Born Small for Gestational Age

Beyond Size at Birth

LINDA LINDSTRÖM
Abstract


Children born small for gestational age (SGA) run increased risk of perinatal morbidity and mortality, but also of long-term health impairment. Risks on long term may vary depending on postnatal growth patterns. The overall aim of the thesis was to gain further knowledge about long-term consequences of being born SGA, as well as the impact of perinatal exposures on postnatal growth patterns. The thesis is based on four register-based cohort studies.

In paper I, risk of chronic hypertension was assessed in 731,008 first-time mothers. Perinatal exposure to pre-eclampsia, being born SGA and preterm were all independently associated with increased risk of chronic hypertension. The risk was further enhanced after combined exposure. The strongest association was seen in combinations including pre-eclampsia.

In paper II, risk of poor school performance at time of graduation from compulsory school was assessed in 1,088,980 children born SGA at term. Being born SGA was associated with increased risk of poor school performance, following a dose-response pattern with increased risk even for birthweight for gestational age (GA) –1.01 to –2 SD. Boys with short adult stature were associated with higher risk of poor school performance than those with non-short stature.

In paper III, differences in postnatal growth patterns depending on SGA status and maternal smoking habits were assessed in 32,493 children. Children born SGA with smoking mothers had a more rapid catch-up growth than those with non-smoking mothers. Compared with children born appropriate for GA (AGA) with non-smoking mothers, only children born SGA with non-smoking mothers were associated with increased risk of short stature at 1.5 and 5 years.

In paper IV, differences in postnatal growth patterns until age five years, depending on SGA status and GA at birth, were assessed in 41,669 children born between 32-40 gestational weeks. Being born SGA and moderate to late preterm was associated with shorter stature and lower BMI, compared with being born AGA at term. SGA status had greater impact on growth and body proportions than GA at birth.

In conclusion, children born SGA are at higher risk of chronic hypertension and cognitive impairment than children born AGA. Postnatal growth patterns vary in children born SGA, depending on intrauterine exposure to smoking and GA at birth. This may modify risks of long-term health impairment.

Keywords: Small for Gestational Age, SGA, Epidemiology, Pregnancy, Postnatal growth, Intrauterine growth restriction, Chronic hypertension, School performance

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Läran om den normala variationsbredden är ett vackert exempel på hur en teoretisk gren av vetenskapen gjort sin entré på det praktiska livets scen. Det är en sanning med modifikation att all teori är grå. Rätt använda kommer torra matematiska siffror till dagligt bruk inom det praktiska livets olika fält, ej minst det medicinska.

Edgar Mannheimer
Praktisk barnavård (1954)
List of Papers

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


Abbreviations

AGA  Appropriate for gestational age
BPD  Biparietal diameter
CI   Confidence interval
DOHaD Developmental Origins of Health and Disease
GA   Gestational age
GH   Growth hormone
ICD  International Classification of Diseases
IUGR Intrauterine growth restriction
IVF  In vitro fertilisation
MBR  Swedish Medical Birth Register
MBRN Medical Birth Registry of Norway
NSR  National School Registry
OR   Odds ratio
PE   Pre-eclampsia
RCOG Royal College of Obstetricians and Gynaecologists
RR   Risk ratio
SD   Standard deviation
SDS  Standard deviation score
SGA  Small for gestational age
WHO  World Health Organization
Preface

Working as obstetricians, we are often confronted with pregnancies where intrauterine growth restriction is suspected. Since there is no treatment available, the pregnancy will remain under close surveillance until the baby is delivered. This is often a period of great parental distress as well as difficult decision-making and agony for both neonatologists and obstetricians. Weighing pros and cons regarding optimal timing and mode of delivery is not an easy task. Are there still benefits from maturation and continued growth? Is the baby at high risk of intrauterine fetal demise and neurological impairment due to oxygen and nutrient deficiency? Or will prompt delivery increase the risks of short- or long-term health problems for the baby? Are there any aggravating factors? Can we trust the estimated fetal weight? Often, we cannot give answers to these questions based on solid evidence from research studies, but have to rely on our clinical experience.

In the autumn of 2013, my senior colleague and role model in fetal medicine, Eva Bergman, kindly invited me to be a part of a new thrilling research project. The aim was to create new Swedish reference standards for fetal weight and growth. Until then, I had not even considered doctoral studies. Surely, I had changed my plans before, from primary care to gynaecology, and now aiming for a future as an obstetrician. But could I do research? My always supportive husband encouraged me, and Eva and I started drawing up plans for the study “Swedish Intrauterine Growth Curves for Fetuses and Children”.

However, a large scale clinical study takes time to launch. In January 2015, Anna-Karin Wikström stepped in as my main supervisor. While preparing for the clinical study, we started working with a register study. Thanks to Anna-Karin’s efficient manners, we had a draft of paper I within two months. Together with Maria Lundgren, Anna-Karin had opened my eyes for the beautiful world of epidemiology. In September 2015, I was accepted as a PhD student, and a few days later the first study subject was included in the clinical study.

In parallel with running the clinical study, another three register studies took shape and I decided to write a fully epidemiological thesis. By completing this thesis, I have added a little piece of knowledge to the great puzzle of understanding fetal growth and its long-term consequences. In the near future, the
reason why I decided to begin my PhD studies is approaching its goal. With a
great passion for obstetrics and epidemiology, I look forward to take part in
the creation of new Swedish reference standards for fetal weight and growth.
With better tools, we can be more accurate in detecting fetuses who are truly
small for gestational age and hence improve surveillance of pregnancies and
evaluation of the risk of short- and long-term consequences. By identifying
children with poor intrauterine growth, we can plan their entrance into the
world outside the womb and give them the best premises possible. Thus, we
can make a difference for their future health.
Introduction

Developmental Origins of Health and Disease

In the early 1970s, the East German endocrinologist Günter Döner and his research group published a series of papers suggesting a relationship between adverse events during fetal life and later risk of arteriosclerosis and obesity, and introduced the term ‘programming’ (1, 2). During the 1970s and 1980s, several research groups presented further evidence of associations between adverse events during fetal life and later cardiovascular and metabolic disease (2). In the early 1990s, Barker and Hales formulated a model describing how a fetus during difficult circumstances trades-off growth in order to survive (3). As a consequence of this trade-off, the gene expression of the fetus might be altered, with potential adverse effects on health later in life. The model is often called ‘the thrifty phenotype hypothesis’, ‘the Barker hypothesis’ or fetal programming (4, 5).

After re-evaluation and modification, a new evolutionary model was developed in the early 2000s; Developmental Origins of Health and Disease (DOHaD). The new model expresses how all developing organisms go through a process of developmental plasticity. The embryo, fetus or infant adjusts its developmental trajectory according to information from the environment. The adjustments will result in an altered phenotype. Doing so, its’ survival becomes more likely, but at the expense of potentially harmful long-term consequences (2). Even though direct evidence is sparse in humans, epigenetic mechanisms seem to be central as mediators in developmental plasticity (6). In order to establish the causal pathway from adverse events during fetal and early life via epigenetic changes to phenotypic alternations prone to disease, it is necessary to demonstrate reproducible evidence of effects in different domains. First, variability in epigenetic expression in response to environmental exposures has to be shown. Second, the association between an epigenetic variant and disease has to be proven, where the epigenetic variant must precede onset of disease. Last, the functional relevance of the specific epigenetic change must be demonstrated. Large life course studies of environmental exposures with longitudinal biological testing might offer the best conditions for proving the mediating role of epigenetic variation in developmental plasticity (6). Figure 1 illustrates the model behind the DOHaD concept.
Figure 1. A model of how adverse environmental exposures in utero potentially alter tissue physiology, hormone production and metabolism, speculatively through epigenetic changes (Saffery R. Epigenetic change as the major mediator of fetal programming in humans: Are we there yet? Annals of nutrition & metabolism. 2014;64(3-4):203-7.). T2D = type 2 diabetes. Copyright © 2014 Karger Publishers, Basel, Switzerland, reproduced with permission of Karger.

Epigenetic changes

Epigenetic mechanisms regulate the activity of the genome. Gene expression is regulated by activating or repressing DNA transcription, or by altering the structure or accessibility of a genomic region. These modifications are generated by DNA methylation and altered histone structure. In the next step, epigenetic changes modify the gene expression without changing the underlying nucleotide sequence. This might in turn affect which phenotype the child develops (7).

The DNA methylation profile is very important to enable a proper development during early embryogenesis. These epigenetic processes seem to be essential in differentiation and development, and the DNA methylation profile remain highly dynamic during pregnancy and early childhood. Epigenetic changes seem to adapt in response to cumulative environmental influences, and vary between individuals and tissues. However, ethical considerations and the dynamic nature of epigenetic modifications make it difficult to establish
causal chains from adverse events via epigenetic changes to disease susceptibility (6).

Perinatal exposures

The intrauterine environmental factors and adverse events during fetal and neonatal life that might alter the developmental trajectory are often referred to as perinatal exposures (2). Such perinatal exposures are among others maternal obesity, gestational diabetes, pre-eclampsia, maternal substance abuse, preterm birth, asphyxia and intrauterine or postnatal growth restriction.

Pre-eclampsia

Pre-eclampsia (PE) is a pregnancy-induced hypertensive disorder that complicates 2-8% of all pregnancies (8, 9). The current definition of PE used in health practice comprises de novo systolic blood-pressure ≥140 mm Hg or diastolic blood-pressure ≥90 mm Hg in combination with proteinuria ≥300 mg in 24 hours arising after gestational week 20 (10-12).

Depending on gestational age (GA) at disease onset, pregnancies complicated by PE differ regarding risk factors, biological markers, prognosis and clinical signs (10, 13). The pathogenesis of preterm PE, especially if GA is less than 34 weeks at onset, is closely related to poor placentation, inflammation and oxidative stress. Term PE on the other hand often seems to occur secondary to microvascular disease, endothelial dysfunction and cardiovascular maladaptation to increased volume load in pregnancy (13-15). Term PE can largely be seen as a maternal disorder, in contrast to the placental disorder in preterm disease (13, 16).

When a pregnancy is complicated by PE, the consequences may be severe for mother as well as child. Hypertensive conditions cause marked maternal morbidity and are responsible for 9-25% of maternal deaths worldwide (10, 17-19). However, PE is not only associated with increased risk of maternal mortality and morbidity in direct connection to pregnancy and childbirth. Women with history of PE suffer increased risks of chronic hypertension and cardiovascular diseases, such as stroke and ischemic heart disease later in life (20, 21). In addition to maternal morbidity, PE and eclampsia influence neonatal morbidity and mortality. Adverse neonatal outcome is overall increased after hypertensive pregnancies, and the graver hypertensive disease, the higher neonatal risks (8, 22). Preterm PE in particular is associated with neonatal morbidity due to the high risk of severe maternal disease requiring preterm
delivery (13). Furthermore, placental origin with intrauterine growth restriction (IUGR) is common in preterm PE, whereas pregnancies complicated by term PE often carry a large for gestational age infant (15).

Preterm birth

The definition of preterm birth is delivery before 37 gestational weeks. The incidence of preterm birth varies throughout the world, from rates as low as 5% in some countries in northern Europe, around 10% in the United States, and up to rates exceeding 15% in some low-income countries (23). Iatrogenic, or medically indicated, preterm birth counts for approximately one third of the preterm births, and is often, but not always, a result of PE or IUGR (23, 24). Spontaneous preterm birth often follows preterm premature rupture of membranes, which is often caused by infections, or preterm labour. Preterm labour in turn may be caused by infection, inflammation, stress, haemorrhage or uterine overdistension (24). Several of the risk factors associated with preterm birth, such as maternal smoking, are overrepresented in women with low socioeconomic status.

Morbidity and mortality are intimately connected to GA at birth in children born preterm, with higher complication rates among children with low GA (23, 25). However, even for late preterm births, the morbidity is substantial with short-term as well as long-term sequelae (26).

Preterm birth is associated with a multitude of subsequent long-term health issues. Neurodevelopmental impairment after preterm birth spans from behavioural problems and slight reduction in IQ scores to cerebral palsy, severe mental retardation and epilepsy (27). Respiratory problems, including bronchopulmonary dysplasia, infections and asthma are common (28). Further, multiple studies report an association between preterm birth or very low birthweight and elevated blood pressure, which may be an indicator of the metabolic syndrome with adverse impact on long-term health (26, 29). However, separating the exposures is important, as the association between low birthweight and adult hypertension seems to be caused by poor fetal growth rather than preterm birth per se (30).

Fetal growth

Placental function

Size at birth depends on the length of the pregnancy in which the child is born, i.e. the GA, as well as the growth velocity during fetal life. Six or seven days
after fertilization, the embryo implants in the endometrium of the uterus. Implantation is followed by a series of events, where the trophoblasts grow and expand into the decidua. As the placenta establishes, trophoblasts invade the spiral arteries of the decidua and the underlying myometrium. The walls of the spiral arteries are remodelled during the first half of the pregnancy. The arteries are then transformed from muscular vessels with narrow lumens into a low-resistance system (31). The remodeled spiral arteries are vital for the placental function to make sure that nutritional exchange will remain adequate.
throughout the pregnancy. Figure 2 illustrates normal and suboptimal trophoblast invasion. A defect placentation with remaining high-resistance blood flow is associated with PE, IUGR and preterm birth (32). The increased resistance in the placental bed can be estimated using Doppler ultrasound. Increased pulsatility index in the uterine artery is a reflection of remaining high-resistance blood-flow in the maternal part of the placenta (33).

A well-functioning placenta with sufficient nutrient supply to the fetus plays a significant role in normal fetal growth. Substances are transported through the placental barrier, either by simple diffusion, as in the case with oxygen and carbon dioxide, or by facilitated diffusion, which applies to e.g. glucose and amino acids (34-36). If the placental transport of nutrients fails to deliver enough nutrients and oxygen, fetal growth velocity will decline. Subsequently, the fetus will be at risk of becoming growth restricted. The nutrient transport depends on several factors, most importantly placental size and uteroplacental blood flow (37). Moreover, adequate occurrence of nutrients in the maternal circulation and favourable gene expression are of importance to optimize fetal growth (36).

Variation in size at birth is not solely a matter of nutrition. Maternal genes, as well as the fetal genome, are involved in determining fetal weight and size at birth. Even though maternal height and weight are more important to fetal growth and size at birth than paternal anthropometry, both parental genomes contribute to fetal size; the genetic growth potential (38, 39). Besides nutritional supply and genetic growth potential, environmental factors, like socioeconomic status and smoking, are known to affect fetal growth (40).

During the first trimester of pregnancy, organogenesis takes place with establishment of tissue patterns and organ systems, and thus an adverse environment might result in fetal malformations or miscarriage. In the second trimester, suboptimal intrauterine conditions are likely to affect growth. Major cellular adaptation and increase in body size takes place, and deviant growth results in a fetus proportionally small in length and weight (41). During the third trimester, organ systems mature and body weight significantly increases. In contrast to postnatal growth, which is mainly regulated by growth hormone (GH) and insulin-like growth factors, fetal growth is predominantly restricted by placental function and maternal factors, and coordinated by growth factors (41).
Low birthweight
The World Health Organisation (WHO) defines low birthweight as a birth-weight less than 2500 g (42). The definition does not take GA at birth into account. This implies that children born very preterm but at a weight and length appropriate for gestational age (AGA) are classified together with children born term but growth restricted. Therefore, consequences related to preterm birth can be misinterpreted as effects of low birthweight and vice versa if low birthweight is used as a proxy for IUGR.

Small for gestational age
The term small for gestational age (SGA) is a statistical term that describes estimated fetal weight or birthweight in relation to GA. Children with a birth-weight lower than a specific threshold below average fetal weight or birth-weight for GA and sex according to a reference curve for fetal growth or birthweights are considered SGA (43). There is no global consensus regarding the definition of SGA, but commonly used thresholds are 10th, 5th or 2.3rd percentile; the latter corresponding to -2 standard deviations (SD). Groups of experts among obstetricians and paediatricians have presented consensus documents arguing for their proposed definition of SGA (44, 45). Despite these recommendations, the definition of SGA in studies and clinical work still varies, with no international consensus for obstetrics, paediatrics or endocrinology (43).

In the Nordic countries, including Sweden, obstetricians as well as paediatricians use -2 SD as cut-off for SGA. In other parts of Europe, obstetricians often use the 10th percentile as cut-off, whereas paediatricians most commonly define SGA as -2 SD.

The cut-off at 10th percentile has been widely used since the 1960s. Multiple studies demonstrate increased mortality in children with birthweight less than 10th percentile compared with AGA (43, 46). This cut-off can seem arbitrary, as later research has shown an inverse relationship between risk of perinatal mortality and morbidity and size at birth (47). It seems likely that the risk of adult morbidity associated with SGA birth follows the same pattern, and hence there is a risk of missing individuals at risk if using a too low cut-off, e.g. -2 SD. Further, the pattern of risk increase is also affected by other factors, such as prematurity. Boulet et al. showed that when 10th percentile is used as threshold for SGA, the risk of mortality in term children is overestimated, whereas the risk in severely preterm children is underestimated (48).

Fetuses with structural or chromosomal anomalies, like Turner’s syndrome and Silver-Russel syndrome, as well as those with familial short stature, have
a lower growth potential than fetuses without anomaly or family history (49). Yet, the statistical term SGA does not separate a healthy, constitutionally small fetus from a fetus prevented from reaching its individual growth potential. Thus, all fetuses below the chosen threshold are classified together, even though long and short-term health consequences for the constitutionally small and growth-restricted fetuses differ.

Intrauterine growth restriction

IUGR occurs when a fetus fails to reach its biological growth potential. Unlike SGA, it is a measurement of fetal growth rate rather than size. There are multiple causes of IUGR, e.g. fetal infections, placental dysfunction, multiple gestation, maternal malnutrition and smoking (49-53). As in the case with SGA, there is no internationally established definition of IUGR. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) attempted to reach international consensus regarding the definition of late IUGR (GA ≥32 weeks). In this definition, fetuses without congenital anomalies with a solitary finding of ultrasonically estimated fetal weight or abdominal circumference less than 3rd percentile are classified as growth restricted (54). By lowering the cut-off from the most commonly used 10th to the 3rd percentile, ISUOG aims to detect the majority of fetuses with unfavourable long-term outcomes. Already in the 1980’s, the use of a lower cut-off for SGA was shown to detect a large proportion of children truly IUGR, with affected blood flow in the umbilical artery (55). Further, by combining ultrasound biometry with functional parameters, such as umbilical artery Doppler velocimetry, growth restricted fetuses with estimated weight exceeding the 3rd percentile can also be detected with higher precision (54, 56).

Smoking and fetal growth

Maternal smoking is one of the most well-known, avoidable causes of SGA birth, low birthweight and preterm birth (24, 57-59). The effect of maternal smoking on birthweight follows a dose-response pattern, with lower birthweight the higher the maternal tobacco consumption during pregnancy (49, 60-63). The primary effect of maternal smoking upon birthweight is thought to be mediated by placental dysfunction and IUGR, but the underlying mechanisms remain unclear. The pathophysiological effect of maternal and second hand smoking on fetal growth is probably multifactorial, with several different mechanisms including toxins that can affect the fetus directly as well as indirectly (63).

During placentation, the placental villous systems are developed. Placentas from smoking mothers have altered gene and protein expression, reduced
number of cytotrophoblasts, increased membrane thickness and accumulation of cadmium. These changes are partly due to reduced fetal capillary volume and limited passage of oxygen and nutrients from maternal to fetal circulation (63). The placental dysfunction is further aggravated by nicotine exposure, which causes a transient reduction of placental blood flow (63). Maternal vascular disease and decreased maternal oxygen-carrying capacity due to increased levels of carbon monoxide further deprives the fetus of sufficient amounts of nutrients. Hence, the fetus runs the risk of not reaching its growth potential (64).

The smokeless oral moist tobacco product snuff is frequently used in Sweden. In 2016, 0.7% of Swedish pregnant women reported snuff use in pregnancy week 32 (65). Being smokeless, snuff users are not exposed to carbon monoxide and other products of combustion, but the nicotine content may influence fetal growth. In a Swedish study, children to snuff users had lower birthweight and increased risk of preterm birth compared with those whose mother did not use tobacco during pregnancy (66). Moreover, snuff use during pregnancy is associated with SGA, even though the association is not as strong as for tobacco smoking (67). The difference in risk estimates might be explained by the presence of growth restricting nicotine, but absence of combustion products in snuff users.

Social adversity and SGA

Socioeconomic status is a term that describes the economic and social position of a person or family. Socioeconomic status is defined by income, level of education, occupation and private means. There is a strong gradient between low socioeconomic status and risk of multiple health issues, including cardiovascular disease, diabetes, metabolic syndrome and adverse birth outcomes (68). Figure 3 presents a simplified model of the relationship between socioeconomic status, health and illness.

Low maternal socioeconomic status has repeatedly been associated with higher risk of low birthweight and SGA, even though evidence is somewhat less consistent regarding SGA (69, 70). In a large epidemiologic study, low socioeconomic status was found to be one of the dominant determinants of SGA, where smoking habits and impaired maternal health partially accounts for the association (71).
Gestational age assessment

A reliable dating of the pregnancy accurately predicts the expected date of delivery and GA. A correct estimation of GA is crucial for assessing the relationship between GA and estimated fetal weight or birthweight. Historically, expected date of delivery was calculated applying Nägele’s rule to the first bleeding day of the last menstrual period. This gives a pregnancy length of 280-283 days, with the uncertainty of varying lengths of the menstrual cycle and imperfect recall of last menstrual period. A more reliable method of estimating GA is by ultrasound measurements of fetal biometry (72-74).

Pregnancy dating during the first trimester is recommended by ISUOG (75). Crown-rump length is often seen as the preferred dating method, even though there are studies showing early biparietal diameter (BPD) measurement to be superior in accuracy with less measurement error and lower rate of post-term birth (75-78). In Sweden, the Swedish Society of Obstetrics and Gynaecology recommend dating with ultrasound to be performed between 11 and 22 gestational weeks, and preferably when BPD measures 21-55 mm (79). In the case
of second trimester dating, ISUOG recommends the use of head circumference rather than BPD, as BPD varies according to fetal head shape (80-82).

Screening of small for gestational age fetuses

Being born SGA is associated with increased risk of perinatal mortality (83). Further, adverse events in the neonatal period, e.g. respiratory complications, hypotension, hypoglycaemia and necrotizing enterocolitis, are more frequently occurring in children born SGA than AGA (49). Even with the increased complication rate after SGA birth, the risk of adverse neonatal outcome is reduced if SGA status is known before delivery (84, 85).

Risk for complications in early pregnancies is assessed by risk factors, e.g. maternal characteristics, medical and family history. Screening for SGA fetuses in a low-risk population is traditionally performed by serial measurements of the symphysis-fundus distance from gestational week 25 and onwards. If serial measurements of symphysis-fundus distance are performed in a standardized manner, the sensitivity for detecting SGA with a cut-off at -2 SD is approximately 30-50% in term pregnancies (86). Despite the rather low detection rate, symphysis-fundus measurements can be performed in all pregnant women at a low cost. Royal College of Obstetricians and Gynaecologists (RCOG) thereby recommended symphysis-fundus distance as primary screening in a low-risk population (45).

Compared with symphysis-fundus measurements alone, an early third-trimester ultrasound scan might increases the sensitivity and specificity for detecting SGA (87-89). However, study-specific differences in SGA definitions and assessments of screening sensitivity and accuracy make it difficult to compare screening methods.

Women with a major (odds ratio (OR) >2) risk factor for SGA birth, such as previous SGA infant, previous stillbirth or chronic hypertension, should be offered more thorough screening for SGA fetuses, according to the Green-top Guideline no. 31 from RCOG (45). Serial ultrasound measurements of estimated fetal weight or abdominal circumference and umbilical artery Doppler are recommended for women with at least one major risk factor. Women with three or more minor risk factors, such as age >35 years, smoking and in vitro fertilization, are instead recommended screening with uterine artery Doppler in gestational week 20-24. Serial ultrasound scans should subsequently be offered women with pathologic Doppler scan (45).
Increasing evidence promotes the use of first-trimester screening with biomarkers to detect abnormal placentation, and hence identify pregnancies with increased risk of PE and IUGR (90-93). Even though biomarkers alone have a low accuracy for detecting PE and SGA, combinations of biomarkers, clinical risk factors, fetal biometry and uterine artery Doppler assessment have been evaluated for early detection of high SGA risk in a low-risk population (94). Moreover, second-trimester screening with fetal biometry, uterine artery Doppler and biochemical markers can be used for detecting pregnancies with high risk of SGA birth (95). Using this algorithm, high-risk pregnancies can be followed by third-trimester ultrasound scans in order to detect a large proportion of the pregnancies complicated by restricted fetal growth, especially those in need of preterm delivery.

Results from a large randomized controlled multicentre trial, SPREE, has shown that combined first-trimester screening including maternal characteristics, medical history, mean arterial pressure, uterine artery Doppler and biochemical markers is superior to screening based on maternal characteristics and medical history alone in detecting pregnancies at high risk of developing PE (96). The SPREE trial showed that such combined screening could detect more than 80% of pregnancies at high risk of preterm PE. Prophylactic use of acetylsalicylic acid from the first trimester has been shown to promote spiral artery remodelling and lower the incidence of PE (10). By prophylactic use of acetylsalicylic acid in women at high risk of PE, the ASPREE trial could demonstrate a significant reduction in incidence of preterm PE (97). There was a tendency towards a decreased risk of SGA birth in women without PE, but the trial was not powered for such secondary outcomes. Further, when high-risk pregnancies identified with combined first-trimester screening for PE are treated with acetylsalicylic acid, the incidence of preterm SGA could be reduced by 30-40%, and by 70% for very preterm SGA (<32 weeks) (98). The reduced incidence was mainly related to the reduced incidence of PE.
Long-term consequences of being born small for gestational age

Besides the increased perinatal mortality and morbidity, long-term health issues are more common in children born SGA. Children born preterm are more often SGA than children born in term pregnancy (99, 100). Even in the absence of severe perinatal complications, infants born preterm and SGA usually spend a considerable share of their early life, between birth and the time they were expected to be born, hospitalized. Instead of continuous nutrient supply and rapid intrauterine growth, the preterm infant is subjected to a variety of factors with potentially adverse impact on metabolism and vascular health. Therefore, it is of uttermost importance to evaluate health consequences in children born SGA after preterm and term pregnancies separately. Moreover, due to the strong correlation between preterm birth and low birthweight, it is of particular interest to describe long and short-term consequences of low birthweight and SGA separately.

Cardiovascular and metabolic disease

Cardiovascular disease, such as myocardial infarction, cerebral infarction and intracranial bleedings, are among the most common causes of death globally. Low birthweight and SGA are associated with elevated risks of metabolic risk factors for cardiovascular disease, e.g. insulin resistance, type 2 diabetes and obesity (5, 49, 101-104). Changes in the hormonal axes regulating GH, insulin-like growth factor, adrenal and gonadal hormones are seen in children born SGA (49, 103). It is likely that epigenetic changes alter regulatory gene expression in children born SGA, and that this at least in part explains the hormonal changes and increased risk of the metabolic syndrome (6, 49). The exact mechanisms are not sufficiently investigated, and further research in this area is needed.

Chronic hypertension

Chronic hypertension is one of the most important risk factors for cardiovascular disease. Further, hypertension is a common complication of metabolic disorders, e.g. diabetes and obesity. Hypertension affects one billion people worldwide, and is involved in more than nine million deaths every year (105). The prevalence of chronic hypertension dramatically increases with increasing age (106). Among women of fertile age, the prevalence of chronic hypertension is reported to be more than 6%, and complicates 1-5% of pregnancies (11, 106).
Being born SGA is associated with increased blood-pressure and hypertension (30, 107, 108). The increased susceptibility to hypertension might be the consequence of regulatory changes in several organ systems. Children born SGA display changes in vascular reactivity as well as regulation of the hypothalamic-pituitary-adrenal axis (7). The vascular resistance is increased, with reduced elasticity in small and large vessels; a functional impairment of the arterial walls indicating endothelial cell dysfunction (109). Moreover, the number of cardiomyocytes and nephrons are reduced, which may be followed by changes in the renin-angiotensin system and ultimately altered fluid and electrolyte balance (7).

Perinatal exposures with negative impact on the developing vascular system have a very long induction time, i.e. the time from exposure until the development of disease. The long induction time and the inverse relationship between age and prevalence of chronic hypertension entail practical obstacles when associations between perinatal exposures and chronic hypertension are studied. Instead, an increase in blood-pressure in children or adolescents has often been used as a proxy for cardiovascular risk or pre-hypertensive disorders.

Cognitive development
Apart from the impact on physical health, being born SGA also affects the neurodevelopment in a negative manner. In most studies, intelligence quotient, IQ, is slightly lower in children born SGA than AGA. Similar associations have been shown for other cognitive variables, where worse neurocognitive outcome in children born SGA follows a dose-response pattern (110-113). A recently published Finnish study of IQ in adults born late preterm showed a reduction in IQ for those who were born both SGA and late preterm (114). The authors conclude that the double burden of being born SGA and late preterm, a critical period in fetal brain development, seems more harmful to neurodevelopment than late preterm birth alone. A reduction in IQ and cognitive abilities might at least in part explain the link between being born SGA and poor academic achievements (115, 116). Not only cognitive disabilities have been associated with SGA. Being born SGA has also been associated with increased risk of anxiety and depression (117).

The pathophysiological background to impaired cognitive development in children born SGA is not fully elucidated. An increasing amount of evidence demonstrates micro- and macrostructural changes in the brain of children born SGA (118, 119). Moreover, studies using magnetic resonance spectroscopy have identified significant cerebral metabolic changes in fetuses born SGA with normal umbilical blood flow (120). Such changes can reflect a delay in
normal maturational processes, neuronal loss or injury and reduced myelination.

The increased risk of neurocognitive impairment after SGA birth seems to be modifiable. This developmental plasticity is demonstrated by the effect of catch-up growth in height, which diminishes the negative impact on cognitive abilities after being born SGA (111, 121, 122). The seemingly neuroprotective effect of catch-up growth is further demonstrated by evidence of a more pronounced reduction in brain volume and morphology in children born SGA with persisting short stature compared with children born SGA with normal stature during childhood (118).

Postnatal growth
Postnatal growth after being born small for gestational age
The vast majority, about 85-90%, of children born SGA encounter accelerated, or compensatory, growth during early childhood and reach normal final height (123). Accelerated growth in height is referred to as linear catch-up growth. Despite the high prevalence of catch-up growth, the risk of short adult stature is increased compared with children born AGA (123-127). Most children show catch-up growth very early and reach normal height within the first year of life (123).

There are two suggested models of the catch-up growth mechanism. The first model proposes adaptations of the neuroendocrine system which lead to generally increased growth. The second model suggests a decline in normal growth-inhibiting conditions leading to a more rapid cell proliferation in the skeletal growth plates as well as in non-skeletal tissues (128, 129). Regardless of which model we use for explanation of catch-up growth, the endocrine adaptations and their consequences in children born SGA are not completely understood. As earlier mentioned, children born SGA have altered levels of growth regulating factors and hormones (49, 130-132). Children without catch-up growth develop different patterns of growth factor secretion compared with children with catch-up growth (103, 133, 134).

There is unambiguous evidence that children exposed to maternal smoking have an increased risk of IUGR. Whether or not postnatal growth is affected by prenatal exposure to smoking is less clear. Several studies have shown an accelerated postnatal growth with complete catch-up during childhood (135-137). However, some authors report a reduced growth rate during the first year of life, with or without a complete catch-up later (138, 139). Moreover, there are studies showing a persistent short stature in children prenatally exposed to
smoking (57, 140, 141). The majority of the larger studies conducted have a short time of follow up, rarely more than two years (136-138). Studies with longer follow-up have small study populations or do not separate children born SGA, AGA or LGA (57, 139-141). Thus, even though smoking during pregnancy has been extensively studied, there are still important gaps in our knowledge.

Postnatal growth after being born moderate preterm

Moderate preterm birth, defined as birth between 32 and 36 gestational weeks, occurs at a point of time when the fetus experiences an intense intrauterine growth phase (142). When a child is born moderate preterm, this intended peak growth is likely to be missed as the extrauterine environment is highly different from the intrauterine (143). Feeding problems and infections further add to the likelihood of extrauterine growth restriction.

Most research on postnatal growth in children born preterm has focused on children born very preterm, before gestational week 32 (142). The few studies that included children born moderate preterm, after gestational week 32, showed suggested evidence that these children have a higher risk of short stature during childhood, especially if born SGA (143-145). However, knowledge on postnatal growth patterns is limited in children born moderate preterm.

In a systematic review from 2015, Ong et al. summarize evidence of postnatal growth and later health outcomes in children born preterm. The authors conclude that there is consistent evidence supporting neurocognitive benefits from rapid growth in head circumference. Evidence linking postnatal growth patterns to adverse impact on metabolic and cardiovascular health after preterm birth is limited, particularly in children born moderate preterm (146, 147).

Catch-up growth – beneficial or harmful?

Catch-up growth has been suggested to alter the long-term health impact of being born SGA. Numerous studies have shown adverse effects on metabolic profiles after rapid catch-up growth in weight in children born SGA or with low birthweight, especially after a large increase in weight and BMI (148-150). The evidence is, however, somewhat contradictory, as there are also studies that have not shown any association between catch-up growth, body composition and metabolic profile (151). Results from animal and human models of growth restriction indicates that the association between size at birth and cardiovascular and metabolic effects at least in part are mediated by rapid
catch-up growth and adiposity (151). During infancy, BMI increases gradually and reaches a peak at age 6-12 months, sometimes referred to as the infancy BMI peak. A higher and earlier infancy BMI peak increases the risk of later cardiovascular and metabolic disease (152, 153). Additionally, numerous studies have found an association between breastfeeding duration, growth rate and body composition (154, 155). Whether or not breastfeeding duration per se, rather than residual confounding of socioeconomic factors, is responsible for the altered growth rate is less clearly stipulated (156).

Whilst rapid catch-up growth in weight and BMI seems to have a negative impact on metabolic health, catch-up in head circumference and height seems to be beneficial for cognitive development (49, 121, 157-161). Moreover, children born preterm are exposed to a multitude of potentially adverse factors. Thus, the cost-benefit balance might be different for children born term and preterm.

Treatment with GH is an alternative for children born SGA with insufficient catch-up growth. In Europe, children born SGA who fail to show catch-up are considered for GH therapy if their height at age 4 years is below -2.5 standard deviation scores (SDS) of the population, and below -1 SDS of their own target height, as determined by their parents’ height (162). GH therapy can effectively normalize the stature in children born SGA as well as children with idiopathic short stature (163-165). It is still unclear if GH therapy has an impact on neurodevelopment. Some evidence indicates that children born SGA who receive GH therapy have an improved cognitive development compared with their counterparts not receiving GH therapy (166). The potential effect of GH therapy on cognitive development in children born SGA with inadequate catch-up growth needs further investigation.
Aims

The overall aim with the thesis was to gain further knowledge about long-term health consequences after being born SGA, as well as the impact of perinatal exposures on postnatal growth patterns.

The specific aims of the studies were:

I  To study single and combined perinatal exposure to PE, being born SGA and preterm, and subsequent risk of chronic hypertension among women by the time of their first childbirth.

II To study different thresholds for SGA in relation to subsequent risk of poor school performance at the time of graduating from compulsory school and to assess if adult stature modifies the association.

III To study if postnatal growth in height and weight until five years of age is altered after SGA birth, depending on maternal smoking habits during pregnancy.

IV To study postnatal growth patterns until five years of age in children born SGA between gestational week 32 and 40, depending on GA at birth.
Material and methods

Overview of the studies

Table 1. Overview of the studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Study design</th>
<th>Exposure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>731,008 mother-daughter pairs from Norway (1967-2009) and Sweden (1973-2010)</td>
<td>Observational register-based cohort study</td>
<td>PE, SGA, preterm birth</td>
<td>Chronic hypertension in offspring</td>
</tr>
<tr>
<td>II</td>
<td>1,088,980 children born 1973-1988 in Sweden</td>
<td>Observational register-based cohort study</td>
<td>Level of SGA</td>
<td>Poor school performance</td>
</tr>
<tr>
<td>IV</td>
<td>41,669 children born 2000-2015 in Uppsala county and visiting child health care in the county</td>
<td>Observational register-based cohort study</td>
<td>Preterm birth and SGA</td>
<td>Postnatal growth</td>
</tr>
</tbody>
</table>
Data sources

Swedish Medical Birth Register

The Swedish Medical Birth Register (MBR) contains data on all births in Sweden. The register was founded in 1973, and all Swedish delivery and neonatal units continuously register data. MBR contains information on pregnancy, delivery and neonatal outcome from births in Sweden from 22 completed gestational weeks. MBR is based on mandatory notifications. The first antenatal visit usually takes place before 13 weeks of pregnancy. The midwife interviews the mother regarding her social situation, medical history, earlier pregnancies and smoking habits, and measures height and weight.

Maternal characteristics are registered using checkboxes in the antenatal medical records. Since 1982, smoking habits are registered in early pregnancy. Further, smoking habits in pregnancy week 32 are recorded since 1990, and three months before pregnancy since 1999. Smoking habits are classified as non-smoking, 1-9 cigarettes a day or ≥10 cigarettes a day. Medications used during pregnancy are recorded continuously through antenatal care. The midwife who delivers the child registers information on pregnancy complications, labour and delivery. Data from the delivery embraces mode of delivery, complications and neonatal characteristics such as birthweight and length, head circumference and Apgar score. Obstetric and neonatal diseases and complications registered in MBR using International Classification of Disease (ICD) codes by the responsible doctor for the delivery and neonatal care. The statistics cover 96-99% of the Swedish deliveries throughout the years (65).

Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN) contains data on all pregnancies in Norway from 16 completed gestational weeks. The register was founded in 1967. In conformity with the Swedish MBR, MBRN is based on compulsory notifications on maternal characteristics and medical history, pregnancy complications, labour and delivery and neonatal outcome.

National School Register

The National School Register (NSR) contains data on final grades from compulsory school, in which municipal schools are obliged to register since 1988. Private schools are obliged to register final grades since 1993. During the years 1988-1992, private schools comprised less than five percent of the students in compulsory school (167). Children born before 1982 were graded with a norm-referenced grading system. A five-point scale was used for each subject, and the grade point average was calculated for each student and used
for comparison. For children born 1982 and later, the grading system was changed into goal-oriented criterion-referenced grades. A summary score of 16 subjects was calculated and used for comparison (168).

Swedish Conscript Register
The Swedish Conscript Register contains information from health examination, including height and weight, as well as results from psychological tests, including an intelligence test, on conscripts for military service. Until 2010, conscription was mandatory for Swedish males without severe handicaps or chronic diseases.

Uppsala Mother and Child Database
Uppsala Mother and Child Database is a prospectively collected population based cohort. The cohort consists of all children born in 2000-2015 at Uppsala University Hospital and registered in child health care in Uppsala County. The database includes information from the MBR, the Uppsala County Child Health Register, the Register of Total Population and the Register of Education. The personal identity number allows linkage between the different registers. Hence, the database contains data on pregnancy and birth, breastfeeding and parental smoking habits during childhood, as well as anthropometric measurements of weight, height and BMI from 18 months to 5 years of age.

Study population and study design
Paper I
Paper I was an observational population-based cohort register study. We studied associations between perinatal exposure to PE, being born SGA or preterm and subsequent risk of chronic hypertension in women at the time of the first childbirth. The cohort consisted of all mother-daughter pairs registered in the Swedish and Norwegian Birth Register, from 1973 to 2010 for the Swedish population, and from 1967 to 2009 for the Norwegian population. In other words, the women were first registered as new-borns (pregnancy of first generation), and later as mothers (pregnancy of second generation). In order to investigate every woman only once, we excluded women of the second generation who were not primiparous. The final cohort consisted of 731,008 mother-daughter pairs. Figure 5 illustrates the selection of the study population.
The exposure variables PE, born SGA and preterm delivery were identified in the first generation of women. ICD codes were used to identify PE. SGA was defined as birthweight <10\textsuperscript{th} percentile of expected birthweight for GA and sex according to the Swedish reference for fetal weight (169). SGA was further divided into severe (birthweight <3\textsuperscript{rd} percentile) and moderate (birth-weight 3rd to <10\textsuperscript{th} percentile) SGA. Preterm birth was defined as delivery before 37 gestational weeks. The outcome of the study was chronic hypertension in the women of the second generation, defined as diagnose of chronic hypertension before pregnancy or blood-pressure ≥140/90 before gestational week 20.

**Paper II**

Paper II was an observational population-based cohort register study, where we studied associations between being born SGA, with and without catch-up growth in height, and risk of poor school performance. The cohort consisted of all term born children registered in MBR between 1973 and 1988. Data on final grades after compulsory school were available for 564,071 eligible boys and 544,909 eligible girls, in total 1,088,980 children. Figure 6 illustrates the selection of the study population.

![Figure 5. Selection of study population paper I](image)

**Figure 5. Selection of study population paper I**

![Figure 6. Selection of study population paper II](image)

**Figure 6. Selection of study population paper II**
Birthweight for GA and sex was calculated according to the Swedish reference for birthweights (170) and classified as mild SGA (-1.01 to -2 SD of expected birthweight for GA), moderate SGA (-2.01 to -3 SD), severe SGA (<-3 SD), AGA (-1 to 0.99 SD) and LGA (LGA, ≥1 SD). Poor school performance was measured at time of graduation from compulsory school and defined as final grades <10th percentile.

Paper III

Paper III was an observational population-based cohort register study of postnatal growth patterns in children born SGA after perinatal exposure to maternal smoking. We included all term born children with known birthweight who were born 2000-2015 and registered in the Uppsala Mother and Child Database. The final cohort included 32,493 children, see Figure 7. The cohort was stratified according to smoking status into AGA with non-smoking mother, SGA with smoking mother and SGA with non-smoking mother. SGA was defined as birthweight <10th percentile of expected for GA and sex according to the Swedish reference for birthweights.

![Figure 7. Selection of study population paper III](image)

The exposure maternal smoking was defined as self-reported maternal smoking in pregnancy week 32. Mothers who negated smoking three months before pregnancy, at first antenatal visit and in pregnancy week 32 were classified as non-smokers. The outcome of the study was postnatal growth in height and weight. Anthropometric measurements of height and weight were performed by a nurse at age 1.5, 3, 4 and 5 years as part of standard clinical care.
Paper IV

Paper IV was an observational population-based cohort register study, in which we studied if SGA status in moderate to late preterm birth was associated with deviations in postnatal growth. All children born in pregnancy week 32 to 40 in 2000-2015 who were registered in the Uppsala Mother and Child Database were included in the cohort. The final cohort consisted of 41,669 children, see Figure 8.

![Figure 8: Selection of study population paper IV](image)

The exposures were studied in two separate models. Birthweight for GA and sex was calculated using the Swedish reference for birthweight (170). In the first model, birthweight and GA were used as continuous variables. SGA was defined as birthweight at the 3rd percentile (standardized SGA, sSGA) and AGA as birthweight at the 50th percentile (standardized AGA, sAGA). The outcome was estimated for children born sSGA and sAGA in gestational week 32+0, 35+0 and 40+0, respectively. In the second model, SGA was defined as birthweight for GA <10th percentile, and the cohort was stratified according to GA as moderate preterm (32-34 weeks), late preterm (35-36 weeks), early term (37-38 weeks) and late term (39-40 weeks). Postnatal growth was measured by a nurse at age 1.5, 3, 4 and 5 years as part of standard clinical care, and was included as a continuous variable.
Statistical methods

Paper I

Using log-binominal regression models, the risk ratio (RR) with corresponding 95% confidence intervals (CI) of chronic hypertension was calculated for women perinatally exposed to PE, severe SGA, moderate SGA and preterm birth. Potential confounders were selected using Directed Acyclical Graphs (DAGs). The models were adjusted for age, country of birth and cohabitation in the first generation, educational level and year of birth in the second generation and combined main exposure. Only women with a complete set of covariates were included in the adjusted models. In a second step, the risk of chronic hypertension after single and combined perinatal exposure to PE, SGA (<10th percentile) and preterm birth was calculated. In both analyses, women without any of the included exposures were used as reference category. A sub-analysis was made of 353,976 Swedish mother-daughter pairs with known data on smoking habits and BMI in the women of the second generation. The models for chronic hypertension was adjusted for the same covariates as above, and smoking habits and BMI were added to a second model.

Paper II

Rate of poor school performance was first calculated. The risk of poor school performance across birthweight groups was estimated using multivariate, unconditional logistic regression models. Potential confounders were selected using DAGs. Children born AGA were used as reference category, and the model was adjusted for parental educational level. The cohort was divided into two time-period groups, based on the two grading systems that were used during the study period. To investigate the possible impact of short adult stature on school performance, we performed a sub-analysis of boys born 1982 or later with known adult stature (n=111,759). In the sub-analysis, the cohort was stratified into six groups according to stature and birthweight for GA. Short stature was defined as height less than -2 SD at conscription. Odds ratios (OR) with 95% CI was calculated and adjusted for parental educational level. In a second model we also adjusted for maternal height in order to account for genetic contribution to short stature. Only subject with complete data on all covariates were included in model 2 (n=107,977; 97% of the children included in the sub-analysis, 10% of the total cohort). Boys born AGA with non-short adult stature were used as reference category.
Paper III
The cohort was stratified according to exposure status as AGA with non-smoking mother (AGA-NS), SGA with smoking mother (SGA-S) and SGA with non-smoking mother (SGA-NS). A generalized linear mixed effects model was applied, including the anthropometric measurements at birth and each clinical visit, as well as the interaction between anthropometrics and the exposure (SGA status and maternal smoking status). Potential confounders were selected using DAGs. The model was adjusted for sex, maternal age, level of education, height, country of birth and parental cohabitation. The estimated marginal mean height and weight with 95% CI were calculated for the exposure groups.

Next, the RR with 95% CI for short stature at age 1.5 and 5 years was calculated using log-binomial logistic regression models. Short stature was defined as height <10th percentile according to the national references for childhood growth (171). AGA-NS was treated as reference group, and the models were adjusted for maternal age, level of education, height, country of birth and parental cohabitation. Only subjects with complete data on all covariates were included in the adjusted models.

Paper IV
First, we applied a generalized least squares model. The regression model included the anthropometric measurements at each visit to child health care (at age 1.5, 3, 4 and 5 years), and the interaction between birthweight and GA. Birthweight and GA were used as continuous variables. Potential confounders were selected using DAGs. The model was adjusted for sex, maternal age, BMI, diabetic disease, smoking habits at gestational week 32, country of birth and breastfeeding at age two months. The model described the growth trajectories according to birthweight and GA. Using the model, means of height, weight and BMI was estimated for children born sSGA (birthweight 3rd percentile) and sAGA (birthweight 50th percentile) at gestational week 32+0, 35+0 and 40+0.

Next, contrasts with 95% CI were calculated between children born sSGA or sAGA at week 32+0, 35+0 and 40+0 and the reference value. sAGA 40+0 was used as reference. In a second step, sSGA was compared with sAGA in the same gestational week. The contrast of estimated mean BMI was calculated as the ratio between the estimated mean BMI and the reference value of estimated mean BMI.

Incomplete baseline variables were imputed. Model parameters were separately estimated in each imputed data set and their estimates and standard
errors were combined using Rubin’s rules. For comparison, a complete case analysis was performed.

Lastly, the cohort was classified according to birthweight, as AGA or SGA, and GA (late term, early term, mild preterm and moderate preterm). The anthropometric measurements at age 5 years were used to calculate the proportion of children with normal BMI and compared the groups using a Chi-Square test.

**Ethical considerations**

The study for paper I was approved by the Regional Ethics Committee of the Karolinska Institutet (No. 2011/195-312 and No. 2013/2192-32). The studies for papers II-IV were approved by the Regional Ethics Committee of the Medical Faculty of Uppsala University (No. 2014/103 for paper II, No. 2012/410 and 2012/410/1 for paper III and IV). The studies were performed in accordance with the ethical standards of the 1964 Helsinki declaration.
Summary of results

Paper I

The cohort consisted of 731,008 primiparous women. The rate and absolute number of women of the second generation with chronic hypertension was 0.4%, or 3161 women. The rate of chronic hypertension was slightly lower among Norwegian (0.3%) than Swedish women (0.5%). Likewise, all three perinatal exposures were of less frequent occurrence in the Norwegian part of the cohort.

Figure 9 shows the adjusted RR with 95% CI for chronic hypertension by each perinatal exposure, with SGA separated into moderate and severe SGA. Perinatal exposure to PE was associated with the highest risk of chronic hypertension.

![Figure 9](image)

*Figure 9.* Relative risk of chronic hypertension by each perinatal exposure with 95% CI. Adjusted for age, socioeconomic factors and country of birth in 1st generation, year of birth in 2nd generation and combined perinatal exposure to PE, SGA or pre-term birth.
Table 2 shows the risk of chronic hypertension by single and combined perinatal exposures, with no exposure as reference category. All exposures were individually associated with increased risk of chronic hypertension. Interaction analyses did not show any evidence of multiplicative or additive interaction between the exposures. PE in combination with SGA or preterm birth was associated with the highest risks.

Table 2. Risk of chronic hypertension in primiparous women by perinatal exposure (n=711,913). The risk ratios (RR) were adjusted for age, socioeconomic factors and country of birth in 1st generation and year of birth in 2nd generation.

<table>
<thead>
<tr>
<th>Perinatal exposure</th>
<th>Chronic hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>SGA</td>
</tr>
<tr>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

Paper II

In the cohort of 1,088,980 children born term, poor school performance was more often observed when factors related to low socioeconomic status were present; these include low maternal age, low parental educational level, maternal smoking and obesity. Further, boys were more likely to have poor school performance than girls.

Table 3 shows risk, presented as OR with 95% CI, of poor school performance by standardized birth weight for GA and sex at the time of graduation from compulsory school. Due to the use of two grading systems during the study
period, the results are stratified by year of birth. Being born SGA was associated with an increased risk of poor school performance, for mild SGA (birth-weight for GA -1 to -2 SD) as well as moderate to severe SGA (birthweight for GA <-2 SD). We observed a dose-response pattern with more severe SGA resulting in higher risk of poor school performance. For children born in the first part of the study period, the risk estimates were slightly higher, but the associations followed the same dose-response pattern.

Table 3. Risk of poor school performance at time of graduation from compulsory school in children by standardized birth weight. Odds ratios (OR) were adjusted for parental educational level (n= 496,888 for birth years 82-88 and 611,537 for birth years 73-81).

<table>
<thead>
<tr>
<th>Birth weight for GA (SD)</th>
<th>N of cases</th>
<th>aOR (95% CI) 1982-1988</th>
<th>N of cases</th>
<th>aOR (95% CI) 1973-1981</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;–3 SD</td>
<td>171</td>
<td>1.63 (1.38-1.93)</td>
<td>55</td>
<td>1.85 (1.65-2.07)</td>
</tr>
<tr>
<td>–3 to –2.01 SD</td>
<td>1068</td>
<td>1.45 (1.36-1.56)</td>
<td>2048</td>
<td>1.50 (1.43-1.58)</td>
</tr>
<tr>
<td>–2 to –1.01 SD</td>
<td>6106</td>
<td>1.27 (1.23-1.30)</td>
<td>9840</td>
<td>1.25 (1.22-1.28)</td>
</tr>
<tr>
<td>–1 to 0.99 SD</td>
<td>33,970</td>
<td>1.00</td>
<td>44,668</td>
<td>1.00</td>
</tr>
<tr>
<td>1 to 1.99 SD</td>
<td>6989</td>
<td>0.91 (0.88-0.93)</td>
<td>8281</td>
<td>0.94 (0.92-0.96)</td>
</tr>
<tr>
<td>&gt;2 SD</td>
<td>1507</td>
<td>0.99 (0.93-1.04)</td>
<td>1893</td>
<td>1.10 (1.05-1.15)</td>
</tr>
</tbody>
</table>

After the publication of paper II, a sub-analysis was made of the subgroup with known data on maternal smoking habits. Table 4 shows the unpublished data adjusted for parental educational level and maternal smoking habits. The associations were weaker but remained significant for all SGA-groups after adjustment for maternal smoking.
Table 4. Rates and risk of grade score ≤140 by standardized birth weight for children born 1982-1988. Odds ratios (OR) were adjusted for parental educational level, n=496,888.

<table>
<thead>
<tr>
<th>Birth weight for GA (SD)</th>
<th>aOR¹ (95% CI)</th>
<th>aOR² (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;–3 SD</td>
<td>1.63 (1.38-1.93)</td>
<td>1.35 (1.12-1.63)</td>
</tr>
<tr>
<td>–3 to –2.01 SD</td>
<td>1.45 (1.36-1.56)</td>
<td>1.24 (1.16-1.34)</td>
</tr>
<tr>
<td>–2 to –1.01 SD</td>
<td>1.27 (1.23-1.30)</td>
<td>1.14 (1.08-1.15)</td>
</tr>
<tr>
<td>–1 to 0.99 SD</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1 to 1.99 SD</td>
<td>0.91 (0.88-0.93)</td>
<td>1.00 (0.98-1.03)</td>
</tr>
<tr>
<td>&gt;2 SD</td>
<td>0.99 (0.93-1.04)</td>
<td>1.17 (1.10-1.24)</td>
</tr>
</tbody>
</table>

¹adjusted for maternal and paternal education
²adjusted for maternal smoking habits and maternal and paternal education

Figure 10, which was not published in the original paper, is a polynomial trend line which illustrates the inverse relationship between poor school performance and size at birth, stratified by adult stature.

![Figure 10](image-url)
Table 5 shows a sub-analysis of boys born 1982-1988 with known adult stature. Being born mild SGA with non-short adult stature was associated with a slightly increased risk of poor school performance. Children born mild SGA with short adult stature had 60% increased risk of poor school performance compared with children born AGA with normal adult stature. For moderate or severe SGA with short adult stature, the adjusted model did not reach statistical significance. However, the fully adjusted model only included 16 subjects born moderate or severe SGA with short adult stature.

Table 5. Rates and risks of poor school performance in boys by standardized birth weight and adult stature. Odds ratios (OR) were adjusted for parental educational level and maternal height (n=111,759).

<table>
<thead>
<tr>
<th>N of cases</th>
<th>Rate %</th>
<th>OR (95% CI)</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA non-short</td>
<td>6073</td>
<td>6.4</td>
<td>1.00</td>
</tr>
<tr>
<td>AGA short</td>
<td>188</td>
<td>10.2</td>
<td>1.70 (1.46-1.98)</td>
</tr>
<tr>
<td>Mild SGA non-short</td>
<td>947</td>
<td>7.9</td>
<td>1.28 (1.20-1.38)</td>
</tr>
<tr>
<td>Mild SGA short</td>
<td>68</td>
<td>10.5</td>
<td>1.74 (1.35-2.24)</td>
</tr>
<tr>
<td>Moderate/severe SGA non-short</td>
<td>173</td>
<td>9.2</td>
<td>1.51 (1.29-1.77)</td>
</tr>
<tr>
<td>Moderate/severe SGA short</td>
<td>24</td>
<td>11.4</td>
<td>1.92 (1.26-2.94)</td>
</tr>
</tbody>
</table>

Paper III

In the cohort consisting of 32,493 term born children, mothers to those born SGA-S had higher rates of factors associated with low socioeconomic status. Mothers to children born AGA-NS were the tallest, but there was no difference in maternal height between SGA-S and SGA-NS. Children born SGA with and without a smoking mother (SGA-S and SGA-NS) were both significantly shorter at birth than children born AGA with non-smoking mother (AGA-NS), both p<0.001. SGA-S were 0.4 cm shorter at birth than SGA-NS children, p=0.012 for difference. There was no significant difference in birthweight between SGA-S and SGA-NS, p=0.084.
Figure 11 shows the adjusted mean heights during the first five years of childhood for children born AGA-NS, SGA-S and SGA-NS. The model showed that over time, there was a significant difference in mean height between the groups, p<0.001. The difference persisted after adjustment for sex, maternal age, maternal level of education, maternal height, maternal country of birth and parental cohabitation, p<0.001. At 1.5 years of age, both SGA groups were shorter than children born AGA-NS, but there was no significant difference in height between SGA-S and SGA-NS children. At age five years, children born SGA-NS were shorter compared with children born AGA-NS and SGA-S.

Figure 12 presents the adjusted mean weight from birth until age five years in children born AGA-NS, SGA-S and SGA-NS. Over time, there was a significant difference in weight between the groups, p<0.001, a difference that persisted after adjustment for the same factors as in the model for mean heights. At age 1.5 years, even though SGA-S had approached AGA-NS, both SGA groups were still significantly lighter than AGA-NS children. At age five years, children born SGA-S were of comparable weight as AGA-NS, but
SGA-NS were 1.5 kg lighter than AGA-NS children. There was also a significant difference between the SGA groups, where children born SGA-NS were 1.2 kg lighter than SGA-S.

Table 6 presents the RR of short stature. Compared with AGA-NS, the adjusted RR of short stature at age 1.5 years for SGA-S was not significantly increased, whereas SGA-NS had a three times higher risk of short stature. At age five years, the RR of short stature remained comparable for AGA-NS and SGA-S and more than doubled for SGA-NS.

Figure 12. Mean weight in cm during early childhood for children born AGA-NS, SGA-S and SGA-NS, adjusted for sex, maternal age, maternal level of education, maternal height, maternal country of birth and parental cohabitation.
Table 6. Risk of short stature at age 1.5 and 5 years presented as risk ratio (RR) with 95% CI for children born AGA-NS, SGA-S and SGA-NS. Adjusted for maternal age, maternal level of education, maternal height, maternal country of birth and parental cohabitation.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Cases</th>
<th>Rate (%)</th>
<th>RR (95% CI)</th>
<th>aRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age 1.5 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGA-NS</td>
<td>20496</td>
<td>1042</td>
<td>5.1%</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>SGA-S</td>
<td>102</td>
<td>10</td>
<td>9.8%</td>
<td>1.9 (1.1;3.5)</td>
<td>1.5 (0.8;2.9)</td>
</tr>
<tr>
<td>SGA-NS</td>
<td>1196</td>
<td>217</td>
<td>18.1%</td>
<td>3.6 (3.1;4.1)</td>
<td>3.0 (2.6;3.4)</td>
</tr>
<tr>
<td><strong>Age 5 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGA-NS</td>
<td>16430</td>
<td>1112</td>
<td>6.8%</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>SGA-S</td>
<td>94</td>
<td>10</td>
<td>10.6%</td>
<td>1.6 (0.9;2.8)</td>
<td>1.3 (0.7;2.4)</td>
</tr>
<tr>
<td>SGA-NS</td>
<td>914</td>
<td>169</td>
<td>18.5%</td>
<td>2.7 (2.4;3.2)</td>
<td>2.3 (2.0;2.7)</td>
</tr>
</tbody>
</table>

**Paper IV**

Of the 41,669 children included in the study, 532 (1.3%) were born moderate preterm (32-34 gestational weeks), 1692 (4.1%) late preterm (35-36 weeks), 11,271 (27.0%) early term (37-38 weeks) and 28,174 (67.6%) late term (39-40 weeks). Birthweight and birth length for GA and sex were the lowest in children born moderate preterm. In all gestational ages, a large proportion were missing information on breastfeeding habits at age two months (37.3% of the total study population).

Figure 13 illustrates differences in estimated mean height, weight and BMI at ages 1.5 to five years between children born sAGA (birthweight 50th percentile) and sSGA (birthweight 3rd percentile) from gestational week 32+0 to 40+0. From three years of age, children born sAGA and moderate to late preterm were as tall as children born sAGA at 40+0 weeks. Children born sSGA and moderate to late preterm were both shorter and lighter with a lower BMI.
than the reference group, with a pattern of greater differences the more pre-term born. The differences in estimated height, weight and BMI remained significant over the follow-up period of five years.

Figure 13. Estimated mean height, weight and BMI in children born sAGA and sSGA at age 1.5, 3, 4 and 5 years. Model adjusted for maternal height, BMI, diabetic disease, smoking habits at gestational week 32, country of birth, breastfeeding at age two months and gender.
Figure 14. Estimated mean height, weight and BMI from age 1.5 to 5 years in children born ≤AGA and ≤SGA in gestational week 32+0, 35+0 and 40+0. Model adjusted for maternal height, BMI, diabetic disease, smoking habits at gestational week 32, country of birth, breastfeeding at age two months and gender.
Figure 14 illustrates differences in the estimated height, weight and BMI between children born sAGA and sSGA at the same GA from 1.5 to five years of age. In comparison with children born sAGA at week 32+0, 35+0 and 40+0, those born sSGA at the corresponding GA were shorter, lighter and had a lower BMI at all follow-up ages. A pattern of larger differences the shorter the GA was seen.

Figure 15 shows the proportion of children with low, normal and high BMI at age five years. Normal BMI (10th-90th percentile) varied according to SGA-status and GA at birth. Children born SGA (<10th percentile) and moderate preterm (32-34 weeks) were less likely to have a normal BMI compared with children born AGA (10th-90th percentile) and late term (39-40 weeks) (p<0.05). There was a J-shaped pattern among children born SGA and moderate preterm with a tendency of more subjects with high BMI, but even more children with low BMI at 5 years.
Discussion

The studies included in this thesis were epidemiological observational cohort studies of long-term consequences of being born SGA. Being born SGA, as a single exposure or in combination with other perinatal exposures such as pre-term birth, was associated with increased risk of chronic hypertension, poor school performance and aberrant postnatal growth patterns. The chosen methodology has some important strengths and limitations, which should be considered before any conclusions are drawn regarding the implications of the results.

Methodological considerations

Epidemiological studies aim to identify and evaluate potential causal associations between different factors (exposures) and diseases or conditions (outcomes). In a biological context, such as the human body, there are a multitude of exposures that can contribute to the development of a specific disease. Epidemiologists often use the term “web of causation” to describe this complex multifactorial origin of disease. The web of causation does not provide the causal inference, rather it is a tool to depict the complex interrelationship between specified biological and social exposures and diseases (172). Apart from the multitude of contributing factors involved in disease causation, a factor can have direct as well as indirect effects on the subject, which may give rise to disease, or outcome. Direct causes are factors such as micro-organisms and toxins, whereas indirect causes have an effect on the outcome that is mediated through intermediate factors (173). Figure 16 is an example of a web of causation, linking some of the perinatal factors, or exposures, associated with the long-term outcome adult disease.
In a biological context, there is always a long succession of factors that differ between individuals. If these factors are associated with the exposure as well as outcome, they are considered as potential confounders. Due to individual variation, the prevalence of different confounders often differ between exposed and un-exposed subjects. Randomization is a method to control confounding by assuming that all confounding factors thereby are equally distributed between the treatment arms of the study. In contrast to randomized studies, observational studies need to handle confounding differently, e.g. by the use of statistical adjustment methods. Hence, the measures of association are meant to show only the direct effect of the exposure on the outcome. Drawing causal diagrams, or directed acyclic graphs (DAGs), is a way to identify which confounders to control for. By adjusting for appropriate confounders, non-causal pathways are blocked, that otherwise might distort the results of an observational study (173). Figure 17 shows different factors and their relationship to exposure and outcome.
Study design

Results from observational studies are often considered as low grade of evidence for the causal relationship between exposure and outcome. However, long-term outcomes associated with being born SGA are seldom possible to study in randomized controlled trials. First, it is not ethically justifiable to use a study setting to expose fetuses to factors with potentially adverse influence. Second, the induction time, i.e. the period of time between exposure and outcome, after adverse perinatal exposures is often very long. Hence, the follow-up time would be unreasonably long. Third, the outcomes of interest are rare and we would thus need a very large study population to detect possible associations. Due to the long induction time, such studies would be very expensive and involve a high rate of loss to follow up. Considering this, an observational cohort study is a suitable study design for the outcomes of this thesis. Moreover, Sweden is a particularly apt setting for cohort studies, with multiple national population-based registries that can be linked using the personal identification numbers assigned to all Swedish inhabitants.

The large study populations allowed us to study rare exposures and outcomes. In paper I, 730,000 women were included. Despite this, only a handful of women were simultaneously exposed to all three included perinatal exposures and subsequently developed the rare outcome chronic hypertension in fertile age after an induction time of 20-40 years.

All four papers included in the thesis are population-based register studies. In paper I and II, the study population consisted of all children born in Sweden during a specified time period. In addition, all children born in Norway were included in paper I. In paper III and IV, all children born in Uppsala County who had later visited child health care in the same county, were included in the study population. As antenatal, delivery and child health care in Sweden is free of charge, and all pregnancies and births after 22 gestational weeks currently are mandatory to register, a majority of the children of the true populations were part of the study populations, minimizing selection bias. Furthermore, Uppsala County has a high attendance of child health care, which results in a high follow-up rate in paper III and IV (174). The results are thereby reasonable to see as generalizable to other populations in similar settings.

Measurement of exposure

The main exposure of this thesis was being born SGA. Measurement of this exposure consists of both GA and birthweight, exposures considered “acceptable” and “good”, respectively in the MBR (175). In paper I and II, most pregnancies were dated using last menstrual period. In paper III and IV,
most pregnancies were dated using fetal biometry measured with ultrasound during the second trimester, which is considered more reliable. The study populations in paper III and IV were born during the 21st century, and more than 92% were dated using modern ultrasound apparatuses allowing precise measurements of fetal biometry. Thereby, the risk of misclassification error due to irregular menstrual cycles or incorrect ultrasound measurement was minimized. In cases of very early growth restriction, there is a risk of underestimating GA in the second trimester. Considering that only term born children were included in paper III, the risk of differential misclassification error with unequal distribution of misclassification error among exposed and non-exposed children should be minor, as children with early severe IUGR seldom reach term GA. In study IV, children born moderately preterm are included. Hence, the risk of differential misclassification bias is somewhat larger. If children born SGA and moderate preterm are misclassified due to underestimation of GA in the second trimester, the true GA in this group would be higher (e.g. if an early growth restricted fetus with true GA 18+0 is dated with ultrasound in the second trimester, with estimated GA 17+0, the GA is underestimated with 7 days. If labour is induced due to fetal compromise in week 31+2 according to the ultrasound dating, the true GA at birth would be 32+2). If a large proportion of the children classified as moderate preterm SGA are misclassified as <32 weeks and hence excluded from the study, it might result in underestimating the association between combined exposure to moderate preterm birth and SGA, and deviant postnatal growth.

Both MBR and Uppsala County Child Health Register are based on prospectively collected information. This prospective design, where exposure data is registered before the outcome is known, precludes recall bias in registration of exposure, potential confounders and outcome.

In paper I, perinatal exposure to PE was studied. PE was identified through ICD codes, which has both strengths and limitations. A strength is the low risk of misclassification, as PE with its corresponding ICD code is diagnosed by a physician according to national definitions of the disease. However, the prevalence of PE in the study was only 2%, which raises the question if the perinatal exposure to PE is underestimated, leading to systematic information bias. Presumably, this misclassification is non-differential. Moreover, PE has been evaluated with a positive predictive value of 93% during 1987-1993 in Sweden, and 84% during 1999-2010 in Norway (176, 177). Thus, we believe that those classified as PE in the registries are truly PE. The Norwegian validation study has further explored PE in MBRN by calculating sensitivity and specificity of the diagnosis. The sensitivity was low, 43%, indicating that a large proportion of the children exposed to PE were classified as un-exposed, which may lead to underestimation of the association and reduction of the precision of the risk estimates. Due to a limited sample size, the risk associated
with simultaneous exposure to all three risk factors had a low precision with broad CI. However, since PE incidence is relatively low, we expect that only a small proportion of the individuals classified as non-exposed were truly exposed to PE. As such, the possible impact of the misclassification in the reference group is likely small.

In paper II, the studied exposures were size for GA at birth and short adult stature. SGA was used as a proxy for IUGR, and short adult stature as a proxy for inadequate catch-up growth. It is important to stress that even though SGA is not equal to IUGR, SGA is the best available measurement of fetal growth in the national registries during the study period. In addition, genetically short children are erroneously classified as growth restricted, even though they have been able to reach their growth potential. By adjusting for maternal height, we could at least in part compensate for this misclassification. A limitation of the study is the lack of information on paternal height.

The identification of short adult stature in the Conscript Register includes several limitations. Most important is the restriction to almost exclusively male conscripts. If data from MBR had been available for a longer time period in our dataset, we would have been able to identify adult height in women who have become mothers as well. Either way, there is a risk of introducing selection bias since subjects with severely affected cognitive development are less likely to conscript for military service or become parents. Hence, subjects with potentially the largest adverse impact of the exposure will not be included in the study. Thereby, a type 2 error may be introduced, where the null-hypothesis is accepted, even though a true association exists, or the strength of the association is underestimated.

In paper III, intrauterine exposure to maternal smoking and size for GA at birth were studied. Smoking is advised against during pregnancy as it exposes the fetus to toxins. As smoking is self-reported, there is a risk that pregnant women do not admit smoking during pregnancy. By defining non-smokers as women who denied smoking three months before pregnancy, at first antenatal visit and in pregnancy week 32, the risk of misclassification was reduced. Due to the large cohort size, we still had power to perform the statistical calculations with reasonable precision.

In paper III and IV, exposure to SGA and preterm birth was studied. As earlier mentioned, these variables are robust with good internal and external validity. When calculating standardized birthweight, we used the Swedish reference for birthweight for GA and sex. Using a reference standard based on birthweights in new-borns rather than fetal weights estimated with ultrasound has advantages as well as disadvantages. First, there are important differences between the methodologies used when the Swedish references were made.
The reference standards for birthweights were developed using birthweights of all healthy infants in a cohort including all children born in Sweden 1977-1981 (170). The Swedish reference for fetal weight, on the other hand, was based on ultrasound measurements in a small number of pregnancies (169). Second, as children born preterm are more often born SGA than term born children, reference standards based on birthweight run the risk of under-estimating normal mean birthweight. This implies that children born preterm and SGA run the risk of being wrongly classified as AGA. In paper III, only term born children were included. The robustness of the reference standards for birthweights in a cohort of term pregnancies makes the choice of standards predominantly advantageous. In paper IV, being born mild to moderate pre-term was one of the main exposures. Hence, the choice of reference standards is more doubtful. By choosing a reference standard based on birthweights, the proportion of children born SGA may be underestimated. This may even out differences between the groups, and potentially introduce a type 2 error.

Measurement of outcome
In paper I, the outcome was chronic hypertension at time of first childbirth. Hypertension was registered by a medical professional, which makes the diagnosis more reliable than if self-assessed. In Sweden, the diagnosis was recorded as a checkbox filled in by the midwife responsible for antenatal care at first antenatal visit or as an ICD-code noted by the responsible physician at discharge from hospital after delivery. In Norway (1967-1998), hypertension was identified as free text, which was later coded by MBRN into ICD-codes. From year 1999 and onwards, hypertension was instead identified using checkboxes filled in by the responsible midwife. The method for recording the outcome might explain the difference in prevalence of chronic hypertension between the countries. To explore the suspected underreport in MBRN, we stratified for country of origin and re-ran the analyses. The patterns of risks of chronic hypertension were similar, but the risk was no longer significantly increased after exposure to SGA and preterm birth in Norway. It is plausible that the loss of statistical significance results from loss of statistical power due to few cases and underreport of the exposure.

Chronic hypertension was found in 0.4% of the study population. The prevalence of chronic hypertension is lower than in other similar populations; 6% among women of fertile age and 1.5% among pregnant populations (11, 106). This can partly be explained by underreport of the outcome, as previously discussed. Further, the exclusion of parous women entails a lower mean age with lower expected prevalence of hypertension. Lastly, the study design of registers comprising two generations of women within 40 years implies that most of the women of the second generation are still in their fertile years. Thus, skewness towards lower maternal age will be present compared with
other populations of pregnant women, resulting in fewer women with chronic hypertension compared with the whole population of first-time mothers. This skewness should be non-differential, i.e. the misclassification is similar in both the exposed and the unexposed groups, and leads to a bias that underestimates the association. If the cohort was followed for a longer time, the skewness would be less prominent, and it is possible that risk estimates after single as well as combined exposure would be higher. A longer follow-up time would thereby increase the generalizability. The present study could be considered as generalizable to a young pregnant cohort in a similar high-income setting.

During the study period of paper II, Sweden changed grading system. The relative grades, used during the first part of the study period, were normally distributed and the mean used for comparison followed a Gaussian distribution curve. The goal-oriented criterion-referenced grades used a summary score for comparison, which was skewed towards greater values. In order to be able to compare the risks in similar ways for both age groups, a threshold of 10th percentile was used as definition of poor school performance. Even though the risk estimates were slightly higher for the children with relative grades, the results and risk patterns were similar for both groups. This can be regarded as a strength of the study, with reproducibility in two different grading systems. Children born severe SGA more often had missing information for the outcomes school performance and adult stature. The loss to follow-up may be caused by a more marked cognitive dysfunction compared with children born mild SGA or AGA. If this is the true case, the associations will be underestimated, and the results only generalizable for children born mild to moderate SGA.

In paper III and IV, the outcome growth in height, weight and BMI was measured and registered by a professional nurse, which minimizes information and recall bias. Since 2005, anthropometrics are registered electronically in the Uppsala County Child Health Register, thus data is missing in Uppsala Mother and Child Database for the younger ages in children born before 2003. Only measurements performed within two months of the recommended time window for standard check-up for each age are included, which increases the proportion of children with missing values, but decreases the inter-individual variation due to differences in age. Hence, paper III and IV can be regarded as studies with high internal and external validity, and the results should be generalizable to children under age six years in similar settings.

Confounding
In all four studies, the databases included information on several important confounders. Socioeconomic confounders are of great importance to non-
communicable risk factors and diseases, such as chronic hypertension and obesity. However, socioeconomic confounders such as level of education and maternal smoking are strongly correlated. If several correlated confounders are adjusted for, the statistical power is reduced and possible causal inference cannot be demonstrated. By constructing a DAG, a minimal set of covariates are selected for adjustments, and statistical power is maintained. The aim is to block all non-causal paths by adjusting for a restricted number of confounders, instead of multiple adjustments for correlated factors.

In register studies, missing information might decrease the robustness of the results. In the multivariable analyses performed in the papers, only subjects with a complete set of variables were included. Hence, with a large proportion of missing values, only a subset of the study population will be included in the analyses. There are different ways to handle this issue. In paper I, data on BMI and smoking were only available for Swedish women. We re-analysed our data in the Swedish subset and included adjustments for BMI and smoking. The adjustments only had minor impact on our results, and the conclusion was drawn that the original results for the whole study populations were valid.

Another approach is to replace missing data with imputed values. In paper IV, missing baseline variables were imputed under fully conditional specification. In order to evaluate the robustness of the imputed dataset, a complete case analysis was performed to ensure that the results of the imputed dataset were valid.

In paper II, smoking was regarded as a mediator of SGA birth rather than a confounder of poor school performance. It is further argued that there is no proven causative association between maternal smoking and poor school performance. One can speculate that the association might only mirror low socioeconomic status, which is adjusted for by parental educational level. This reasoning has two potential problems. First, a mediator does not exist prior to the exposure, but represents the potential link between the exposure and the outcome. According to this definition, smoking cannot be viewed as a mediator as smoking precedes the growth restriction and there is unambiguous evidence of a causal relationship between smoking and SGA birth. Second, it is hard to determine whether parental educational level fully adjusts for socioeconomic status. It is true that a causal effect of smoking on poor school performance has not been proven. However, it cannot be ruled out that residual confounding from differences in socioeconomic status is present, even after adjustment for parental educational level. Moreover, if e.g. exposure to toxins from second hand smoking has an effect on the outcome poor school performance, smoking should be regarded as a confounder and hence adjusted for. In the sub-analysis performed after publication of paper II, the associations between being born SGA and poor school performance remained statistically
significant after adjustment for smoking habits and maternal BMI in addition to parental educational level, even if the risk estimate were lower.

We did not have data on paternal height in any of the datasets. This was a limitation, as parental height is equally important for postnatal growth (39). As paternal height was missing in the dataset, we could not estimate the genetic growth potential, or target height. If target heights were available, we would have been able to use an individualized cut-off for catch-up growth that more completely includes the genetic growth potential.

Statistics

In paper I, II and III, relative risks were estimated for the outcomes chronic hypertension, poor school performance and short stature. In paper I and III, the strength of the association was expressed as the relative effect measure risk ratio (RR). In paper II, we used odds ratio (OR) instead to estimate relative risks. In cases of a rare outcome, the OR is approximately equal to the RR. If the outcome is common, with a prevalence more than 5-10%, the OR and RR will not be comparable. In such circumstances, using OR will overestimate the relative risk of the outcome if the RR exceeds one and underestimate the relative risk if the RR is below one. However, the risk of over-estimating the relative risk by using OR as relative effect measure is limited when the OR is less than three (173).

In paper I, the outcome chronic hypertension was rare (0.4%). The low prevalence of the hypertension implies that the use of OR would have given similar risk estimates as RR. In paper II, the outcome was more common, with a cut-off of 10th percentile for the outcome. A dose-response pattern was seen. This indicates that the outcome was much more common in children exposed to severe SGA birth. Hence, the OR might over-estimate the strength of association. However, the OR was not exceeding two, and when the analyses were re-run using RR, the risk estimates were comparable. In paper III, RR was correctly used as relative effect measure in order to get a robust result as the cut-off for the outcome short stature was set at 10th percentile.

In papers III and IV, the outcome postnatal growth was measured at several different ages during the first five years of life. The measurements are not independent from each other, as the measurement was repeated several times in one study subject. In paper III, we used a generalized mixed effect model, and in paper IV a generalized least squares model to account for repeated measures of the outcome.
General discussion

Since the early hypotheses of long-term morbidity and mortality in consequence of perinatal exposures were drafted in the 1970s, the research field has greatly expanded. Cardiovascular and metabolic outcomes have dominated the research on DOHaD, but birthweight has been shown to affect a range of conditions, from osteoporosis and cancer to mental disorders and cognitive functions (2). In this thesis, two of the explored long-term consequences of being born SGA are chronic hypertension and body composition, both well-known risk factors for cardiovascular and metabolic disease. We also studied poor school performance and short stature. Impaired cognitive development with lowered IQ is likely to be followed by poor school performance. The theory behind the DOHaD concept stipulates that changes in the phenotype of the embryo, fetus or infant as a response to environmental changes are part of the normal developmental plasticity. In line with this theory are the findings of lower IQ and cognitive impairment in children with unsatisfying linear catch-up growth with persistent short stature after being born SGA (111, 121, 122). It is appealing to apply the same reasoning to cardiovascular and metabolic health and catch-up growth, with potential changes in phenotype according to postnatal growth patterns. However, even though multiple studies point towards negative effects on cardiovascular and metabolic health after rapid catch-up growth in weight, the evidence still is ambiguous (147).

The results of the four papers concordantly show associations between being born SGA and increased risk of long-term complications in the form of chronic hypertension, cognitive dysfunction and deviations in postnatal growth patterns. A dose-response pattern between perinatal exposure and long-term effects on health and growth was apparent in paper I, II and IV, with multiple exposures or more severe SGA associated with more pronounced effects. By broadening the definition of SGA, we have also shown an effect on cognitive development, measured as poor school performance, already at -1 SD of expected birthweight for GA and sex, which has not been shown previously.

Children born preterm are more often SGA than children born in term pregnancy (100). Taking into account the frequently concurrent occurrence of preterm birth and SGA, it is important to bear in mind the potential confounding of preterm birth when exposure to SGA is analysed. Being born SGA and preterm have independently been associated with increased blood-pressure in early adulthood as well as impaired cognitive function, with higher risks after combined exposure. This indicates the importance of considering possible interactive effects of combined perinatal exposures. Similarly to the study design in paper II and III, subjects born preterm are sometimes excluded in
order to address the difficulties regarding causal inference in observed associations. However, it is important to remember that by excluding preterm study subjects, the results of the study cannot be generalized to the whole population, but only to term born children. If there is an interaction between SGA and preterm birth, the strength of association might be much greater after multiple exposures. The findings in paper IV, and the general dose-effect relationships observed in this thesis highlight this remark.

Chronic hypertension in elderly is more strongly associated with cardiovascular disease than slight elevations of blood-pressure in adolescents (178). Despite this, exploration of small differences in blood-pressure in children or adolescents is a far more common outcome than chronic hypertension in clinical trials due to the long induction time from perinatal exposure to development of chronic hypertension. Largely, previous findings of subsequent chronic hypertension or elevated blood pressure after perinatal exposure to PE, being born SGA or preterm, are in line with the findings in paper I. To our knowledge, there is no previous study analysing separate and joint effects of these perinatal exposures. Confounding by other exposures entails a risk of overestimating the effect of each perinatal exposure. In paper I, the large cohort allowed stratification by single or combined exposure. It contributes with new knowledge about combined exposure by disentangling the effects on chronic hypertension by each separate exposure.

Paper II presents a modest but significant association following a dose-response pattern between level of SGA and poor school performance. A similar dose-response relationship has been shown for blood-pressure after perinatal exposure to preterm birth, with higher blood pressure being associated with early preterm birth (<34 weeks) compared with moderate preterm birth (34-36 weeks) (179). In paper IV, the combined exposure to being born SGA and preterm had larger effect on postnatal growth-patterns the shorter the GA. One can speculate that similar adverse dose-dependent impact on various aspects of health and development might follow perinatal exposure to SGA and preterm birth. This further illustrates the difficulty in stating a threshold for when SGA should be considered a clinically relevant risk factor.

In paper III, children born SGA with smoking mothers were found to have a more rapid catch-up growth in height as well as in weight, compared with children born SGA without smoking mothers. SGA was used as a proxy for IUGR. Using this approach, we were able to study the subjects most severely affected by maternal smoking. Earlier findings on intrauterine exposure to tobacco smoke and postnatal growth patterns are diverse, and mainly comprises children of all birthweights, and not exclusively children born SGA (135-138, 140). Intrauterine growth is dependent on maternal as well as fetal and placental factors. Thus, children born SGA comprises a broad spectrum
of children, from genetically small, but healthy, children to growth restricted infants with severe illnesses. By selecting the children most severely affected by maternal smoking or placental insufficiency, and then separate them by the underlying cause of their smallness, we may come a little bit closer to understanding how different intrauterine exposures affect growth and development.

Being born SGA is associated with deviating postnatal growth patterns, with higher risk for children born preterm or with comorbidities (180, 181). Even though children born SGA have higher risk of postnatal growth restriction compared with those born AGA, deviating growth trajectories are more common the shorter the GA at birth (182, 183). Hence, both children born preterm SGA and preterm AGA are likely to be exposed to postnatal growth restriction followed by accelerated growth. Since catch-up growth may affect future metabolic health, children born preterm of all birthweights are at risk of this adverse exposure (146, 184). It is reasonable to believe that combined exposures entail the greatest risks. Concordantly, paper IV showed that combined exposure to being born SGA and moderate to late preterm resulted in more aberrant growth patterns, compared with a single exposure. Moreover, as BMI is a function of height and weight, the combined exposure not merely increases the risk of a slower linear growth, but also has an impact on body proportions. Postnatal growth in height is largely genetically and growth hormone dependent. Thus, the growth hormone axis does not seem to be heavily influenced by moderate preterm SGA birth. However, consequences of deviant growth in weight, and the tendency of J-shaped pattern of BMI at five years of age after being born SGA and moderate preterm might have an impact on metabolic and cardiovascular future health.

In conclusion, children born SGA in combination with other adverse perinatal exposures are at higher risk of developing a phenotype with increased risk of chronic hypertension and cognitive impairment compared with children having only one single perinatal exposure. The risk of impaired health and development is modified during childhood, e.g. by means of postnatal growth patterns. Deviating growth patterns are more common in children born SGA than AGA, especially if combined with other possible adverse exposures. As rapid catch-up growth in height has positive impact on cognitive function, but rapid growth in weight potentially has negative effect on cardiovascular and metabolic health, further research is needed in order to evaluate the most beneficial growth pattern after being born SGA.
Clinical implications

Pregnancies that result in an infant born SGA are often, but not always, complicated by PE or preterm birth. Screening for PE and SGA fetuses can identify pregnancies at high risk of developing PE and SGA. The identification of such high risk pregnancies has two major advantages. First, prophylactic treatment with acetylsalicylic acid can reduce the incidence of both PE and SGA birth by improving spiral artery remodelling and proper placentation. Second, early identification of reduced growth velocity enables close surveillance of the SGA fetus. Through monitoring, timing of delivery can be optimized and neonatal care planned for. By such interventions, perinatal morbidity and mortality can be minimized. In the absence of potentially adverse perinatal events, the genetic imprinting and developmental plasticity may result in a less disease-prone infant.

Prevention of SGA birth by prophylactic treatment with acetylsalicylic acid primarily reduces preterm PE and growth restriction on the basis of placental dysfunction. However, a large proportion of SGA births, and particularly those at term, are not preventable by acetylsalicylic acid treatment. Thus, even if universal first trimester screening was introduced, antenatal, delivery and neonatal care would continue to discover and treat children born SGA. Continued research on children born SGA with the aim to gain profound knowledge about best treatment practice for these children is needed. Efforts on finding a balance between the positive and negative effects of rapid catch-up growth in height and weight should also be strived for.

Nutrition in early infancy seems to be of importance for postnatal growth patterns. Early nutritional care can reduce postnatal growth restriction in children born very preterm (185). Children born moderate preterm have lower rates of comorbidity, but still early feeding difficulties are more common in children born moderate preterm than term. Moreover, the prevalence of breastfeeding is lower and the duration is shorter in infants born preterm or with smoking mothers compared with those born term or infants to non-smoking mothers (186-189). Even though the long-term effects have not been evaluated, long breastfeeding duration is associated with less rapid catch-up growth, both in children born SGA and in children with smoking mothers (130, 137, 190). It is however difficult to draw conclusions about a possible causal pathway between breastfeeding and catch-up growth patterns. Breastfeeding, food habits and obesity are all parts of an intricate network of factors strongly correlated with socioeconomy. Moreover, it is not known if feeding practices per se affect postnatal growth patterns in children with smoking mothers or in children born moderate preterm. However, in theory, children born SGA might benefit long-term by improved early nutrition if postnatal growth restriction is reduced and neuroprotection promoted. Further,
interventions aiming to support breastfeeding and establish healthy eating and exercise habits might reduce the negative impact on cardiovascular and metabolic health in children born SGA.

Exposure to multiple perinatal risk factors are associated with the highest risks of adverse health outcomes. Moreover, there seems to be a dose-response relationship between size at birth and long-term complications. In the Nordic countries, -2 SD is used as a cut-off for SGA. Globally, the definition varies from -2 SD, which corresponds to the 2.3rd percentile, up to the 10th percentile. The dose-response relationship implies difficulties in establishing a suitable discriminating level between AGA and SGA. By using a definition that includes only the most severely affected children, we might be missing a large number of children in need of extra support and care during childhood. By using a wider definition, a larger proportion of children born SGA will be genetically small and healthy. Thus, keeping the increased risk of long-term health consequences in mind, it is important for clinicians to pay special attention to children with birthweight that is borderland classified as SGA, especially when other risk factors or adverse perinatal exposures are present.
Conclusions

Paper I
Perinatal exposure to PE, being born SGA and preterm is associated with increased risk of chronic hypertension in women by the time of their first childbirth. Each exposure has an individual effect on the risk, with the strongest association observed for perinatal exposure to PE. There is a joint effect, with multiple perinatal exposures being associated with an almost four-fold risk increase in chronic hypertension.

Paper II
Being born SGA at term is associated with increased risk of poor school performance at time of graduation from compulsory school. The risk increases with increasing severity of SGA, with a statistically significant risk increase even for mild SGA (birthweight for GA–1.01 to –2 SD). Among boys, the risk of poor school performance is higher for those with short adult stature compared with those with non-short adult stature.

Paper III
Children born SGA with a smoking mother have a more rapid catch-up growth during their first five years of life than children born SGA with a non-smoking mother. Compared with being born AGA with a non-smoking mother, being born SGA with a smoking mother is not associated with increased risk of short stature at 1.5 or 5 years, whereas children born SGA with a non-smoking mother have increased risk of short stature at both ages.

Paper IV
Compared with being born AGA and term, being born SGA and moderate to late preterm is associated with shorter stature and lower BMI during the first five years of life. SGA has a greater impact on growth and body proportions than GA at birth.
Future perspectives

A better understanding of the complex interplay between perinatal exposures and long-term consequences for health and growth is vital for improving clinical practice. As there seems to exist a joint effect between multiple perinatal exposures and health outcomes, we need to find ways to optimize obstetric and neonatal care for these children. As long-term consequences by definition have long induction times, it is reasonable to believe that clinical intervention trials still need to be followed up by large cohort studies. The creation of large, population-based cohorts that follow children born SGA over time may thus be helpful to disentangle the effects of different perinatal exposures.

Given the study design, information on risk factors and interventions can be updated within the cohort. With increased early pregnancy screening there will be more data, e.g. on biomarkers, available for future research. Thus, new risk factors for being born SGA can be found, and different types of aberrant intrauterine growth patterns may be distinguished. Subjects with exceedingly high risk of long-term negative health outcomes can be identified and targeted for more comprehensive follow-up and care. Such cohorts can be national, such as the MBR and the National School Register, regional, such as the Uppsala Mother and Child Database, or local in the form of biobanks and cohorts of subjects with a specified exposure or disease.

The pathophysiological mechanisms underlying SGA births are not fully understood. Further, research on the effects on genetic imprinting and gene expression that follows adverse perinatal exposures is only in its infancy. Increased knowledge on how SGA and other perinatal exposures affect epigenetic changes and gene expression may help realizing the full extent of health implications. Subsequently, interventions to promote future health and a satisfactory neurocognitive development can be studied.

Estimation of fetal weight and growth is an important part of antenatal care, especially in high-risk pregnancies where IUGR and preterm birth is more common. Fetal size and growth can be assessed using ultrasound. Estimated fetal weight or abdominal circumference are commonly used as markers of fetal size. With serial ultrasound scans, the fetal growth trajectory can be eval-
ated. Reliable standards, or charts, of biometric variables assessed by intrauterine ultrasound measurements are necessary for correct estimation of fetal size and weight. In 2014, new international standards for fetal size and growth were presented by the INTERGROWTH-21st Project (77, 191). Three years later, in 2017, WHO published another proposal for international standards of ultrasound biometric measurements and fetal weight (192). Both standards are based on well-performed international multi-centre studies using longitudinal data. However, the results point in somewhat different directions. The INTERGROWTH-21st Project study displayed similar growth in all settings. On the contrary, the WHO charts showed a significant difference in fetal size between the study sites. The authors therefore suggest adjusted curves to fit different populations. An assessment study has been done to evaluate the fit of the INTERGROWTH-21 and WHO charts. The authors advise to assess the suitability of these references before adopting them rather than population specific references (193).

The Swedish reference standards for fetal growth were published in 1996 (169). The standards are based on ultrasonically estimated fetal weights in 51 Swedish and 35 Danish pregnant women. All pregnancies were dated using ultrasound; 72 by measurement of the biparietal diameter in early second trimester, and 14 by crown-rump length in the first trimester. Moreover, 24% of the women were smokers.

During my PhD studies, planning and carrying out the observational study “Swedish Intrauterine Growth Curves for Fetuses and Children” under supervision of Eva Bergman has been a large part of my research education. The study aims to create new national standards for fetal weight and growth. The standards are meant to be applicable to the present Swedish setting. The last women included in the study are expected to give birth by the time this thesis is published. The design is a prospective, multicentre study where 681 women with low-risk pregnancies were randomly assigned to a scheme of five ultrasound scans during their pregnancy. Primiparous as well as parous women living in the Swedish cities Uppsala, Falun, Katrineholm, Västerås and Örebro are included in the study. All pregnancies were spontaneously conceived and we excluded all individuals with complications such as preterm birth or conditions associated with increased risk of aberrant fetal growth. The statistical analyses will take place in 2019, and we are planning to submit the results to a peer-reviewed scientific journal with me as the first author.

We did not include pregnancies conceived through in vitro fertilisation (IVF), as there seems to be a difference in growth trajectories between spontaneously conceived and IVF pregnancies (194, 195). Further, for pregnancies conceived through IVF, it appears to be a difference in fetal growth rate between children born after fresh and frozen embryo transfer (196). A second phase of “Swedish
Intrauterine Growth Curves for Fetuses and Children” is planned to start in spring 2019, and I am member of the steering committee for this study. The new study “Fetal Growth after IVF, Frozen versus Fresh Embryo Transfer” will comprise 350 women from the Swedish cities Uppsala and Örebro with IVF pregnancies, of which 175 will have had fresh and 175 frozen embryo transfer. The study will evaluate if there is a difference in intrauterine growth between the two embryo management techniques.
Sammanfattning på svenska


Hur olika faktorer samvarierar och vilken påverkan det har på framtida hälsa och intellektuell funktion är emellertid fortfarande otillräckligt utforskat. Det finns även stora kunskapsluckor när det gäller tillväxtnilheter hos barn som föds lätta för tiden, i synnerhet för de barn som utsätts för andra faktorer med möjlig negativ påverkan på hälsa och tillväxt. I avhandlingens fyra delstudier undersöktes därför långtidskonsekvenser och tillväxtnilheter hos barn födda lätta för tiden, ensamt eller i kombination med andra ogynnsamma faktorer.


I den andra delstudien undersöktes risken för svaga skolprestationer i grundskolans årskurs nio. Studien omfattade alla svenska barn födda 1973-1988 med slutbetyg från grundskolan, totalt 1 088 980 barn. De barn som fötts lätta
för tiden hade en ökad risk för svaga skolprestationer jämfört med de som fötts normaltunga för tiden. Risken var högst för de barn som fötts mycket lätt för tiden, men även de barn som i klinisk praxis i Sverige hamnar just utanför gränsen för lätta för tiden hade en ökad risk för svaga skolprestationer. Eftersom tillväxt under barnaåren tidigare har visat sig kunna påverka intellektuella funktioner hos barn som fötts lätta för tiden, gjordes en under-gruppsanalys av de män i studiegruppen som mönstrat för vämplikt och där långd registrerats. De barn som under barndomen vuxit ikapp sina jämnåriga och nått en normal slutlängd hade lägre risk för svaga skolprestationer än de som förblev korta som vuxna. De långsiktiga konsekvenserna för intellektuella funktioner, i form av svaga skolprestationer, var med andra ord större ju lägre födelseväkt i förhållande till graviditetslängd. Dessutom tycks en god tillväxt under barnaåren verka som en skyddande faktor för intellektuella funktioner.


I den fjärde delstudien undersöktes tillväxtmönster under de fem förstalevnadsåren hos barn som fötts lätta för tiden och lätt till mätligt för tidigt. I studien inkluderades 41 669 barn födda mellan graviditetsvecka 32 och 40 på Akademiska sjukhuset i Uppsala mellan 2000-2015 och som skrivits in i barnhälsovården i Uppsala län. Barn födda lätta för tiden och lätt till mätligt för tidigt (graviditetsvecka 32 till 36) var kortare och hade lägre BMI jämfört med barn födda normaltunga för tiden i graviditetsvecka 39 till 40. Att vara född lätta för tiden hade större påverkan på tillväxt och kroppproportioner än graviditetslängd vid födseln. Studien visar att långtidskonsekvenserna för tillväxtmönstret var större för barn som fötts lätta för tiden i kombination med
lätt till måttligt för tidig födsel, än för barn som endast fötts lätta för tiden eller lätt till måttligt för tidigt.

Sammanfattningsvis har delstudierna visat att barn födda lätta för tiden ökad risk att drabbas av högt blodtryck och påverkan på tillväxtmönstret under barndomen, vilket i sig ökar risken för hjärt-kärlsjukdom och metabola sjukdomar senare i livet. Vidare har barn födda lätta för tiden en högre risk för påverkad intellektuell förmåga med svaga skolprestationer. Framförallt gäller detta de barn som inte vuxit ikapp sina jämnåriga under barnaåren.

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