Born Small for Gestational Age

Impact of Linear Catch-up Growth

BY

MARIA LUNDGREN
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Abstract

The purposes of the thesis were to study associations between size at birth, short adult stature and risks of subnormal intellectual performance, high blood pressure, and overweight among males, and to study associations between size at birth, short adult stature and risk of overweight and giving birth to small for gestational age (SGA) infants among females.

The effect of short adult stature on intellectual performance among males was analyzed in two population-based cohort studies. Data were obtained from the Swedish Birth Register which was individually linked to the Swedish Conscript Register. Being born SGA was associated with increased risks of subnormal intellectual performance in all four dimensions included in the test, and lack of catch-up growth leading to short adult stature further increased this risk. If anything, logical performance was found to be most affected.

To estimate the risk of high blood pressure in males born SGA we used the Birth Register linked to the Conscript Register. Being born SGA was associated with a slightly increased risk of high systolic blood pressure, and being born light and ending up with short adult stature further increased this risk.

Association between short adult stature and overweight was analyzed in both males and females born SGA, in two different studies. In the male cohort data from the Birth Register was linked to the Conscript Register. In females the Birth Register was used twice, when the females were born and when they gave birth to their first child. In both the male and female cohort, there was an increased risk of becoming overweight among those born SGA who also ended up with short adult stature.

Finally, an intergeneration study was performed using the Birth Register to analyze associations between being born short for gestational age and giving birth to short infants. Catch-up growth to normal adult stature among women born short-for-gestational age was associated with reduced risk of giving birth to a short-for-gestational age infant.

Conclusions. Among males born SGA, short adult stature is associated with increased risk of subnormal intellectual performance, high blood pressure and overweight compared to those with normal adult stature. Similarly, among females born SGA, there is an increased risk of becoming overweight in those with short adult stature, compared with those not short as adult. Females born short for gestational age, with short adult stature are at increased risk of giving birth to a short infant.

Maria Lundgren, Department of Women's and Children's Health, Uppsala University, SE-75183 Uppsala, Sweden

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LIST OF PAPERS

This thesis is based on the following papers:


III Linear catch-up growth does not increase the risk of elevated blood pressure and reduces the risk of overweight in males. J Hypertension. 2001 Sep;19(9):1533-8.


V Catch-up growth in females born short for gestational age reduces the risk of giving birth to short-for-gestational-age infants. Hormone Research (in press).

The papers will be referred to by their Roman number in the following text.
## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>IP</td>
<td>Intellectual performance</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<td>PP</td>
<td>Psychological performance</td>
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<tr>
<td>SD</td>
<td>Standard deviation(s)</td>
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<tr>
<td>SDS</td>
<td>Standard deviation score(s)</td>
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<tr>
<td>SGA</td>
<td>Small for gestational age</td>
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<td>AGA</td>
<td>Appropriate for gestational age</td>
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<tr>
<td>GA</td>
<td>Gestational age</td>
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INTRODUCTION

During the past decades, size at birth has repeatedly been associated with mortality and morbidity in adulthood (above all cardio-vascular mortality), intellectual capacity and final stature [1-3]. Most commonly, birth weight is used as definition of size at birth. The importance of short birth length is less studied, even though studies have shown that birth length is a strong predictor of adult height [4, 5].

Most infants born small for gestational age (SGA), in either birth weight or birth length, catch-up in height during the first years, but around 10% do not [4-6]. Short adult stature is associated with increased risks of mortality and minor neurological damages [1, 7-9]. Whether spontaneous catch-up growth reduces the risks associated with being born SGA is to our knowledge not known.

The purposes of this thesis were to study associations between size at birth, short adult stature and risks of subnormal intellectual performance, high blood pressure, and overweight among males, and to study associations between size at birth, short adult stature and risk of overweight and giving birth to small for gestational age (SGA) infants among females.
BACKGROUND

Definition and etiology

The term small-for-gestational-age (SGA) is generally based on a statistical definition of size at birth and should be separated from the more dynamic concept intrauterine growth retardation/restriction (IUGR). There are no general standards in the definition of being born SGA. In Sweden, an infant is considered SGA when birth length and/or birth weight are below –2 Standard Deviation Scores (SDS) for gestational age, compared to the Swedish birth weight standard. In other countries centiles are used for cut off, most commonly the 10th percentile [10]. IUGR should be defined as a pathological restriction of fetal growth due to environmental or genetic influences. Thus, all infants born SGA are not IUGR. Moreover, the IUGR infants do not necessarily need to be SGA. For example, if a mother who has previously given birth to a large infant, suffers from pre-eclampsia and gives birth to an infant with appropriate size, the infant might be growth restricted, but not necessarily SGA. In 40% of infants born SGA there is no pathology to be found [10].

The size of the newborn is related to gender and gestational age and also to maternal and paternal anthropometric and demographic factors. It has therefore been proposed that birth weight for gestational age standards should be constructed, taking maternal non-pathological characteristics influencing fetal growth (i.e., ethnicity, pregnancy weight, height and parity) into consideration [11].

Normal growth of the fetus

Embryogenesis is an autonomic process, whereas growth in later gestation is depending on sufficient nutrition and oxygen supply. Fetal growth is from implantation to the 16th week, primarily mediated by cell hyperplasia. From week 16 to week 32, both the sizes and the number of cells increase, and after 32 weeks the growth is mainly mediated through cellular hypertrophy. The different tissues in the
fetal body grow and mature in different ‘critical periods’ of rapid cell division. Growth in length takes above all place in the end of the second trimester, and the length growth velocity has its maximum around the 20th week. Weight gain, in contrast, is primarily processed through cellular hypertrophy in the last trimester [12].

Standards for measuring size at birth
Growth chart standards vary in different countries and between different ethnicities. Growth standards are normally adjusted for gender and gestational age. Estimation of gestational age is either based on last menstrual period (LMP) or ultrasound examinations. Ultrasound is known to be more reliable in estimating expected date of delivery than LMP [13-15], and reduces the proportion of postterm births [14]. Compared to growth charts based on LMP, a higher proportion of preterm births and a lower proportion of SGA born infants was found after the introduction of growth charts based on ultrasound [13], for review see Bakketeig et al [16].

The Swedish birth weight and birth length curves used in the present studies, are based on a 5-year birth cohort (1977-81), adjusted for gender and gestational age, where gestational age is predominantly based on the LMP [17]. The birth data are collected when the infants are born, and do not necessarily represent the intrauterine population. It probably contains systematic errors, and may for example lead to underestimation of small-for gestational age infants, especially among those born preterm and very preterm [18, 19]. Marsal et al [19] have shown a negatively skewed distribution when infants born before 34 weeks were plotted on a growth curve based on intrauterine data. Among preterm born infants, the intrauterine curves showed values almost 100g above the postnatal curves.

It has been proposed that the fetus has its own ideal growth curve, affected not just by gestational age and sex, but also by parental characteristics. Customized growth charts i.e., computer analyses for each pregnancy based on maternal anthropometric and demographic factors where an individual birth weight is predicted [11], do perhaps have better capacity in identifying growth restricted infants due to pathological reasons [14, 20]. The use of customized curves may
reduce the risk of overestimating the proportion of growth restricted infants. Still, customized birth weight might lead to normalizing a growth restricted infant. For example, a child born to a short mother due to a pathological reason, might be considered normal, when it is in fact growth restricted.

Factors Influencing fetal growth
Fetal growth is not just a result of nutrition and oxygen supply, but it is also influenced by several physiological and pathological factors. Anthropometric factors, such as maternal height, BMI and weight gain during pregnancy is known to be positively associated with the infants’ size at birth [21, 22]. Paternal anthropometric factors do have an impact, but maternal size is thought to be more important [23]. Demographic factors are also known to influence fetal size [21]. SGA born infants are more common among young [24] and older (>45) mothers compared mothers in their 20ties and 30ties and primegravidas are more likely to give birth to SGA infants than multiparous women [25]. Inter-pregnancy interval has been found to be associated with SGA birth, with the highest risk with the shortest intervals. Socioeconomic factors might also be of importance [21]; however, socioeconomic factors might be confounded by smoking habits, parity and age at delivery. Toxic exposures and maternal diseases are well-known risk factors of fetal growth restriction. Smoking is one of the best identified toxic exposures associated with fetal size and dose-response relations have been reported [20, 21, 26]. Other toxic agents known to influence size at birth are alcohol and narcotics and even moderate alcohol consumption during pregnancy affects the fetal size negatively [27]. Fetal infections, such as Rubella and cytomegalo virus (CMV) may have severe consequences on fetal growth [28]. Hypertension is one of the most important maternal factors influencing fetal growth negatively. Preeclampsia and other hypertensive diseases may cause thickening and infarction in the placental wall and restriction of blood supply to the fetus. Other diseases such as cyanotic heart disease, cystic fibrosis, severe asthma and other pulmonary diseases may impair maternal oxygen delivery to the fetus. Inflammatory bowel diseases such as ulcerative colitis and Crohn’s disease impair the maternal absorption from the intestines and may influence the nutrition supply to the fetus. Other well known
maternal diseases affecting fetal size are diabetes mellitus and renal diseases, for review see Pollack et al [29].

Intrauterine growth also depends on the genetic potential of the fetus. Short parents have smaller infants than taller and maternal size seems to be more important than paternal size [23]. Male fetuses, tend to be bigger than females fetuses, especially in late pregnancy [19]. Various genetic abnormalities have also been associated with growth restriction, including trisomi 21, trisomi 13, Turner’s syndrome and also a number of congenital malformations [29].

Classification – growth restriction.

The body composition of the newborn indicates the timing of the growth disturbance during fetal life. Infants with a normal head circumference and slightly reduced birth length but a low birth weight are often referred to as asymmetric. Their ponderal index (weight/length³) is low. The growth restriction is believed to be due to extrinsic factors in the last trimester, such as reduced placental capacity of nutritional supply. Asymmetrical growth restriction is more common and postnatal catch-up growth is often seen. The brain and skeletal growth is generally not affected in asymmetrical growth restricted infants. In contrast, growth restricted infants with a symmetric body have a growth disturbance in all tissues. The etiology is quite different, including prolonged starvation [10, 30], but the fetus is often also influenced by factors such as genetic diseases, congenital syndromes, infections and toxic effects. Symmetric growth retardation is considered to be the most severe form with a higher risk of short adult stature [30]. However, the classification of growth retardation into symmetric and asymmetric has been criticized. It has been argued that asymmetric growth retardation is merely a reflection of the severity of fetal malnutrition [21]. Kramer et al found that the more severely growth restricted infants were more disproportional than less severely affected infants, with longer birth length and larger heads for their weight, and the main factor influencing the degree of disproportionality was the severity of growth restriction [21].
Catch-up growth
Most infants born SGA catch-up in height during the first years, but about 10% do not and end up with short adult stature [4-6]. Growth in children and height in adults are often used as indicators of nutrition and well-being [31-33]. A positive correlation between height and intelligence has generally been reported [34, 35], and also between height and morbidity [36]. In a study of young Danish men, intelligence test scores were above the mean among tall men, but below in short men [37]. A Swedish study recently demonstrated that apparently healthy short young men had lower intellectual performance compared to taller men, and mean intelligence test score generally increased with height [38]. Whether catch-up growth is associated with cardiovascular disease is debated. It has been suggested that a catch-up growth in height might lead to raised blood pressure [3, 39], whereas others claim the opposite [40]. Studies from Finland indicate that there is an association between increased risk of cardiovascular disease in females born short with tall adult stature, and an increased risk in males born with low birth weight and being overweight as adults [41]. It has recently been demonstrated that catch-up growth in SGA children induced by growth hormone treatment does not influence blood pressure or BMI in adolescence [42].

Fetal programming
It has been argued that coronary heart disease originates in utero [43]. Undernutrition leading to growth restricted infants has been found to be associated with increased risk of insulin resistance, hypertension and lipid disorders in adulthood [1, 3, 44]. The fetal programming hypothesis suggests that the fetus adapts to undernutrition and may permanently change its metabolism and physiology. This may lead to impaired insulin response to glucose and changes in cholesterol metabolism, to changes in blood pressure and to increased mortality and morbidity in coronary heart disease. For review see Barker [45]. However this hypothesis has been debated. Some authors claim that the infants have a genetic programming in both being small and ending up with insulin resistance syndrome [46]. Barker et al [47] suggested that different body proportions are linked to different adult
abnormalities, and that the body proportions reflect the time of growth restriction during fetal life. Infants born short (stunted) tend to develop hypertension exclusively, whereas infants born thin are predominantly at increased risk of developing the insulin resistance syndrome, previously known as syndrome X (insulin resistance, hypertension, lipid disorders).
AIMS OF THE STUDIES

The overall aim was to analyze the effect of catch-up growth on risk factors for individuals born SGA. In the papers the specific aims were:

I. To analyze if body size at birth among males is associated with subsequent intellectual and psychological performance, and if there is any associations between catch-up growth in height in boys born SGA and intellectual or psychological performance in early adulthood.

II. To study the relations between size at birth, gestational age, final height and different dimensions of intellectual performance.

III. To investigate the relationship between size at birth and risks of high adult blood pressure and overweight in males, and to study whether catch-up growth in height modifies these associations.

IV. To estimate the risk of short adult stature in women born small for gestational age, and to study if catch-up growth in height is related to the risk of overweight in females born SGA.

V. To study the effect of catch-up growth on the offspring’s length at birth among females born short-for-gestational-age.
MATERIAL AND METHODS

Data sources

The Swedish Birth Register
The Swedish Birth Register, held by the National Board of Health and Welfare contains data on more than 99% of all births in Sweden since 1973 [48]. The registry includes data on maternal demographics, reproductive history, and complications during pregnancy, delivery and the neonatal period. All births and deaths are validated every year against the Register of Total Population, held by Statistics Sweden, using the mothers’ and the infants’ unique personal identification number, assigned to each Swedish resident at birth.

The Swedish Conscript Register
The Swedish Conscript Register includes information about Swedish males conscripted for military service. Conscription is mandatory and enforced by law. Most men are conscripted at 18–25 years of age. Those with known severe handicaps, congenital malformations or chronic diseases are not conscripted (about 2.4% in each birth cohort).

The studied cohorts
In papers I, II and III, information on young males’ birth characteristics were obtained from the Birth Register and linked to the Conscript Register by using the males’ unique personal identification
numbers. The Swedish Birth Register contained information about 312,159 live-born male infants in the period 1973-78. In all, 3,402 males died before 18 years. In order to increase the homogeneity of the study population, multiple births, infants with congenital malformations and infants to non-Nordic mothers were excluded (n=32,724). Of the remaining 276,033 boys, 21,607 (7.8%) males were not conscripted between January 1991 and January 1997. Of 254,426 conscripted males, data on intellectual performance and psychological performance were available in 97% and 91% respectively (paper I). Information about blood pressure and body mass index (BMI) were available in 94% and 97%, respectively (paper III). Paper II was restricted to males born between 1973 and 1976 who were conscripted before 1994 (n=168,068).

In papers IV and V, we used information from the Birth Register to link birth characteristics of women to anthropometric characteristics when these women gave birth to their first child. This linkage was made possible by using the personal identification number, assigned to each Swedish resident at birth. Since 1982, data is collected using copies of standardized antenatal, obstetric, and pediatric records, which are forwarded to the National Board of Health and Welfare [48]. At the first visit to antenatal care, the women are interviewed by midwives about current health, smoking habits, family situation, previous pregnancies, deliveries, and information about diseases in the family. Weight is measured and current height is either measured or, if known, self reported. Information about complications during pregnancy and delivery, delivery hospital, mode of delivery as well as age and parity is collected when the females leave the hospital. At the same time, information of the baby is collected including sex, birth weight, birth length, head circumference, single or multiple birth, congenital malformations, and other diagnoses. Complications and malformations are classified according to the Swedish versions of ICD-8, ICD-9 or ICD-10, according to year of birth.

In papers IV and V, we used information from the Swedish Birth Register on birth characteristics of 47,781 females, who were included in the Birth Register both as babies and mothers. These women were born from 1973 through 1983, and delivered their first infant between
1989 and 1999. As in the male cohort, females born in multiple births, having congenital malformations, and females born to non-Nordic mothers (n=3 602), were excluded in order to increase the homogeneity of the study population. To improve the probability that the women had reached their final height when becoming pregnant, we also excluded all women younger than 16 years at delivery (n=280). Moreover, women with very low final height (<130 cm) or weight (<39 kg) were excluded (n=27). The remaining 43 872 females constituted the study population in paper IV.

In paper V, we also excluded women with offspring born in multiple births or with congenital malformation (n=1 238). Of the remaining 42 634 females, 1 363 (3.2%) were born short for gestational age, i.e., with birth length more than 2 standard deviation scores (SDS) below the mean birth length for gestational age [17]. These women constituted the study population in paper V.

### Outcome measurements

At conscription (papers I, II and III), all males undergo a thorough health examination, including height and weight, blood pressure measurements, and a number of tests. The information is computerized and the personal identification number of each subject ensures individual record linkage to other information sources. Height is recorded in cm without shoes and weight in kg in light indoor clothes. Right arm blood pressure (BP) is measured after five minutes rest in a sitting position by trained nurses. If BP is elevated (systolic BP ≥ 135 or diastolic BP ≥ 85), a second measurement is performed, and the lowest value is recorded. Diastolic BP is determined as the disappearance of Korotkoff sounds.

General intellectual performance (IP) is measured by a time-limited test package including four dimensions: logical/inductive, verbal, spatial, and theoretical/technical. The test questionnaire contains 160 items, 40 from each dimension, and is computerized since 1994 [38].
Psychological performance during mental stress (PP) is evaluated by specialized psychologists using semi-structured interviews with the aim of measuring how the conscript might be able to manage difficult situations during stress. The results are acknowledged to reflect different aspects of personality. The results are presented in a numerical scale, standard nine score (stanine scores), from 1 to 9, where 5 is mean and 9 is the best result. In paper I, the general intellectual performance was measured, whereas the different dimensions of the test were analyzed in paper II. Subnormal performance was defined in both papers as a stanine score of 3 or lower (i.e. $\leq -1$ SD). The 10% scoring 2 or less in intellectual performance can be expected to have difficulties in ordinary basic education programs (i.e., the compulsory nine years of school), and the 20% scoring 3 or less can not be expected to be successful in higher education. In paper II, data on the different dimensions of intellectual performance were available for 86% of all conscripts. Around 10 000 individuals were recorded with stanine score 0 in theoretical performance and these data were considered as missing. The individuals with stanine score 0 did not differ from the cohort with regard to mean values of the other dimensions of intellectual performance, birth characteristics, preterm birth and final stature.

In paper III, a high systolic and diastolic blood pressure was defined as a blood pressure above the 90th percentile, based on the distribution of blood pressure in the studied cohort. As systolic blood pressure is positively correlated to height [49], we calculated a height-standardized systolic blood pressure by forming 9 groups of 5 cm intervals according to the height at conscription. For each group, the 90th percentile cut-point for systolic blood pressure was calculated. A high height-standardized systolic blood pressure was defined as a systolic blood pressure equal to or above the 90th percentile ($\geq 140$-$144$ mm Hg for the different heights). Risks of high diastolic blood pressure were examined similarly.

Body mass index (BMI) was calculated as the ratio between adult weight and squared adult height ($\text{kg/m}^2$) for all subjects. In the male cohort (paper III) BMI was calculated using weight and height measures collected at conscription, whereas in females (papers IV and V), we used weight and height measured at the first visit to antenatal care (e.g. usually at 8-12 weeks of gestation). Normal BMI for both
males and females was defined as BMI between 18.5 and 24.9, overweight as BMI ≥25, and obesity as BMI≥30, as suggested by the World Health Organization [49]. Since the cohort was young, the risk of overweight is underestimated when using the cut off BMI≥25 kg/m². Adult height SDS was computed as: (individual measurement minus cohort mean measurement)/cohort SD, and stratified into short adult stature (<-2 SDS), normal adult stature (-2 to 2 SDS) and tall adult stature (>2 SDS).

**Birth characteristics**

Information about birth weight, birth length, and gestational age was obtained from the Birth Register. Gestational age was estimated from the date of the last menstrual period and stratified into very preterm (<32 completed weeks), moderately preterm (32-36 weeks) and term births (≥37 weeks). Birth weight for gestational age was categorized into three categories. Light for gestational age was defined as more than 2 standard deviation scores (SDS) below mean birth weight for gestational age, appropriate weight for gestational age as birth weight between –2 and +2 SDS, and heavy for gestational age was defined as birth weight more than 2 SDS above the mean [17]. Birth length for gestational age and head circumference was defined analogously. Small for gestational age (SGA) was defined as < -2 SDS in either birth length or weight for gestational age, and divided into three different subgroups: born short only, born light only, and born both short and light for gestational age, as suggested by Albertsson-Wikland [4]. The cut off at –2 SDS (i.e. around the 3rd percentile) is commonly used to define small size for gestational age. Children shorter than –2 SDS are also those, in whom investigation for growth hormone deficiency may be considered. Linear “catch-up growth” was defined as being born SGA and being above –2 SDS in height at conscription. In papers I and III, individual catch-up growth was analyzed, defined as being born SGA and gaining at least 1 SDS in height. As a similar pattern was seen when using continuous variables, the results were dichotomized and presented as on group level to improve the understanding.
In paper V, we introduced the term relative catch-up growth. This was done in order to analyze the effect of growth in height, controlling for maternal birth length. Relative catch-up growth was defined as:

\[
\frac{100 \times (HSDS - BLSDS)}{BLSDS} - BLSDS
\]

Where:

- **HSDS** = Maternal adult height SDS
- **BLSDS** = Maternal birth length SDS

Relative catch-up growth in per cent measures the increase towards population mean height = 0 SDS. Accordingly, this measure is dependent on the females’ birth length and final height. For example, females born with birth length = -4, -3 or -2 need 100% catch-up to reach height = 0 SDS. To reach -1 SDS in height a relative catch-up growth of 75, 67 and 50% respectively is needed.

**Statistical methods**

For all papers the standard statistical package SPSS (version 10.0 for paper I and version 10.1 for paper II and IV, version 11.0 for paper II and V) for WINDOWS was used in the statistical calculations. The analyzes of risks were performed by using bivariate and multiple logistic and linear regression analyzes. Odds ratios (OR) were presented with 95% confidence intervals (CI). In analyses of data from huge populations, most associations tend to be statistically significant. When presenting the results, we therefore have chosen to dichotomize the outcome variables as well as birth characteristics and we have used logistic regression analyses instead of linear regression analysis. Both types of analyses yielded similar results.

In paper II, data on the different dimensions and the total index of intellectual performance are given as stanine scores. In theory for the studied cohort these scores should have a mean of 5 and a standard
deviation of 2. However, data in this study yielded values somewhat different from these figures (Table y).
In order to make the different dimensions numerically comparable, Z-transformations were performed:

\[ Z_s = \frac{(\text{Observed value} - \text{mean cohort value})}{\text{cohort standard deviation}} \]

These Z-values have a mean of 0 and a standard deviation of 1. In order to further make data conform to stanine scores the Z-values were transformed:

\[ Z_s = Z_s \times 2 + 5, \]

where \( Z_s \) now will have a mean of 5 and a standard deviation of 2.
RESULTS

Intellectual performance, paper I and II

Paper I
Males with birth length below –2SDS for gestational age had a lower mean intellectual performance score than those born above –2SDS, and similar patterns were seen when analyzing birth weight and head circumference. Males born preterm, especially those born very preterm, had lower mean intellectual performance scores than those born at term or postterm. Mean intellectual performance consistently increased with height at conscription. A similar pattern was seen when analyzing psychological performance during stress.

When analyzing men born SGA exclusively, low mean scores in intellectual and psychological performance were constantly more common among those without catch-up growth than those with catch-up. The highest mean score in intellectual performance was seen in the subgroup born short with a normal adult height, and the lowest score was obtained in the group born both short and light, who still were short at conscription (Table 1).

Among males born short, those with short adult stature had a 45 % increased risk of subnormal intellectual performance compared with those with normal adult stature. Compared with males born short with normal adult height, males born light who were short at conscription had an almost 90 % increased risk of subnormal intellectual
performance. In those born short and light, the corresponding risk was doubled. A similar pattern was seen for psychological performance.

Distribution of stanine scores of intellectual performance of infants born both short and light is shown in Figure 1. Low mean scores of intellectual performance were constantly more common among those without compared to those with catch-up growth, and a similar tendency was seen for psychological performance. We also analyzed the distribution of stanine scores in the other subgroups of SGA infants (born short only and born light only), and found very similar results.

Paper II
Intellectual performance was further analyzed by studying the four different dimensions, logical, theoretical, verbal, and spatial performance (paper II). In males born SGA, the increased risk of subnormal performance was found in all four subtests of intellectual capacity, and being born short for gestational age or light for gestational age was associated with around 20% increased risk in all subtests. However, within the subgroups of males born SGA, being born with a small head circumference or ending up with a short adult stature further increased the risk of subnormal performance, and the risk was most pronounced in the logical dimension (Table 2).

Blood pressure, final height and overweight, paper III and IV

Paper III
Compared to males not being SGA at birth, males being light for gestational age were at increased risk of adult high systolic blood pressure [OR 1.33 (95% CI 1.20-1.46)], and a short adult stature was associated with a further increased risk [OR 1.65 (95% CI 1.13-2.40)]. Being born short for gestational age was associated with a slightly increased risk of high systolic blood pressure [OR 1.16 (95% CI 1.04-
1.29)], and linear catch-up growth in height did not significantly increase this risk. Males born short-for-gestational-age, who also were short at conscription, had an increased risk of overweight, expressed as a BMI $\geq 25.0$ [OR 1.65 (95% CI 1.25-2.19)].

Paper IV

In females, being born SGA was associated with increased risk of a short adult stature but the risk varied substantially within the different subgroups born SGA: being born light-for-gestational-age was associated with a two-fold increased risk [OR 1.90 (95% CI 1.41-2.54)] of a short adult stature, and short for gestational age was associated with a five-fold increase in risk [OR 4.86 (95% CI 3.72-6.35)]. Among females born short-for-gestational-age, lack of linear catch-up growth was associated with an increased risk of a high BMI in early pregnancy.

Intergeneration

Paper V

Among females born short for gestational age, maternal height and BMI were positively associated with the offspring’s birth length and birth weight, while maternal smoking was associated with reduced birth length and birth weight. Short adult stature was associated with a three-fold increased risk of giving birth to a short infant [OR 3.08, 95% CI (1.73-5.50)], whereas overweight (BMI 25-29.9 kg/m$^2$) was associated with a 50% reduced risk [0.46 (0.22-0.96)]. Smoking during pregnancy was associated with a dose-dependent increased risk of short-for-gestational-age births.

The effect of short adult stature on the offspring’s birth length was further studied by analyzing relative catch-up growth. Women with a catch-up growth of 50% or less gave birth to the shortest infants (Figure 2). Thereafter, the association between relative catch-up
growth and the infant’s birth length was positive and linear up to a catch-up growth of 150 %. Even if catch-up growth to normal height was associated with a reduced risk of giving birth to a short infant, the mean birth length of the infants was still lower compared to the infants of mothers born appropriate for gestational age (mean difference 1.2 cm (95 % CI 1.0-1.4 cm).
Tables and Figures

Table 1
Mean intellectual and psychological performance for males born SGA in relation to birth characteristics and adult height. Adjusted odds ratios (OR) with 95% confidence intervals (CI) of subnormal intellectual and psychological performance are also given.

Intellectual Performance

<table>
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<tr>
<th>Adult height (SDS)</th>
<th>Mean</th>
<th>OR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>At birth</td>
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<tr>
<td>Short</td>
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<tr>
<td>&lt;-2</td>
<td>4.30 (1.92)</td>
<td>1.45 (1.21-1.70)</td>
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<tr>
<td>≥-2</td>
<td>4.80 (1.93)</td>
<td>1.00*</td>
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<tr>
<td>Light</td>
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<tr>
<td>&lt;-2</td>
<td>4.15 (1.95)</td>
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<td>≥-2</td>
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<td>Short &amp; Light</td>
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<tr>
<td>&lt;-2</td>
<td>3.99 (1.88)</td>
<td>2.01 (1.79-2.23)</td>
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<tr>
<td>≥-2</td>
<td>4.58 (1.89)</td>
<td>1.18 (1.06-1.30)</td>
</tr>
</tbody>
</table>

Psychological Performance

<table>
<thead>
<tr>
<th>Adult height (SDS)</th>
<th>Mean</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>At birth</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;-2</td>
<td>4.48 (1.69)</td>
<td>1.30 (1.04-1.57)</td>
</tr>
<tr>
<td>≥-2</td>
<td>4.82 (1.79)</td>
<td>1.00*</td>
</tr>
<tr>
<td>Light</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;-2</td>
<td>4.34 (1.68)</td>
<td>1.43 (1.07-2.23)</td>
</tr>
<tr>
<td>≥-2</td>
<td>4.83 (1.79)</td>
<td>0.98 (0.85-1.10)</td>
</tr>
<tr>
<td>Short &amp; Light</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;-2</td>
<td>4.19 (1.70)</td>
<td>1.74 (1.49-1.98)</td>
</tr>
<tr>
<td>≥-2</td>
<td>4.72 (1.77)</td>
<td>1.11 (0.98-1.24)</td>
</tr>
</tbody>
</table>

* Reference group, males born short for gestational age with adult height above –2 SDS
Figure 1. Distribution of intellectual performance scores in males born both short and light for gestational age with final height below or above −2 SDS.
Table 2. Adjusted Odds ratios (OR) with 95% confidence intervals (CI) of subnormal† performance in different dimensions related to head circumference at birth and final adult stature among males born small for gestational age.

<table>
<thead>
<tr>
<th></th>
<th>Logical</th>
<th>Spatial</th>
<th>Theoretical</th>
<th>Verbal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head circumference (SDS)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; -2</td>
<td>1502</td>
<td>1.33 (1.15-1.55)</td>
<td>1.08 (0.94-1.25)</td>
<td>1.20 (1.04-1.38)</td>
</tr>
<tr>
<td>≥ -2</td>
<td>5122</td>
<td>1.00†</td>
<td>1.00§</td>
<td>1.00§</td>
</tr>
<tr>
<td>Height (SDS)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; -2</td>
<td>627</td>
<td>1.52 (1.25-1.84)</td>
<td>1.50 (1.25-1.81)</td>
<td>1.37 (1.14-1.65)</td>
</tr>
<tr>
<td>≥ -2</td>
<td>5958</td>
<td>1.00†</td>
<td>1.00§</td>
<td>1.00§</td>
</tr>
</tbody>
</table>

† Subnormal performance defined as stanine score 1-3.
* Adjusted for Birth length, Birth weight, Gestational age, height and BMI.
**Adjusted for Birth length, Birth weight, Head circumference, Gestational age and BMI.
§ Reference group
Table 3

Adjusted* odds ratios (OR) with 95% confidence intervals (CI) of high systolic blood pressure and overweight [body mass index (BMI) \( \geq 25 \text{ kg/m}^2 \)] in early adulthood. Males born small-for-gestational –age (SGA) with normal or short adult stature.

<table>
<thead>
<tr>
<th>At birth</th>
<th>Adult height (SDS)**</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short</td>
<td>&lt;-2</td>
<td>0.97 (0.70-1.35)</td>
<td>1.65 (1.25-2.19)</td>
</tr>
<tr>
<td></td>
<td>( \geq -2*** )</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Light</td>
<td>&lt;-2</td>
<td>1.65 (1.13-2.40)</td>
<td>0.82 (0.50-1.32)</td>
</tr>
<tr>
<td></td>
<td>( \geq -2*** )</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Short and light</td>
<td>&lt;-2</td>
<td>1.41 (1.07-1.86)</td>
<td>1.18 (0.88-1.58)</td>
</tr>
<tr>
<td></td>
<td>( \geq -2*** )</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*The risk of high systolic blood pressure adjusted for BMI and gestational age and the risk of overweight adjusted for gestational age.
**SDS, Standard deviation scores
***Reference group
Table 4
Adjusted* odds ratios (OR) and 95% confidence intervals (CI) of high height-standardized systolic blood pressure, in males born small for gestational age.

<table>
<thead>
<tr>
<th>At birth</th>
<th>BMI</th>
<th>N</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short &lt;18.5</td>
<td>210</td>
<td>0.64 (0.42-0.97)</td>
<td></td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>2517</td>
<td>1.00**</td>
<td></td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>354</td>
<td>1.24 (0.94-1.64)</td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>88</td>
<td>1.89 (1.23-2.90)</td>
<td></td>
</tr>
</tbody>
</table>

| Light <18.5     | 398   | 0.62 (0.45-0.87) |
| 18.5-24.9       | 2692  | 1.00** |
| 25.0-29.9       | 329   | 1.26 (0.95-1.69) |
| ≥30             | 77    | 1.90 (1.22-2.93) |

| Short and light <18.5 | 281   | 0.44 (0.29-0.68) |
| 18.5-24.9            | 2264  | 1.00** |
| 25.0-29.9            | 299   | 1.30 (0.97-1.75) |
| ≥30                  | 79    | 1.16 (0.71-1.91) |

*Adjusted for adult height and gestational age.
** Reference group
Figure 2. Effect of relative catch-up growth (%) on the offspring’s birth length among mothers born short for gestational age.
DISCUSSION

Summary
The main interest of this thesis was to study the effect of catch-up growth and final height in young adults born small for gestational age. The data show that around 10% of the infants born SGA did not catch-up in height and ended up with a short adult stature. The results indicate that catch-up growth was associated with reduced risk of subnormal intellectual and psychological performance in males and with reduced risk of overweight in both males and females. The results do not support the hypothesis that catch-up growth in height is associated with increased risk of high blood pressure. In females born SGA, short adult stature was associated with increased risk of giving birth to a short for gestational age child, compared to females with normal adult stature.

Methodological discussion

Cohort studies
Cohort studies are observational studies in which a group of individuals exposed and unexposed to a risk factor or a disease are followed over time and incidences of diseases in the groups is studied. One of the major advantages with this type of studies compared to others, such as case control studies, is the opportunity to study several outcomes rather than just one. Another advantage is the opportunity to study exposure before any outcomes have occurred, which reduces the risk of bias. We used cohorts of individuals born SGA and compared the outcomes between the individuals with and without catch-up
growth/short adult stature. All information was taken from the Birth Register and Conscript Register, and we were able to study several outcome variables. However, we were limited to information included in different registers. For example, we did not have any information of paternal height and socioeconomic status of the parents, which might have influenced our results.

Internal validity (Chance, Bias, Confounding)
As bias or systematic errors can not be adjusted for in the analyzes, it is important to minimize them in the design of the study. All data from the Birth Register were collected prospectively which practically eliminates the risk of recall bias. At conscription, the test of intellectual performance was computer-based. Thus, we had no reasons to suspect misclassifications of the test results, due to final height, neither did we have reason to believe that possible misclassifications of the test results and medical examinations should differ with regard to birth characteristics.

Exclusion criteria
There was a rather high proportion of congenital malformations in the studied cohorts. We chose to exclude all infants from the Birth Register with diagnoses in the International Classification of Diseases (ICD), 8th revision (ICD-8 covering the years 1968-1986) codes 740.99 to 779.99, the 9th revision (ICD-9, 1987-1996) codes 740A to 759X and the 10th revision (ICD-10, 1998 and forward) codes Q00 to Q99.9, to make sure that all individuals having a malformation with a possible impact on height were excluded. Thus, we also excluded minor malformations including congenital malformations of skin, hair and nails, which could explain the high number of malformations. However, there was a higher number of individuals born SGA compared to those born not SGA excluded due to congenital malformations. We have reasons to believe that some of the results might be underestimated due to the exclusion criteria.
Young cohorts
The studied cohorts consisted of rather young individuals. The males were aged 18-24 and females 16-26 years. Thus, some individuals might thus not have reached their final height. The relationship between size at birth and risks of high adult blood pressure and overweight might have been even more interesting to study if the males had been older. In papers III and IV, body mass index (BMI) was defined according to the standard set by the World Health Organization [50]. The BMI increases with age during adulthood and the risk of overweight might have been underestimated due to young age [51].

Confounding occurs when an association between an exposure and an outcome is affected by another exposure. The confounder is independently associated with the exposures and the outcome. We tried to minimize influence of possible from confounding factors by studying cohorts that were relatively homogeneous, consisting of non-malformed female and male singletons born to mothers with citizenship in Nordic countries. Still, we had limited information on socioeconomic factors, which in other countries are known to influence the risk of giving birth to SGA infants, final height, and education at least in other countries [50]. However, the Swedish society is rather homogenous, and existing socio-economic differences are relatively small. Among Swedish children between 6 month and 5.5 years, Lindgren et al [52] have shown a negligible social class difference in height, weight and head circumference between the upper class and middle class. A 0.5 cm difference in height was found, when compared to height of children from the working class in preschool years, in favor of the upper class, but no difference in weight. Other studies have shown differences in intellectual performance between those born small and those born appropriate for gestational age, even after adjustment for socioeconomic factors [53, 54].

Random error
In large cohort studies it is essential to have a high proportion of follow ups, to avoid bias and random error. We used the Swedish
Birth Register which includes information on all individuals born in Sweden from 1973 and onwards. The male cohort consisted of more than 250,000 males and the female cohort more than 43,000 subjects, which permitted powerful comparisons between different subgroups of SGA born individuals. In the analyzes of the male cohorts (Papers I-III) we had access to information on the vast majority of males included in the original birth cohort. Conscription was until the end of the 1990ties mandatory and enforced by law. Only 2.4% in each birth cohort were not conscripted. In the female cohort we had information about virtually all females born in Sweden 1973-83 who gave birth to their first child between 1989 and 1999.

External validity (Generalizability)

Not conscripted males

In papers I-III, we defined our study population as single born males without congenital malformations who survived until their 18th birthday, and whose mothers had Nordic citizenship. The proportion of the study population that was conscripted varied from 86.8% to 92.2%, dependent on birth year and included years of conscription. Compared with conscripted males (0.3%), there was a higher proportion of very preterm born boys among not conscripted males (0.5%). Similarly, the proportion of short for gestational age boys was 2.5% among conscripted boys and 3.1% among not conscripted boys, while corresponding proportions of light for gestational age were 2.7% and 3.6%, respectively. Thus, the proportion of preterm and SGA born males in the analyzed population was lower than in the general population. Unfortunately, we were not able to analyze outcome variables for non conscripted males. It could be speculated, though, that those with severe growth retardation or disabilities will not be conscripted. This might have lead to an underestimation of the risks associated with being born preterm or small-for-gestational-age.
Female birth characteristics, final height and offspring birth characteristic

In papers IV and V, we used information on female birth characteristics (1973-83) to study the effect on final height and BMI (paper IV) and offspring’s birth characteristics (paper V). As information on outcome measures was collected at the women’s first delivery (1989-99), all women had given birth at a relatively young age (16-26 years, and 92% between 18-26 years). Younger women are known to have increased risk of giving birth to SGA infants [24]. This might lead to a higher proportion of SGA infants, compared to the rest of the population. Whether mothers born SGA give birth at younger age compared to females born appropriate for gestational age is to our knowledge not known.

Causation
The present studies were mainly analytical, and we have analyzed associations between risk factors and outcome. Conclusions on mechanisms behind the associations were not drawn, since these cannot be determined from this kind of studies. Thus, we were not claiming to have established causality between exposure and outcome.

General considerations

Birth length
Birth length is seldom used in the literature as a predictor of risk associated with being born SGA. Compared to measurement of birth weight, birth length measurements have been claimed less reliable. The possible errors in birth length measurements, though, are non-differential with regards to final height and other outcomes later in life. In accordance with previous investigations [5, 55], we found that birth length is a strong predictor of final height. Deviance in birth length may indicate the timing and etiology of growth disturbance during fetal life [12, 21].
In the study of females, those born short for gestational age had an almost five-fold increased risk of short adult stature and those born light a doubled risk. This is in accordance with a previous report on males born SGA [5]. The linear relationship between birth length and adult stature among females was also very similar to the results shown in males [5]. Another Swedish study [55] has shown somewhat different figures. However, in that study, the numbers of crude estimates corresponds to the crude estimates shown in paper IV. Birth length was associated with a five-fold increased risk whereas birth weight was associated with a two-fold increased risk. Thus, despite the fact that birth length is more difficult to measure than birth weight, birth length is a better predictor of final height. Birth weight could therefore be used as an estimate of birth length when this measure is not available.

SGA subgroups
In the present studies, infants born SGA were classified into three subgroups- born short, born light, or born both short and light- as suggested by Albertsson-Wikland [4]. Growth restricted infants are often classified into two subgroups, born with symmetrical or asymmetrical growth restriction [56]. That infants are born symmetrically (short and light) growth restricted may reflect a genetic constitution with a growth disturbance during the first trimester. Infants born asymmetrically growth restricted (only light for gestational age) are considered to have a growth disturbance during the third trimester. The last group is believed to have a severe growth restriction due to extrinsic factors, and catch-up growth in height is often seen. Catch-up growth among infants with proportional growth restriction is less common. Some of these infants are genetically small, whereas others are growth restricted due to intrinsic factors such as fetal infections, toxic effects, or genetic diseases [10]. Infants born only short-for-gestational-age is a less studied subgroup of individuals born SGA. It could be hypothesized that short-for-gestational-age infants have a growth disturbance in the second trimester, and are thus less growth restricted than infants born both short and light.
Catch-up growth

Catch-up growth was defined as being born short for gestational age according to the Swedish growth curves [17], and being above –2 SDS in height as adult. Infants born light did not by definition necessarily have a true catch-up growth to attain an adult height above –2 SDS, but still they had an increased risk of short adult stature. When individual catch-up growth was analyzed as a continuous variable in papers I and III, similar results as analyzing the dichotomized catch-up variable were found. In paper V, the term relative catch-up growth was introduced to separate the effect of delta catch-up from final stature. Delta catch-up growth is simply the difference between adult height in SDS and birth length SDS and gives no information about the severity of gestational growth restriction. An individual might have had a large catch-up, but still end up with short adult stature. Relative catch-up growth measures the effect of catch-up growth in percentage, where 0% indicates no catch-up growth in height and 100% represents catch up to normal final height (i.e., final height =0 SDS = population mean).

Findings

Intellectual performance

In paper I it was shown that preterm birth, small head circumference, and SGA were independently associated with increased risk of subnormal performance in both the intellectual and the psychological tests. It has been demonstrated that infants born preterm have an increased risk of neurodevelopmental disturbances, especially if they are also SGA [57-59]. The effect of catch-up growth on intellectual performance on infants born SGA, though, has to our knowledge not been studied previously. Among males born SGA, lack of catch-up growth was associated with a substantially increased risk of subnormal performance in both the intellectual and psychological tests. When we further analyzed the different dimensions of the test of
intellectual performance (paper II), we found that being born SGA was associated with subnormal performance in all four subtests. Within the subgroups of males born SGA, being born with a small head circumference or ending up with a short adult stature was associated with further increased risk of subnormal performance.

Low birth weight for gestational age was associated with an increased risk of subnormal intellectual performance, which is in accordance with some [57, 59-64], but not all [65-67], previous studies. The vast majority of these studies were done on small cohorts on young children age 6 months to 13 years [57, 59-62, 67]. Studies on Danish conscripts (4300 males) [63] do support the result whereas a study from Norway on young males age 18 do not. The Norwegian study was done on 105 conscripted males with birth weight below 2500g [65]. Intelligence testing was done on 71 of the males and the mean did not differ from the national average. For the first time we were able in the present work to perform large, population based studies on young adults. Independent of weight, we found that birth length is of importance for intellectual and psychological capacity. The different dimensions of intellectual performance were almost equally affected.

Head circumference

Head circumference was analyzed as a predictor of intellectual performance in papers I and II. Unfortunately, there was no information about head circumference at conscription and we did not have the possibility to study “catch-up growth” of the head. Head circumference at birth was found to be negatively associated with increased risk of subnormal intellectual and psychological performance, which is in accordance with previous studies, where a small head at birth has been reported to be associated with low intellectual performance [68] and minor neurological dysfunction [57]. Among those with small head circumference, the risk of subnormal intellectual performance was most pronounced in the logical dimension.

The highest proportion of infants with small head circumference was found among those born both short and light. Still, even after adjustment for birth weight and birth length, a small head
circumference was independently associated with increased risk of subnormal performance.

**Blood pressure**

In paper III, low birth weight for gestational age was associated with a slightly increased risk of a high systolic blood pressure. The association remained essentially unchanged after adjustment for final height, BMI, birth length and gestational age. However, short adult stature, but especially high BMI in young adulthood were found to be better predictors of high systolic blood pressure than birth characteristics. An inverse relationship between birth weight and systolic blood pressure has been presented and replicated in several studies [43, 69, 70]. Some studies indicate that the inverse relationship between birth weight and systolic blood pressure is true only if the individual attains overweight [44, 71-78]. Other investigators have claimed that the correlation persists even after adjustment for BMI [79, 80]. Holland et al found that BMI and birth weight were independently associated with high blood pressure in a study on 1356 males and 1359 females age 36. Low birth weight was defined as ≤ 2500 g, i.e. a mixture of SGA and prematurely born. However, overweight was found to be a stronger risk factor associated with high systolic blood pressure than low birth weight. Blake et al found similar results in a study on 2057 children age 3 to 6 years. In paper III, overweight among males born light for gestational age was associated with increased risk of high systolic blood pressure, whereas no such association was found among males born both short and light. Previous reports have been performed on rather small cohorts (580 – 3000 individuals), except the study done by Seidman et al [71] which includes 32 580 young adults and his data support the results in our population-based study presented in paper III.

Some studies have shown that catch-up growth in height might lead to raised blood pressure [3, 39], whereas others claim the opposite [40]. It has also recently been demonstrated that catch-up growth in SGA children induced by growth hormone treatment does not influence blood pressure negatively [42]. Among boys born short for gestational age, catch-up growth was not associated with a higher risk of high systolic blood pressure, compared with those without catch-up growth.
(paper III). In contrast to previous studies [2], among males born with birth weight below -2 SDS, those who ended up with a short adult stature did actually have a higher risk of high systolic blood pressure, compared to males with adult height within normal.

Overweight
Since BMI in young adulthood was found to be a better predictor of systolic blood pressure than birth characteristics, we wanted to study risk factors for BMI. There have been reports of association between being born large for gestational age and high BMI in adulthood [81]. It has also been shown that both men and women born SGA have an increased mean BMI gain but a lower mean height gain during puberty compared with those born appropriate for gestational age [6]. Sas et al [42] have shown that SGA children with growth hormone induced catch-up growth did not attain BMI above the population mean. The influence of spontaneous catch-up growth in height on risk of obesity among those born SGA has to our knowledge not previously been studied. In both the male (paper III) and female (paper IV) cohorts, being born short for gestational age with a failure to catch-up in height was associated with increased risk of being overweight in early adulthood.

Intergeneration
Several studies have shown intergenerational effects of being born small for gestational age. Only a few have focused on birth length. Still, intergenerational effect of being born short for gestational age has previously been shown [82] in a study on 215 females. This finding was confirmed in the study on our cohort of 1 363 short for gestational age females presented in paper V. We were able to show an almost linear association between maternal and offspring’s birth length. Associations between the mother’s and her offspring’s birth weight have been shown in some [83, 84] but not all [85] previous studies. Among females born short for gestational age, a short adult stature was associated with increased risk of giving birth to a short infant. We found that both final height and catch-up growth in height influenced infants’ birth length. Still, females born short for
gestational age with normal adult stature generally gave birth to shorter infants, than females born appropriate for gestational age.
Conclusions

- In males born SGA, spontaneous catch-up growth in height is associated with reduced risk of subnormal intellectual and psychological performance.
- Lack of catch-up growth among males born SGA, resulting in short adult height is especially associated with risk of subnormal logical performance.
- Catch-up growth is not associated with increased risk of high systolic blood pressure among males born SGA.
- Spontaneous catch-up growth in height is associated with reduced risk of overweight in both males and females born SGA.
- In females, short birth length is the most important of birth factors for prediction of short adult stature.
- Females born short for gestational age have, especially if they end up with short adult stature, increased risk of giving birth to short infants.
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Robert, my husband and best friend. For your tolerance and love and for wanting to have children with me. Valter our son, I love you.
References


44


79. Holland, F.J., et al., *Birth weight and body mass index in childhood, adolescence, and adulthood as predictors of blood


A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series *Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine*. (Prior to October, 1985, the series was published under the title “Abstracts of Uppsala Dissertations from the Faculty of Medicine”.)