, Day F, Scott RA, Langenberg C, Kirk J, et al. Genetic markers of insulin sensitivity and insulin secretion are associated with spontaneous postnatal growth and response to growth hormone treatment in short SGA children: the North European SGA Study (NESGAS). J Clin Endocrinol Metab. 2015; 100(3):E503–7. Epub 2014/12/17. https://doi.org/10.1210/jc.2014-3469 PMID: 25494864

39. Hellstrom A, Ley D, Hansen-Pupp I, Hallberg B, Lofqvist C, van Marter L, et al. Insulin-like growth factor 1 has multisystem effects on foetal and preterm infant development. Acta Paediatr. 2016; 105(6):576–86. https://doi.org/10.1111/apa.13350 PMID: 26833743

40. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005; 365(9461):785–99. https://doi.org/10.1016/S0140-6736(05)17987-2 PMID: 15733721

41. Valensise H, Vasapollo B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. Hypertension. 2008; 52(5):873–80. https://doi.org/10.1161/HYPERTENSIONAHA.108.117358 PMID: 18824660

42. Davidovici BB, Sattar N, Prinz J, Puig L, Emery P, Barker JN, et al. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. J Invest Dermatol. 2010; 130(7):1785–96. Epub 2010/05/07. https://doi.org/10.1038/jid.2010.103 PMID: 20445552

43. Orak U, Celik E, Kavak SB, Demirel I, Atilgan R, Aydin S, et al. Tenascin C levels in patients with mild and severe preeclampsia. J Matern Fetal Neonatal Med. 2016; 29(2):270–3. https://doi.org/10.3109/14767058.2014.998191 PMID: 25567561

44. Aibar L, Puertas A, Valverde M, Carrillo MP, Montoya F. Fetal sex and perinatal outcomes. J Perinat Med. 2012; 40(3):271–6. https://doi.org/10.1515/jpm-2011-0137 PMID: 22505506

45. Simchen MJ, Weisz B, Zilberberg E, Morag I, Weissmann-Brenner A, Sivan E, et al. Male disadvantage for neonatal complications of term infants, especially in small-for-gestational age neonates. J Matern Fetal Neonatal Med. 2014; 27(8):839–43. https://doi.org/10.3109/14767058.2013.845658 PMID: 24047512

46. Mansson J, Fellman V, Stjernqvist K, Group ES. Extremely preterm birth affects boys more and socioeconomic and neonatal variables pose sex-specific risks. Acta Paediatr. 2015; 104(5):514–21. https://doi.org/10.1111/apa.12937 PMID: 25620552

S1 Fig. Directed acyclic graph of the association between preeclampsia and growth with confounders.

Green with arrowhead = exposure
Blue with black bar = outcome
Red = ancestor of exposure and outcome
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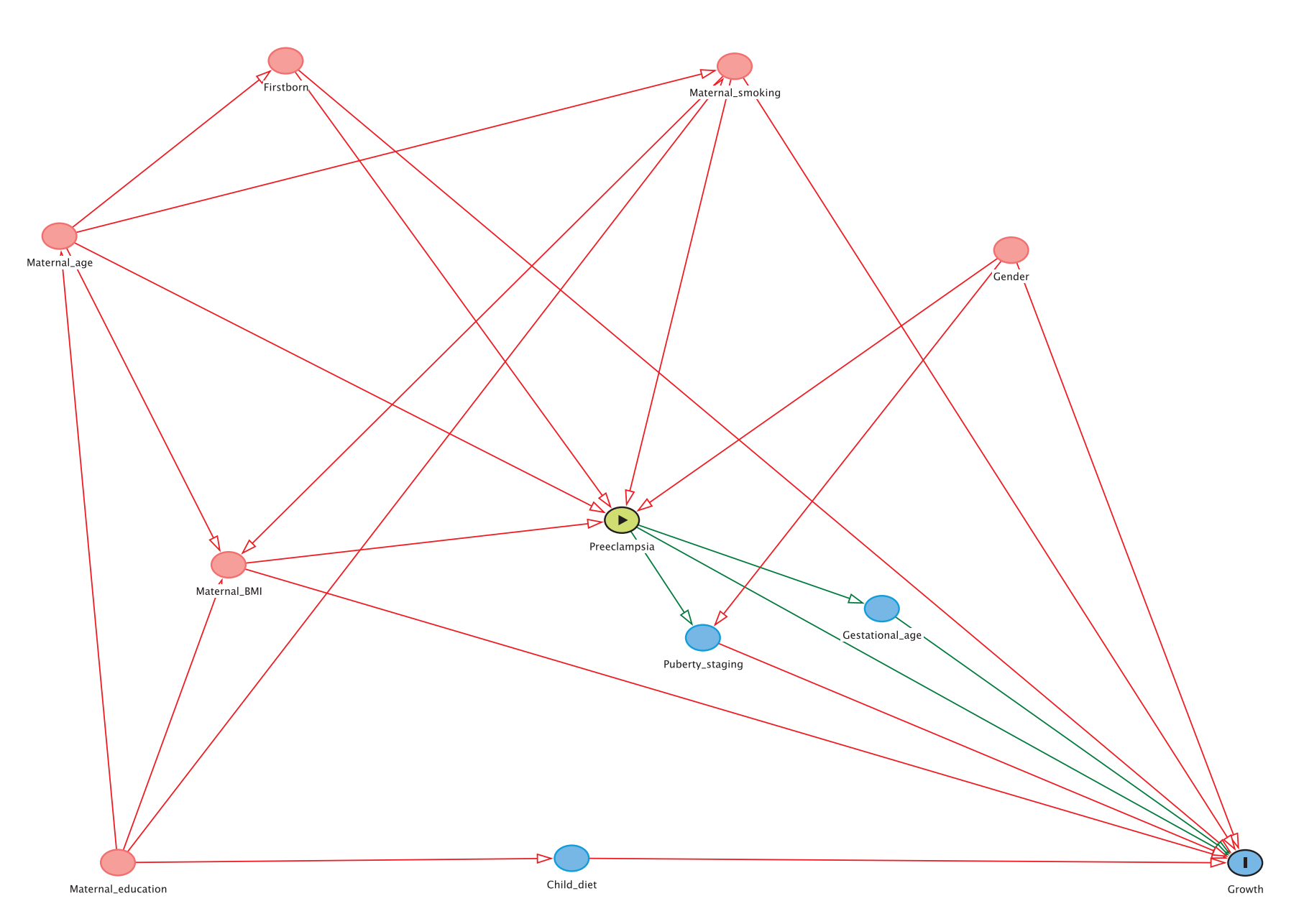
Green arrows = causal path
Red arrows = biasing path


Firstborn
Maternal_smoking
Maternal_age
Gender
Preeclampsia
Maternal_BMI
Gestational_age
Puberty_staging
Maternal_education
Child_diet
Growth

S1 table. Multiple linear regression analyses of waist circumference SDS at 10.8/11.8 and 12.8 years of age in 593 children according to mother's preeclampsia status

	10.8/11.8 years[a], *n* = 519			12.8 years, *n* = 390		
Independent variables	**b**	**95 % CI**	***F*-test *P***	**b**	**95 % CI**	***F*-test *P***
Intercept	-1.71	(-2.29, -1.13)	< 0.001	-1.09	(-1.70, 0.48)	0.001
Preeclampsia			0.098			0.344
None	0.00	Reference		0.00	Reference	
Mild/moderate	0.18	(-0.04, 0.40)		0.04	(-0.19, 0.27)	
Severe	0.27	(-0.14, 0.53)		0.24	(-0.08, 0.56)	
Sex (male)	-0.09	(-0.28, 0.10)	0.352	-0.19	(-0.39, 0.01)	0.056
Maternal BMI (kg/m^2)	0.08	(0.05, 0.10)	< 0.001	0.06	(0.04, 0.09)	< 0.001
Maternal smoking (yes)	0.11	(-0.10, 0.33)	0.301	0.12	(-0.12, 0.36)	0.331

S2 table. Multiple linear regression analyses of triceps skinfold SDS at 10.8/11.8 and 12.8 years of age in 589 children according to mother's preeclampsia status

	10.8/11.8 years[a], *n* = 515			12.8 years, *n* = 389		
Independent variables	**b**	**95 % CI**	***F*-test *P***	**b**	**95 % CI**	***F*-test *P***
Intercept	-1.72	(-2.31, -1.13)	< 0.001	-1.31	(-1.97, -0.66)	< 0.001
Preeclampsia			0.388			0.903
None	0.00	Reference		0.00	Reference	
Mild/moderate	0.15	(-0.07, 0.37)		-0.03	(-0.27, 0.22)	
Severe	0.03	(-0.29, 0.34)		0.06	(-0.29, 0.41)	
Sex (male)	0.20	(0.02, 0.39)	0.031	0.02	(-0.19, 0.24)	0.835
Maternal BMI (kg/m^2)	0.06	(0.03, 0.08)	< 0.001	0.05	(0.02, 0.08)	< 0.001
Maternal smoking (yes)	0.06	(-0.15, 0.28)	0.570	-0.10	(-0.36, 0.16)	0.437

S3 table. Multiple linear regression analyses of waist circumference SDS at 12.8 years of age in 487 children according to mother's preeclampsia status

		12.8 years, *n* = 380	
Independent variables	**b**	**95 % CI**	***F*-test *P***
Intercept	-2.13	(-2.74, -1.52)	< 0.001
Preeclampsia			0.384
None	0.00	Reference	
Mild/moderate	0.15	(-0.07, 0.38)	
Severe	0.10	(-0.22, 0.43)	
Sex (male)	0.12	(-0.08, 0.31)	0.241
Maternal BMI (kg/m^2)	0.07	(0.04, 0.10)	< 0.001
Maternal smoking (yes)	0.13	(-0.11, 0.37)	0.284

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Clinical and Translational Allergy

RESEARCH

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Body mass index and physical activity in early childhood are associated with atopic sensitization, atopic dermatitis and asthma in later childhood

Kristine Kjer Byberg[1*], Geir Egil Eide[2,3], Michele R. Forman[4], Pétur Benedikt Júlíusson[5,6] and Knut Øymar[1,6]

Abstract

Background: The results of studies on the associations of childhood excessive weight/obesity and physical activity with atopic sensitization and atopic diseases are inconsistent. We studied the associations of anthropometry and physical activity in childhood with atopic sensitization and atopic diseases in late childhood.

Methods: In a cohort study including cases exposed to preeclampsia during pregnancy and controls, anthropometry and physical activity were assessed at several ages in 617 children. Associations with atopic sensitization and atopic diseases in late childhood were analysed using multiple logistic regression.

Results: Body mass index standard deviation score (BMI SDS) at 1 year and low physical activity at 3–6 years were positively associated with atopic sensitization at 12.8 years [adjusted odds ratio (OR) 1.22; 95 % confidence interval (1.00, 1.49) and OR 2.36; (1.15, 4.81), respectively]. Change in BMI SDS from 1 to 4 years, BMI SDS at 4 years, and high physical activity at 6–10 years were positively associated with atopic dermatitis by 10.8 years [OR 1.46; (1.11, 1.92); OR 1.32; (1.06, 1.65) and OR 1.94; (1.16, 3.24); respectively]. Low physical activity at 3–6 and 6–10 years were positively associated with asthma by 10.8 years [OR 3.61; (1.56, 8.36) and OR 2.52; (1.24, 5.12), respectively].

Conclusions: BMI and physical activity in early childhood were associated with atopic sensitization, atopic dermatitis and asthma in later childhood. Larger cohorts with repeated measurements of both predictors and outcomes are required to further elucidate this issue.

Trial registration Our study was observational without any clinical intervention on the participants. Therefore, no trial registration number is available

Keywords: Allergic rhinitis, Anthropometry, Asthma, Atopic dermatitis, Child

Background

The prevalence of obesity, allergy and asthma has increased worldwide during the last decades [1, 2]. An association between obesity and asthma has been suggested both in early and late childhood [3], where obesity precedes asthma in prospective studies [4]; the association between obesity and allergy is inconsistent [5].

High birth weight or body mass index (BMI; kg/m^2) in early childhood is associated with obesity into later childhood [6]. Atopic sensitization and atopic disease commonly start in early childhood [7], and associations between accelerated weight gain in early childhood and subsequent atopic sensitization, allergic rhinitis [8] and asthma [9], have been suggested, but not for atopic dermatitis. Physical activity during childhood may also be associated with atopy, either directly or due to an influence on body composition [10].

Many of these associations of childhood obesity and physical activity with atopy appear in cross-sectional

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studies [5, 10, 11]. Few longitudinal studies exist, mainly from registers [4, 5, 11].

It is unknown if an accelerated weight gain from birth is associated with an increased risk of atopy. Furthermore, it is unknown if a positive association between BMI and asthma in children is limited to those with atopy.

The present cohort study was derived from a case control study nested within three birth cohorts that focused on preeclampsia, that had repeated anthropometric measurements, linked information across childhood, and measures of atopic disease at clinical follow-ups. The aim was to study whether weight-related anthropometrics, changes in BMI SDS and physical activity at different ages in childhood are associated with atopic sensitization and atopic disease by late childhood. We hypothesized that childhood excessive weight/obesity or accelerated weight gain is positively associated and physical activity negatively associated with atopic sensitization and atopic diseases.

Methods

Study population and design

The study was a part of "the Stavanger study" described in detail previously [12]. From a population-based cohort, a nested case–control study was conducted, where offspring exposed to maternal preeclampsia and unexposed offspring were identified from all births delivered in Stavanger University hospital in 1993–1995. For each exposed offspring, two matched unexposed offspring were selected: one as the next born in the hospital (i.e. a birth match) and one as the next born matched on maternal age (i.e. a risk factor for preeclampsia). 1025 children, 366 in the preeclampsia and 659 in the control group, were invited to participate in a first follow-up study at 10.8 years (girls) and 11.8 years (boys), and a second follow-up at 12.8 years (both sexes) [13]. The ages at follow-up were selected to coincide with the ages of pubertal onset and menarche of the children. Our analyses disregarded the matched pairs due to missing participants. Therefore, in our study, data were analysed as a historical cohort adjusting for preeclampsia and maternal age, including all the children who participated in both follow-ups, with predictors as listed.

The study was approved by the Norwegian Data Inspectorate, the Regional Committee for Ethics in medical research Western Norway, and the Institutional Review Boards of the National Cancer Institute and University of Texas at Austin, United States. Mothers and children signed an informed consent/assent form at follow-up.

Outcomes

The outcomes allergic rhinoconjunctivitis, atopic dermatitis, asthma ever (evaluated at first follow-up), atopic sensitization and current asthma (evaluated at second follow-up) were defined as follows:

Atopic sensitization Blood specific immunoglobulin E (IgE) $\geq$ 0.35 kU/l for at least one common allergen. Blood was drawn at second follow-up and analysed by Phadiatop®, fx5E® and by specific IgE when positive [13]. Included allergens are shown in Fig. 1. The levels of specific IgE $\geq$ 0.35 were added, and high grade sensitization was defined as a sum >3.9 kU/l: above the lower quartile of all children being sensitized. The ordinal outcome variable atopic sensitization was categorized as: no, low grade and high grade sensitization.

Atopic disease: Asthma ever, allergic rhinoconjunctivitis or atopic dermatitis At first follow-up, questions on atopic disease of the child were asked to the mothers: "Has your child ever had doctor-diagnosed asthma or ever diagnosed with allergy in nose/eyes (hay fever) or atopic dermatitis (childhood eczema)?" Response of "yes" was classified as having the respective diagnosis.

Current asthma At second follow-up, the children answered a questionnaire on reported asthma symptoms and medication during the last year according to the International Study of Asthma and Allergies in Childhood (ISAAC) and asthma ever was recorded [14]. Current asthma at second follow-up was defined as asthma ever, in addition to asthma symptoms or the use of asthma medication the last 12 months (Additional file 1).

Predictors

Birthweight and gestational age were abstracted from hospital records. Recordings of length/height and weight measurements were collected from well-baby clinics at the target ages of 3, 6 and 12 months and 4 years. Trained nurse researchers measured height, weight, triceps skinfold and waist circumference twice in offspring at both

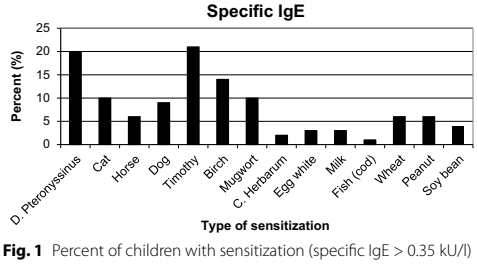

Fig. 1 Percent of children with sensitization (specific IgE > 0.35 kU/l) to common allergens, measured at 12.8 years (n = 388). *D: dermatophagoides, C: cladosporium*

follow-ups, and subscapular skinfold was measured twice at second follow-up; the average of each was used in the analysis [12]. Skinfolds were measured with Harpenden Skinfold Calliper®.

Change in weight and BMI SDS was calculated as the difference between weight and BMI SDS from each target age to the next.

At the first follow-up, the "Stanford Brief Activity Survey", a questionnaire validated for adults, was administered to the mothers requesting responses about physical activity of the child. Specifically the answers to the following questions were extracted: "How active was your child at 3–6 years?" and "How active was your child at 6–10 years?" The response categories were categorized as: passive and/or not so active = low activity, active = normal, very active = high activity [15].

Confounders

Potential confounders included categorical and continuous variables, i.e. sex; gestational age; birth order (firstborn or not); duration of breastfeeding (categories: none; <3; >3 months. This information was extracted from maternal questionnaire, and used in analyses for predictors at target ages ≥6 months); mother's preeclampsia (none, mild/moderate, severe) [16]; mother's BMI (weight at first antenatal visit and height at first follow-up); mother's smoking (at first antenatal visit); mother's doctor-diagnosed asthma [13]; mother's education (from maternal questionnaire: <9; 9–12; >12 years) and mother's age. This is illustrated in a Directed Acyclic Graph (Additional file 1: Figure S1) [17].

Statistical methods

Descriptive statistics were analysed as means, standard deviations, numbers and percentages for the main predictors and outcomes.

There was a wide range of gestational ages at birth due to the inclusion of offspring of preeclampsia and normotensives and a wide age range at later well-child visits, analysing actual values for anthropometrics as predictors would therefore not be appropriate. Instead, standard deviation scores (SDS) based on anthropometric values and actual ages were computed from validated references [18–21]. Conversions into SDS were done using R version 2.6.2 (R Development Core Team, Vienna, Austria).

The associations between anthropometrics and physical activity for each target age (see predictors), and outcomes of atopic sensitization and atopic diseases in late childhood were analysed using multiple binary and ordinal logistic regression analyses (the latter for outcome of atopic sensitization). Separate analyses of the predictors were done for each follow-up time.

Each variable was entered separately into simple regression models. Next, all potential confounders were included in fully adjusted models. Backward stepwise selections were performed to remove non-significant confounders, unless there was ≥15 % change in effect size upon removal of the confounder. Last, final models for each target age included anthropometrics, physical activity, sex of the child and all remaining confounders.

For each predictor, odds ratios with p-values from likelihood ratio tests and 95 % confidence intervals are reported. Interactions between anthropometrics and physical activity with potential confounders were tested. The significance level was 0.05 for all tests.

Also, to study possible non-straight-line associations between BMI SDS and the outcomes, multiple fractional polynomial regression (MFPR) was used with the conservative requirement of $p \leq 0.01$ for non-straight-line terms.

Due to missing values the number of participants varied between the different analyses.

IBM SPSS for windows (version 22.0.0, Chicago, Ill., USA) was used for descriptive statistics and logistic regression, and Stata SE 14 for MFPR.

Results

Characteristics of the participants

The numbers of participants in each follow-up have been published previously [13]. Briefly, 617 children assented to participate at the first follow-up and 470 at the second follow-up. There were more girls with high BMI in the first than second follow-up, and more children with atopic dermatitis in the first than the second follow-up. Otherwise, baseline characteristics were similar between those who assented to the first follow-up only and those who assented to both follow-ups [13]. The percentages of children sensitized to different allergens appear in Fig. 1. Clinical characteristics of the participants appear in Table 1.

Impact of anthropometrics (Tables 2, 3, 4)

BMI SDS at 1 year was positively associated with atopic sensitization at 12.8 years with a borderline significance (Table 2). Change in BMI SDS from 1 to 4 years and BMI SDS at 4 years were positively associated with atopic dermatitis ever at the first follow-up (Tables 2, 3).

Birthweight/BMI SDS and changes in weight or BMI SDS were not associated with allergic rhinoconjunctivitis (Tables 2, 3) or asthma (Table 4 and Additional file 2: Table S1). Skinfolds, waist circumference and waist-to-height ratio at the follow-ups were not associated with atopic sensitization or atopic disease (Additional file 2: Table S2).

Table 1 Descriptive statistics for predictors and outcomes for 617[a] children included in a matched cohort study with follow-up from birth to 12–13 years in the Stavanger area, Norway

Predictors	n	Mean	SD
Birthweight (kg)	606	3.37	0.71
BMI 3 months	541	16.4	1.52
BMI 6 months	559	17.2	1.53
BMI 1 year	559	17.2	1.49
BMI 4 years	477	15.9	1.43
BMI first follow-up[b]	610	18.0	2.91
BMI second follow-up[c]	466	18.8	3.00
Waist circumference (cm) first follow-up	610	63.5	7.80
Waist circumference (cm) second follow-up	466	68.0	7.72
Triceps skinfold (mm) first follow-up	605	11.7	4.63
Triceps skinfold (mm) second follow-up	465	12.1	4.81
Waist-to-height ratio first follow-up	610	0.42	0.04
Waist-to-height ratio second follow-up	466	0.43	0.05
Subscapular skinfold (mm) second follow-up	450	8.21	3.24
	n		**%**
Physical activity 3-6 years	601		
Low	72		12
Normal	370		62
High	159		26
Physical activity 6–10 years	596		
Low	99		17
Normal	376		63
High	121		20
Outcome			
Atopic sensitization at second follow-up[d]	133/388		34
Allergic rhinoconjunctivitis ever by first follow-up	131/595		22
Atopic dermatitis ever by first follow-up	149/596		25
Asthma ever by first follow-up	53/590		9
Current asthma at second follow-up	37/458		8

SD standard deviation, *BMI* body mass index (kg/m^2)

[a] Due to missing values and variation in response, the number of participants varied between the different predictors and outcomes

[b] First follow-up: 10.8 years (girls), 11.8 years (boys)

[c] Second follow-up: 12.8 years

[d] 99 (25.5 %) had high grade atopic sensitization (sum of specific IgE $\geq$ 3.9 kU/l)

Impact of physical activity (Tables 2, 4)

Low physical activity at 3–6 years was positively associated with atopic sensitization at 12.8 years (Table 2). High physical activity at 6–10 years was positively associated with atopic dermatitis ever at the first follow-up (Table 2). Low physical activity at 3–6 and 6–10 years were positively associated with asthma ever at the first follow-up (Table 4). Physical activity was not associated with allergic rhinoconjunctivitis.

In the MFPR analyses, no non-straight-line associations were found for anthropometrics or physical activity with atopic sensitization or atopic diseases (data not shown).

Discussion

In this cohort study of children followed from birth to 12.8 years, after adjusting for potential confounders, BMI in childhood was positively associated with atopic sensitization and atopic dermatitis in late childhood. High and

Table 2 The adjusted odds ratios of atopic sensitization and atopic disease in adolescence in 617 Norwegian children by weight/BMI SDS and physical activity after backward stepwise selection of potential confounders (one model for each predictor variable)

Predictor	Outcome variable (final analyses)											
	Atopic sensitization[a,b]				Allergic rhinoconjunctivitis[a]				Atopic dermatitis[c]			
Age	n	OR	95 % CI	LR-p	n	OR	95 % CI	LR-p	n	OR	95 % CI	LR-p
Weight SDS												
Birth	380	1.05	(0.87, 1.26)	0.609	580	0.92	(0.77, 1.10)	0.338	544	1.04	(0.88, 1.22)	0.638
BMI SDS												
3 months	353	1.13	(0.90, 1.41)	0.315	521	0.91	(0.73, 1.14)	0.427	487	1.04	(0.84, 1.30)	0.694
6 months	363	1.15	(0.93, 1.42)	0.205	537	0.91	(0.74, 1.12)	0.390	503	1.05	(0.86, 1.28)	0.654
1 year	363	*1.22*	*(1.00, 1.49)*	*0.050*	537	0.97	(0.80, 1.18)	0.795	503	1.06	(0.87, 1.28)	0.557
4 years[d]	320	1.01	(0.80, 1.27)	0.934	456	0.86	(0.69, 1.08)	0.191	427	*1.32*	*(1.06, 1.65)*	*0.012*
First follow-up[e]	358	0.95	(0.79, 1.15)	0.612	562	0.87	(0.73, 1.04)	0.126	527	1.11	(0.93, 1.33)	0.225
Second follow-up[e]	354	0.96	(0.79, 1.17)	0.680				N.A.				N.A.
Physical activity												
At 3–6 years[f]	320			*0.039*	456			0.157	427			0.519
Normal	192	1.00	Reference		277	1.00	Reference		259	1.00	Reference	
Low	40	*2.36*	*(1.15, 4.81)*		57	1.60	(0.83, 3.09)		57	1.30	(0.65, 2.61)	
High	88	0.90	(0.50, 1.61)		122	0.77	(0.44, 1.35)		111	1.34	(0.78, 2.30)	
At 6–10 years[g]	358			0.773	562			0.126	527			*0.033*
Normal	234	1.00	Reference		353	1.00	Reference		333	1.00	Reference	
Low	57	1.05	(0.57, 1.96)		93	1.67	(0.97, 2.87)		89	1.49	(0.87, 2.56)	
High	67	0.82	(0.45, 1.49)		116	1.15	(0.68, 1.93)		105	*1.94*	*(1.16, 3.24)*	

First follow-up: 10.8 years (girls) and 11.8 years (boys); Second follow-up: 12.8 years (both sexes)

Italics numbers indicate statistically significant results

n number of participants, *OR* odds ratio, *CI* confidence interval, *LR-p* (likelihood ratio-test p-value) refers to predictor only, *BMI* body mass index (kg/m^2), *SDS* standard deviation score, *N.A.* not applicable

[a] Adjusted for sex, preeclampsia and gestational age

[b] n = 388. Ordinal response: none, low grade, high grade (sum of specific IgE $\geq$ 3.9 kU/l; above the lower quartile of all children being sensitized)

[c] Adjusted for sex, mother's asthma and mother's smoking

[d] Also adjusted for physical activity at 3–6 years

[e] Also adjusted for physical activity at 6–10 years

[f] Also adjusted for BMI SDS at 4 years

[g] Also adjusted for BMI SDS at the first follow-up

low physical activity during childhood was differentially associated with atopic sensitization, atopic dermatitis and asthma assessed in late childhood. BMI and physical activity were not associated with allergic rhinoconjunctivitis.

Anthropometrics and outcomes

In this cohort BMI at 1 year was positively associated with atopic sensitization at 12.8 years with borderline significance. As recently reviewed by Boulet [5], some studies are consistent with and others conflict our results, which may be due to differences in the study design. Studies showing an association have been cross-sectional and therefore unable to assess whether obesity precedes sensitization [5]. In our study, the majority of children were sensitized to airborne allergens. Sensitization to airborne allergens is uncommon in Scandinavian children before the age of 1 year [22]. It is therefore probable that the high BMI at 1 year preceded airborne sensitization. However, sensitization to food allergens may have been present in the first year of life, which we did not assess. In mice, obesity lowered the threshold for atopic sensitization, suggesting that obesity causes atopy [23].

Several mechanisms explaining the association between obesity and atopic sensitization have been suggested [5]. In addition to hormonal and genetic factors, a high BMI is associated with higher body fat and altered adipokines, and in turn might predispose to atopic sensitization through inflammatory changes [24]. Our results could indicate that a high BMI at the age of 1 year is of importance.

Table 3 The adjusted odds ratios of atopic sensitization and atopic disease in adolescence in 617 Norwegian children by changes in weight/BMI SDS after backward stepwise selection of potential confounders (one model for each predictor variable)

Predictor	Outcome variable (final analyses)											
	Atopic sensitization[a,b]				Allergic rhinoconjunctivitis[a]				Atopic dermatitis[c]			
Age	n	OR	95 % CI	LR-p	n	OR	95 % CI	LR-p	n	OR	95 % CI	LR-p
Weight SDS												
Birth to 3 months	361	1.10	(0.87, 1.38)	0.408	534	0.90	(0.74, 1.09)	0.292	500	0.98	(0.80, 1.17)	0.835
BMI SDS												
3–6 months	351	1.15	(0.83, 1.60)	0.413	519	0.96	(0.71, 1.30)	0.794	485	1.15	(0.85, 1.56)	0.363
6 months to 1 year	360	1.30	(0.95, 1.76)	0.100	534	1.11	(0.83, 1.48)	0.470	500	1.07	(0.81, 1.42)	0.638
1–4 years	325	0.82	(0.62, 1.09)	0.173	456	0.82	(0.63, 1.07)	0.150	427	*1.46*	*(1.11, 1.92)*	*0.005*
4 years to first follow-up[d]	315	0.99	(0.78, 1.26)	0.940	450	1.01	(0.80, 1.28)	0.917	422	0.87	(0.70, 1.09)	0.223
First to second follow-up[e]	349	0.96	(0.65, 1.43)	0.843	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A

First follow-up: 10.8 years (girls) and 11.8 years (boys); Second follow-up: 12.8 years (both sexes)

Italics numbers indicate statistically significant results

n number of participants, *OR* odds ratio, *CI* confidence interval, *LR-p* likelihood ratio-test p-value refers to predictor only, *BMI* body mass index (kg/m^2), *SDS* standard deviation score, *N.A.* not applicable

[a] Adjusted for sex, weight/BMI SDS at start of interval, gestational age, preeclampsia (none/mild or moderate/severe)

[b] n = 388. Ordinal response: none, low grade, high grade (sum of specific IgE $\geq$ 3.9 kU/l; above the lower quartile of all children being sensitized)

[c] Adjusted for sex, weight/BMI SDS at start of interval, mother's asthma and mother's smoking

[d] Also adjusted for physical activity at 3–6 years

[e] Also adjusted for physical activity at 6–10 years

In this cohort, change in BMI SDS from 1 to 4 years and BMI at 4 years were positively associated with atopic dermatitis ever at first follow-up. In the ISAAC 3 study, overweight and obesity at 13–14 years was associated with current atopic dermatitis [10]. In a meta-analysis, mainly of cross-sectional studies, a high BMI in childhood, adolescence and adulthood was also associated with atopic dermatitis [25].

Atopic dermatitis usually has its debut in the first years of life and normally precedes any potential overweight or obesity [7]. Therefore, there may be reverse causality, but it may also be possible that overweight/obesity causes atopic dermatitis. Firstly, obesity is associated with an increased risk of dry skin, aggravating underlying skin defects [26]. Secondly, the positive association of a change in BMI SDS and overweight in preschool years with atopic dermatitis could be explained by immunological changes due to increased body fat, and an association between adipokines and atopic dermatitis has been reported [27].

Anthropometric measures were not associated with allergic rhinoconjunctivitis in accordance with previous studies [28].

In the present study, there was no association between anthropometric measures during childhood and asthma in late childhood, without variation by sex. In 2013, six studies were included in a meta-analysis showing that overweight and obesity in childhood is associated with subsequent asthma. However, the results were inconsistent regarding sex [4]. Recently, in a study including >24,000 children, accelerated weight gain from birth to 3 years was positively associated with asthma by 3 years with risk ratio of 1.22 and at 7 years with risk ratio of 1.13 [9]. Our results do not contradict this, as we may have too few participants to show a significant association of a similar low magnitude.

Physical activity and outcomes

In this cohort, low preschool activity level was positively associated with atopic sensitization at 12.8 years. To our knowledge, this is the first study to show such an association. In a cross-sectional study of 2000 Spanish adolescents using questionnaires, there was no association between physical activity and allergy at 13–17 years [29].

In our study we adjusted for BMI, but BMI underestimates the relative amount of fat tissue in the body composition of children [30]. Thus, the association between low activity and atopic sensitization might be due to a higher body fat percentage in children with a low activity level, independent of weight status, with subsequent changes in adipokines that may influence the development of sensitization [24].

In this cohort, a high level of physical activity at 6–10 years was associated with atopic dermatitis ever at

Table 4 The adjusted odds ratios of asthma in adolescence in 617 Norwegian children by weight/BMI SDS and physical activity after backward stepwise selection of potential confounders (one model for each predictor variable)

Predictor	Outcome variable (final analyses)							
	Asthma ever by first follow-up[a]				Current asthma at second follow-up[b]			
Age	n	OR	95 % CI	LR-p	n	OR	95 % CI	LR-p
Weight SDS								
Birth	580	0.93	(0.72, 1.20)	0.587	439	0.95	(0.71, 1.27)	0.716
BMI SDS								
3 months	520	0.88	(0.64, 1.21)	0.437	411	0.96	(0.67, 1.38)	0.835
6 months	536	1.06	(0.79, 1.41)	0.707	425	0.86	(0.61, 1.20)	0.370
1 year	536	1.00	(0.76, 1.32)	0.998	424	0.78	(0.57, 1.08)	0.127
4 years[c]	454	1.09	(0.80, 1.47)	0.596	361	0.91	(0.63, 1.32)	0.627
First follow-up[d]	558	1.02	(0.79, 1.33)	0.849	426	1.10	(0.81, 1.49)	0.561
Second follow-up[d]	N.A.	N.A.	N.A.	N.A.	421	1.25	(0.90, 1.72)	0.176
Physical activity								
At 3–6 years[e]	454			*0.014*	361			0.475
Normal	275	1.00	Reference		220	1.00	Reference	
Low	57	*3.61*	*(1.56, 8.36)*		48	1.92	(0.66, 5.59)	
High	122	1.34	(0.61, 2.97)		93	1.40	(0.55, 3.55)	
At 6–10 years[f]	558			*0.038*	426			0.177
Normal	351	1.00	Reference		274	1.00	Reference	
Low	92	*2.52*	*(1.24, 5.12)*		69	1.98	(0.80, 4.85)	
High	115	1.02	(0.46, 2.28)		83	1.97	(0.83, 4.67)	

First follow-up: 10.8 years (girls) and 11.8 years (boys); Second follow-up: 12.8 years (both sexes)

Italics numbers indicate statistically significant results

n number of participants, *OR* Odds ratio, *CI* confidence interval, *LR-p* likelihood ratio-test p-value refers to predictor only, *BMI* body mass index (kg/m^2), *SDS* standard deviation score, *N.A.* not applicable

[a] After stepwise backward selection, adjusted for sex, gestational age, mother's preeclampsia and asthma

[b] After stepwise backward selection, adjusted for sex, mother's preeclampsia and mother's asthma

[c] Also adjusted for physical activity at 3–6 years

[d] Also adjusted for physical activity at 6–10 years

[e] Also adjusted for BMI SDS at 4 years

[f] Also adjusted for BMISDS at the first follow-up

first follow-up. This is in accordance with the findings in ISAAC 3, where vigorous physical activity in children 13–14 years was associated with current atopic dermatitis, and was attributed to sweat-induced itch [10]. One possible explanation for an association is that after long-term physical activity, natural killer cell cytotoxicity could be increased, which in turn has been associated with atopic dermatitis [31, 32].

We report an association of low physical activity at both 3–6 and 6–10 years with asthma ever, but not current asthma, in late childhood. In the ISAAC 3 study, several hours of TV viewing was associated with symptoms of current asthma in adolescents [10]. Similarly, studies indicate that physical activity could be protective against the development of asthma [11]. We found no association between physical activity and allergic rhinoconjunctivitis. In ISAAC 3, both associations of vigorous physical activity and a sedentary lifestyle at 13 years with allergic rhinoconjunctivitis were found with odds ratios at 1.25 and 1.17, respectively [10]. With the low number of participants in our study, our results do not contradict these results.

Strengths and limitations

Strengths: The study population is homogeneous regarding socio-economic status and ethnicity. Further, the predictor variables have been sampled by repeated measurements from several ages to examine the window of time in childhood the predictors could possibly affect the development of atopic sensitization and atopic diseases.

However, the study also has some limitations. The present study was not primarily designed to answer the current research questions, but this has been accounted for by including the design variable preeclampsia as a potential confounder, and no confounding was present. BMI may

have limited correlation with childhood adiposity [3], and we did not have other adiposity measurements available from the visits at the well-baby clinics. Children who participated in the first follow-up but not in the second follow-up had a higher BMI and more atopic dermatitis. This may have biased our results, as both overweight and atopic dermatitis may be associated with atopic sensitization and other atopic disease. Only the predictors and not the outcomes were measured longitudinally, thus we cannot know if the associations reveal causality, or the direction of the causality. Lastly, due to several statistical analyses, the statistically significant results must be interpreted with care.

Conclusions

The results of this study suggest that BMI and physical activity in early childhood are associated with atopic sensitization, atopic dermatitis and asthma in later childhood. Larger cohorts with repeated measurements of both predictors and outcomes are needed to further elucidate this issue.

Additional files

Additional file 1: Figure S1. Directed Acyclic Graph. Colours of rings: Green = predictor; blue with black dot = outcome; blue = ancestor of outcome; red = potential confounder; black = adjustment set; grey = unavailable/unknown confounders. Red line = biasing path; green line = causal path; black line = closed path. The figure was made by using DAGitty software.

Additional file 2: Table S1. The adjusted odds ratios of asthma in adolescence in 617 Norwegian children by changes in weight/BMI SDS after backward stepwise selection of potential confounders (one model for each predictor variable). **Table S2**. The adjusted odds ratios of atopy in adolescence in 617 Norwegian children according to weight-related anthropometry in adolescence after backward stepwise selection of potential confounders (one model for each predictor variable).

Abbreviations

BMI: body mass index (kg/m^2); IBM SPSS: International Business Machines Corporation Statistical Package for the Social Sciences; IgE: immunoglobulin E; ISAAC: International Study of Asthma and Allergies in Childhood; kU/l: kilo units per litre; MFPR: multiple fractional polynomial regression; SDS: standard deviation score.

Authors' contributions

MRF and KØ participated in the design of the study. KKB finalised the data collection and registration, performed all the statistical analyses and wrote a draft of the manuscript. GEE supervised the statistical analyses. PBJ supervised the planning and the drafting of the manuscript and contributed to the analyses of the data. KØ supervised all parts of the study and writing. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The database belongs to Stavanger University Hospital and cannot be shared unless a special agreement is made with Stavanger University Hospital, department of research.

Ethics approval and consent to participate

The study was approved by the Norwegian Data Inspectorate, the Regional Committee for Ethics in medical research Western Norway (Reference Numbers: First: 078-03, Second: 2010/1375), and the Institutional Review Boards of the National Cancer Institute and University of Texas at Austin, United States. Mothers and children signed an informed consent/assent form at follow-up.

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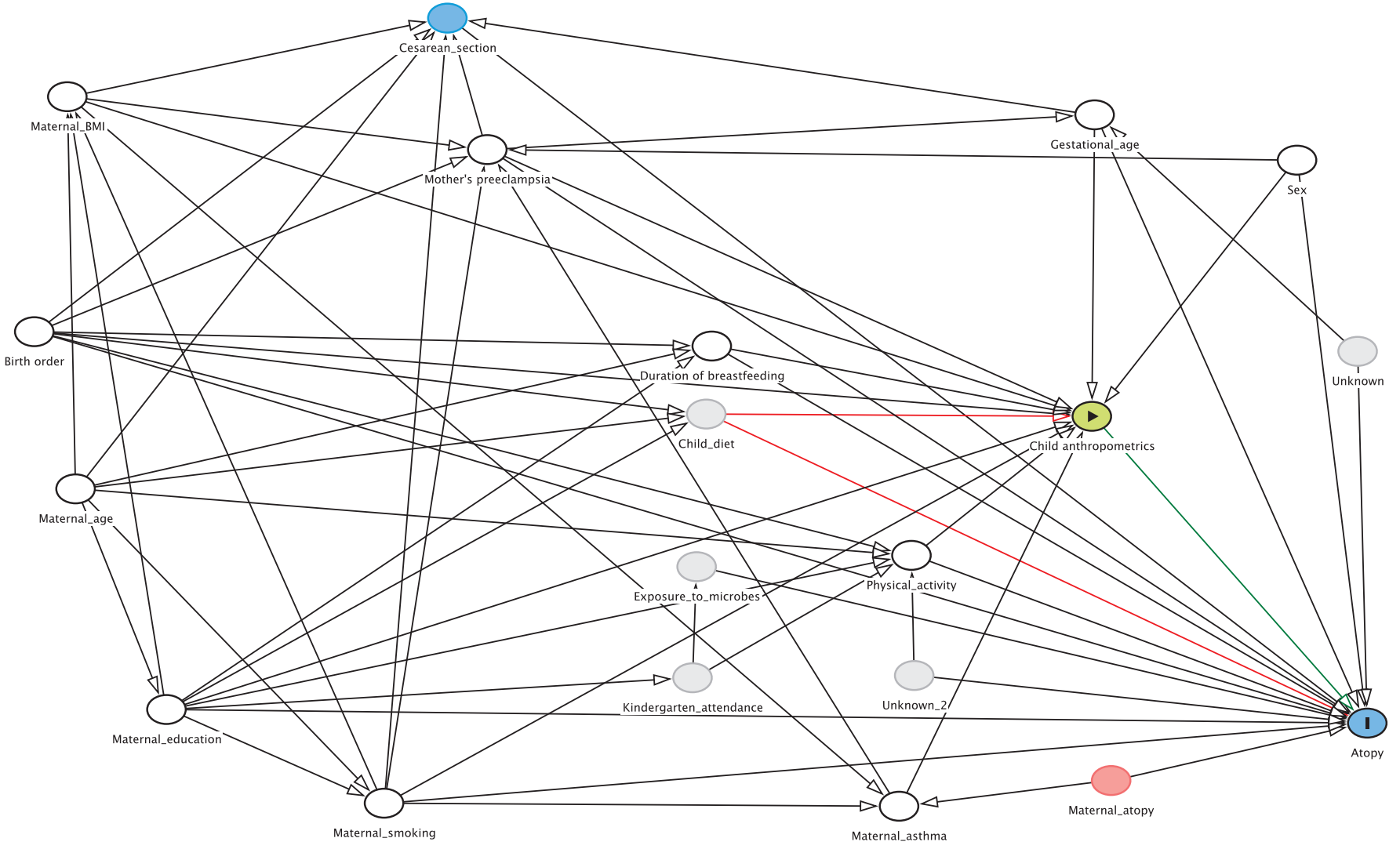
References

1. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766–81.
2. Schernhammer ES, Vutuc C, Waldhor T, Haidinger G. Time trends of the prevalence of asthma and allergic disease in Austrian children. Pediatr Allergy Immunol. 2008;19(2):125–31.
3. Guibas GV, Manios Y, Xepapadaki P, Moschonis G, Douladiris N, Mavrogianni C, Papadopoulos NG. The obesity-asthma link in different ages and the role of body mass index in its investigation: findings from the Genesis and Healthy Growth Studies. Allergy. 2013;68(10):1298–305.
4. Egan KB, Ettinger AS, Bracken MB. Childhood body mass index and subsequent physician-diagnosed asthma: a systematic review and meta-analysis of prospective cohort studies. BMC Pediatr. 2013;13:121.
5. Boulet LP. Obesity and atopy. Clin Exp Allergy. 2015;45(1):75–86.
6. Glavin K, Roelants M, Strand BH, Juliusson PB, Lie KK, Helseth S, Hovengen R. Important periods of weight development in childhood: a population-based longitudinal study. BMC Public Health. 2014;14(1):160.
7. Eller E, Kjaer HF, Host A, Andersen KE, Bindslev-Jensen C. Development of atopic dermatitis in the DARC birth cohort. Pediatr Allergy Immunol. 2010;21(2 Pt 1):307–14.
8. Anderson EL, Fraser A, Martin RM, Kramer MS, Oken E, Patel R, Tilling K, Study P. Associations of postnatal growth with asthma and atopy: the PROBIT Study. Pediatr Allergy Immunol. 2013;24(2):122–30.
9. Magnus MC, Stigum H, Haberg SE, Nafstad P, London SJ, Nystad W. Peak weight and height velocity to age 36 months and asthma development: the Norwegian Mother and Child Cohort Study. PLoS One. 2015;10(1):e0116362.
10. Mitchell EA, Beasley R, Bjorksten B, Crane J, Garcia-Marcos L, Keil U, Group IPTS. The association between BMI, vigorous physical activity and television viewing and the risk of symptoms of asthma, rhinoconjunctivitis and eczema in children and adolescents: ISAAC Phase Three. Clin Exp Allergy. 2013;43(1):73–84.
11. Eijkemans M, Mommers M, Draaisma JM, Thijs C, Prins MH. Physical activity and asthma: a systematic review and meta-analysis. PLoS One. 2012;7(12):e50775.

12. Ogland B, Vatten LJ, Romundstad PR, Nilsen ST, Forman MR. Pubertal anthropometry in sons and daughters of women with preeclamptic or normotensive pregnancies. Arch Dis Child. 2009;94(11):855–9.
13. Byberg KK, Ogland B, Eide GE, Oymar K. Birth after preeclamptic pregnancies: association with allergic sensitization and allergic rhinoconjunctivitis in late childhood; a historically matched cohort study. BMC Pediatr. 2014;14(1):101.
14. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 1998;351(9111):1225–32.
15. Taylor-Piliae RE, Fair JM, Haskell WL, Varady AN, Iribarren C, Hlatky MA, Go AS, Fortmann SP. Validation of the Stanford Brief Activity Survey: examining psychological factors and physical activity levels in older adults. J Phys Act Health. 2010;7(1):87–94.
16. Alsnes IV, Janszky I, Forman MR, Vatten LJ, Okland I. A population-based study of associations between preeclampsia and later cardiovascular risk factors. Am J Obstet Gynecol. 2014;211(6):657.e1–7.
17. Textor J, Hardt J, Knuppel S. DAGitty: a graphical tool for analyzing causal diagrams. Epidemiology. 2011;22(5):745.
18. Niklasson A, Albertsson-Wikland K. Continuous growth reference from 24th week of gestation to 24 months by gender. BMC Pediatr. 2008;8:8.
19. Juliusson PB, Roelants M, Nordal E, Furevik L, Eide GE, Moster D, Hauspie R, Bjerknes R. Growth references for 0–19 year-old Norwegian children for length/height, weight, body mass index and head circumference. Ann Hum Biol. 2013;40(3):220–7.
20. Brannsether B, Roelants M, Bjerknes R, Juliusson PB. Waist circumference and waist-to-height ratio in Norwegian children 4–18 years of age: reference values and cut-off levels. Acta Paediatr. 2011;100(12):1576–82.
21. Brannsether B, Roelants M, Bjerknes R, Juliusson PB. References and cutoffs for triceps and subscapular skinfolds in Norwegian children 4–16 years of age. Eur J Clin Nutr. 2013;67(9):928–33.
22. Nissen SP, Kjaer HF, Host A, Nielsen J, Halken S. The natural course of sensitization and allergic diseases from childhood to adulthood. Pediatr Allergy Immunol. 2013;24(6):549–55.
23. Dietze J, Bocking C, Heverhagen JT, Voelker MN, Renz H. Obesity lowers the threshold of allergic sensitization and augments airway eosinophilia in a mouse model of asthma. Allergy. 2012;67(12):1519–29.
24. Nagel G, Koenig W, Rapp K, Wabitsch M, Zoellner I, Weiland SK. Associations of adipokines with asthma, rhinoconjunctivitis, and eczema in German schoolchildren. Pediatr Allergy Immunol. 2009;20(1):81–8.
25. Zhang A, Silverberg JI. Association of atopic dermatitis with being overweight and obese: a systematic review and metaanalysis. J Am Acad Dermatol. 2015;72(4):606–16.e4.
26. Nino M, Franzese A, Ruggiero Perrino N, Balato N. The effect of obesity on skin disease and epidermal permeability barrier status in children. Pediatr Dermatol. 2012;29(5):567–70.
27. Machura E, Szczepanska M, Ziora K, Ziora D, Swietochowska E, Barc-Czarnecka M, Kasperska-Zajac A. Evaluation of adipokines: apelin, visfatin, and resistin in children with atopic dermatitis. Mediators Inflamm. 2013;2013:760691.
28. Wang R, Custovic A, Simpson A, Belgrave DC, Lowe LA, Murray CS. Differing associations of BMI and body fat with asthma and lung function in children. Pediatr Pulmonol. 2014;49(11):1049–57.
29. Nova E, Martinez-Gomez D, Gomez-Martinez S, Veses AM, Calle ME, Veiga OL, Marcos A. Influence of health behaviours on the incidence of infection and allergy in adolescents: the AFINOS cross-sectional study. BMC Public Health. 2014;14:19.
30. Brannsether B, Eide GE, Roelants M, Bjerknes R, Juliusson PB. Interrelationships between anthropometric variables and overweight in childhood and adolescence. Am J Hum Biol. 2014;26(4):502–10.
31. Del Giacco SR, Scorcu M, Argiolas F, Firinu D, Del Giacco GS. Exercise training, lymphocyte subsets and their cytokines production: experience of an Italian professional football team and their impact on allergy. BioMed Res Int. 2014;2014:429248.
32. Luci C, Gaudy-Marqueste C, Rouzaire P, Audonnet S, Cognet C, Hennino A, Nicolas JF, Grob JJ, Tomasello E. Peripheral natural killer cells exhibit qualitative and quantitative changes in patients with psoriasis and atopic dermatitis. Br J Dermatol. 2012;166(4):789–96.

Additional files to paper III

Figure S1. Directed Acyclic Graph. Colours of rings: Green = predictor; blue with black dot = outcome; blue = ancestor of outcome; red = potential confounder; black = adjustment set; grey = unavailable/unknown confounders. Red line = biasing path; green line = causal path; black line = closed path. The figure was made by using DAGitty software.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Unknown_2
Maternal_education
Atopy
Maternal_smoking
Maternal_asthma
Maternal_atopy

Table S1 The adjusted odds ratios of asthma in adolescence in 617 Norwegian children by changes in weight/BMI SDS after backward stepwise selection of potential confounders (one model for each predictor variable)

	Outcome variable (final analyses)[a]							
Predictor	**Asthma ever by first follow-up**				**Current asthma at second follow-up**			
Age	**n**	**OR**	**95% CI**	**LR-p**	**n**	**OR**	**95% CI**	**LR-p**
Weight SDS								
Birth – 3 months	533	0.89	(0.68, 1.18)	0.453	422	0.90	(0.67, 1.20)	0.492
BMI SDS								
3 – 6 months	518	1.42	(0.92, 2.19)	0.110	410	0.78	(0.45, 1.33)	0.358
6 – 12 months	533	0.92	(0.60, 1.39)	0.680	422	0.77	(0.46, 1.28)	0.310
1 – 4 years	454	1.02	(0.69, 1.50)	0.936	376	1.02	(0.64, 1.60)	0.947
4 years to First follow-up[b]	448	0.96	(0.68, 1.36)	0.827	375	1.19	(0.81, 1.76)	0.380
First to second follow-up [c]				N.A.	422	1.83	(1.02, 3.28)	0.054

Abbreviations: n = number of participants; OR = Odds ratio; CI = Confidence interval; LR-p = (likelihood ratio-test p-value) refers to predictor only; First follow-up: 10.8 years (girls) and 11.8 years (boys); Second follow-up: 12.8 years (both sexes); BMI = body mass index (kg/m^2); SDS = standard deviation score; N.A. = not applicable. a) After stepwise backward selection, adjusted for weight/BMI SDS at start of interval, sex, gestational age, preeclampsia, mother's age and mother's asthma; b) Also adjusted for physical activity at 3-6 years; c) Also adjusted for physical activity at 6-10 years

Table S2 The adjusted odds ratios of atopy in adolescence in 617 Norwegian children according to weight-related anthropometry in adolescence after backward stepwise selection of potential confounders (one model for each predictor variable)

	Outcome variable (final analyses)[a]																			
	Atopic sensitization[a]				Allergic rhinoconjunctivitis[a]				Atopic dermatitis[b]				Asthma ever by first follow-up[c]				Current asthma at second follow-up[d]			
Predictor	**n**	**OR**	**95% CI**	**LR-p**	**n**	**OR**	**95% CI**	**LR-p**	**n**	**OR**	**95% CI**	**LR-p**	**n**	**OR**	**95% CI**	**LR-p**	**n**	**OR**	**95% CI**	**LR-p**
Waist circumference																				
First follow-up	367	0.99	(0.81, 1.20)	0.888	571	0.88	(0.73, 1.06)	0.183	536	0.97	(0.81, 1.16)	0.713	581	1.05	(0.81, 1.36)	0.699	445	1.04	(0.76, 1.42)	0.810
Second follow-up	368	0.98	(0.79, 1.22)	0.853				N.A.				N.A.				N.A.	447	1.15	(0.81, 1.63)	0.438
Waist-to-height ratio																				
First follow-up	367	1.03	(0.85, 1.24)	0.755	571	0.94	(0.78, 1.13)	0.508	536	1.05	(0.88, 1.26)	0.569	581	1.11	(0.85, 1.44)	0.439	445	1.08	(0.80, 1.47)	0.597
Second follow-up	368	1.04	(0.84, 1.29)	0.727				N.A.				N.A.				N.A.	447	1.15	(0.81, 1.63)	0.438
Triceps skinfold																				
First follow-up	364	1.03	(0.84, 1.25)	0.795	567	0.90	(0.75, 1.08)	0.253	532	1.10	(0.92, 1.32)	0.316	576	1.11	(0.85, 1.44)	0.453	442	1.20	(0.87, 1.65)	0.257
Second follow-up	367	1.02	(0.83, 1.26)	0.813				N.A.				N.A.				N.A.	446	1.23	(0.89, 1.71)	0.205
Subscapular skinfold																				
Second follow-up	358	0.98	(0.79, 1.22)	0.862				N.A.				N.A.				N.A.	447	1.15	(0.81, 1.63)	0.438

Abbreviations: n = number of participants; OR = Odds ratio; CI = Confidence interval; LR-p = (likelihood ratio-test p-value) refers to predictor only; First follow-up: 10.8 years (girls) and 11.8 years (boys); Second follow-up: 12.8 years (both sexes); BMI = body mass index (kg/m^2); SDS = standard deviation score; N.A. = not applicable. a) After stepwise backward selection, adjusted for sex, gestational age and preeclampsia; b) After stepwise backward selection, adjusted for sex, mother's smoking and mother's asthma; c) After stepwise backward selection, adjusted for sex and mother's asthma; d) After stepwise backward selection, adjusted for sex

IV