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HENRIKKI NORDMAN

IMPACT OF BIRTH SIZE AND EARLY GROWTH ON CARDIOMETABOLIC RISK FACTORS IN PREPUBERTAL CHILDREN

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ABSTRACT

There is growing evidence that birth size affects the future risk of cardiometabolic diseases. This has been especially explored in children born small for gestational age (SGA), and studies show that metabolic programming starts as early as in the uterus. In recent years, children born large for gestational age (LGA) have also been studied increasingly. The association between birth size and elevated risk for cardiometabolic disease seems to be U-shaped. LGA children have an increased risk for overweight and obesity. The proportion of LGA infants has grown in recent decades. The prevalence of overweight and obese children has also risen at the same time.

Not only birth size but also early childhood growth affects future cardiometabolic risk. Catch-up growth in SGA children and catch-down growth in LGA children are common, but the presence or absence of compensatory growth is known to have an impact on later health issues, including overweight and obesity, and disturbances in glucose metabolism.

In this thesis, we investigated the impact of birth size, especially LGA, and early growth on various cardiometabolic characteristics in prepubertal children. The cohort of 128 children, divided into three birth weight groups (SGA, appropriate for gestational age, and LGA), were studied at Kuopio University Hospital at the age of 5 to 8 years.

LGA children had an increased risk for childhood overweight. SGA children were leaner but they had higher low-grade inflammation than LGA children. Adrenal androgen levels were higher in SGA than in LGA children. Accelerated early growth also predicted higher dehydroepiandrosterone sulfate concentrations. Being born LGA had a positive impact on bone accrual. No significant differences were found in glucose metabolism, lipid concentrations, or blood pressure between the study groups.

In conclusion, our results suggest that both SGA and LGA children have an increased risk for development of cardiometabolic disturbances at prepuberty. In SGA children, the adverse impacts of birth size and catch-up growth on

cardiometabolic risk factors seem to be independent from overweight, whereas in LGA children, retaining normal weight could reduce these adverse outcomes in future, and large birth size could even be beneficial to an extent.

National Library of Medicine Classification: QU 100, QU 120, WD 210, WS 290, WS 440
Medical Subject Headings: Adiposity; Birth Weight; Blood Pressure; Body Composition; Body Height; Body Mass Index; Body Weight; Bone Density; Cardiovascular Diseases; Child; Cohort Studies; Dehydroepiandrosterone Sulfate; Fetal Growth Retardation; Fetal Macrosomia; Growth; Infant, Small for Gestational Age; Insulin Resistance; Metabolism; Pediatric Obesity; Risk Factors

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TIIVISTELMÄ

Syntymäkoon vaikutuksesta kardiometabolisten sairauksien riskiin on enenevää tutkimusnäyttöä. Tämä on osoitettu erityisesti raskauden kestoon nähden pienikokoisina syntyneillä (SGA, small for gestational age) lapsilla, ja tutkimukset osoittavat, että aineenvaihdunnallinen ohjelmoituminen alkaa jo kohdussa. Viime vuosina kiinnostus raskauden kestoon nähden suurikokoisina syntyneitä (LGA, large for gestational age) lapsia kohtaan on lisääntynyt. Aiempien tutkimusten perusteella vaikuttaa siltä, että syntymäkoon ja kohonneen kardiometabolisen riskin suhde on U-käyrän muotoinen. On myös todettu, että LGA-lasten riski ylipainoon ja lihavuuteen on kohonnut. LGA-lasten osuus on kasvanut viime vuosikymmeninä. Myös lapsuusiän ylipainon ja lihavuuden esiintyvyys on lisääntynyt samana aikana.

Syntymäkoon lisäksi lapsuusiän varhaisella kasvulla on vaikutusta kardiometaboliseen riskiin. Saavutuskasvu SGA-lapsilla ja kasvun hidastuminen LGA-lapsilla on tyypillistä, mutta korvaavan kasvun, tai sen puuttumisen, tiedetään vaikuttavan myöhempiin terveysongelmiin, kuten ylipainoon ja lihavuuteen sekä sokeriaineenvaihdunnan häiriöihin.

Tässä väitöskirjassa tutkimme syntymäkoon, etenkin suuren syntymäkoon, ja varhaisen kasvun vaikutusta useisiin kardiometabolisiin muuttujiin keskilapsuudessa. Tutkimuskohortissa oli 128 lasta jaettuna kolmeen ryhmään syntymäkoon perusteella (SGA, raskauden kestoon nähden normaalikokoisena syntyneet ja LGA), jotka tutkittiin 5–8 vuoden iässä Kuopion yliopistollisessa sairaalassa.

LGA-lapsilla oli kohonnut riski lapsuusiän ylipainolle. SGA-lapset olivat hoikempia, mutta heillä oli enemmän matala-asteista tulehdusta kuin LGA-lapsilla. Lisämunuaisten mieshormonitasot olivat korkeammat SGA- kuin LGA-lapsilla. Kiihtynyt varhaiskasvu myös ennusti korkeampia seerumin dehydroepiandrosteronisulfaatin pitoisuuksia. Suurikokoisena syntymisellä oli myönteinen vaikutus luustontiheyteen. Sokeriaineenvaihdunnassa, rasva-arvoissa tai verenpaineissa ei ollut merkitseviä eroja tutkimusryhmien välillä.

Lopuksi voidaan todeta näiden tulosten viittaavan siihen, että sekä SGA- että LGA-lapsilla on keskilapsuudessa lisääntynyt riski myöhempiin kardiometabolisiin häiriöihin. SGA-lapsilla syntymäpainon ja saavutuskasvun haitalliset vaikutukset kardiometabolisiin riskitekijöihin näyttävät olevan ylipainosta riippumattomia, kun taas LGA-lapsilla normaalipainoisena pysyminen voi vähentää tulevia haittoja, ja osaksi suuren syntymäkoon vaikutus voi olla jopa suotuisa.

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Yleinen suomalainen asiasanasto: aineenvaihdunta; androgeenit; insuliiniresistenssi; kasvu; kehonkoostumus; kohorttitutkimus; lapset (ikäryhmät); lihavuus; painoindeksi; rasva-arvot; riskitekijät; sydän- ja verisuonitaudit; syntymäpaino; verenpaine; ylipaino

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know all mysteries and all knowledge, but do not have love, I am nothing." My beloved wife, Maaria, I love you!

Stockholm, January 2019

Henrikki Nordman

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

I Nordman H, Voutilainen R, Laitinen T, Antikainen L, Huopio H, Heinonen S, Jääskeläinen J. Growth and cardiovascular risk factors in prepubertal children born large or small for gestational age. Horm Res Paediatr. 2016;85(1):11-17.

II Nordman H, Voutilainen R, Laitinen T, Antikainen L, Jääskeläinen J. Birth size, body composition, and adrenal androgens as determinants of bone mineral density in mid-childhood. Pediatr Res. 2018;83(5):993-998.

III Nordman H, Voutilainen R, Antikainen L, Jääskeläinen J. Prepubertal children born large for gestational age have lower serum DHEAS concentrations than those with a lower birth weight. Pediatr Res. 2017;82(2):285-289.

IV Nordman H, Voutilainen R, Antikainen L, Jääskeläinen J. Plasma IL-1 receptor antagonist concentration has an inverse association with birth weight in prepubertal children. J Endocr Soc. 2018;2(3):232-239.

CONTENTS

ABBREVIATIONS

%BF Body fat percentage

25(OH)D 25-hydroxyvitamin D

AGA Appropriate for gestational age

AI Atherogenic index

ALP Alkaline phosphatase

ALS Acid-labile subunit

ALT Alanine transaminase

ANCOVA Analysis of covariance

BMC Bone mineral content

BMD Bone mineral density

BMI Body mass index

CI Confidence interval

CRP C-reactive protein

CVD Cardiovascular disease

DBP Diastolic blood pressure

DHEA Dehydroepiandrosterone

DHEAS Dehydroepiandrosterone sulfate

DXA Dual-energy x-ray absorptiometry

GH Growth hormone

GLM General linear model

HDL-C High-density lipoprotein cholesterol

HOMA-IR Homeostasis model assessment for insulin resistance

hs-CRP High-sensitivity C-reactive protein

ICP Infancy-childhood-puberty

IGF Insulin-like growth factor

IGFBP Insulin-like growth factor binding protein

IL Interleukin

IL-1ra Interleukin-1 receptor antagonist

IMT Intima-media thickness

IQR Interquartile range

IUGR Intrauterine growth restriction

LDL-C Low-density lipoprotein cholesterol

LGA Large for gestational age

LM Lean mass

LV Left ventricular

MetS	Metabolic syndrome
MRI	Magnetic resonance imaging
MUL	Mulibrey nanism
PA	Premature adrenarche
PI	Ponderal index
SBP	Systolic blood pressure
SDS	Standard deviation score
SGA	Small for gestational age
T2D	Type 2 diabetes
TBLH	Total body less head
TC	Total cholesterol
TG	Triglyceride
TNF	Tumor necrosis factor
VLDL-C	Very low-density lipoprotein cholesterol
WHtR	Waist-to-height ratio

1 INTRODUCTION

The association between small birth size and later cardiometabolic risk has been established well in past decades (1,2). Recent findings have shown that not only small but also large birth size may cause the same kind of adverse outcomes, and the relationship between birth size and increased cardiometabolic risk is more U-shaped than linear (3-5). Children born large for gestational age (LGA) have an increased risk for overweight in childhood (6). In the recent past, the proportional share of LGA children has risen (7), as well as the prevalence of childhood overweight and obesity (8).

The metabolic programming for later diseases starts before birth (9). Several studies have shown the association between intrauterine growth restriction (IUGR) and later cardiovascular morbidity (10). The Barker hypothesis, which suggests that impaired growth in the early years of life affects cardiometabolic risk in adulthood, was introduced in 1990 (11). A decade later, Hattersley and Tooke proposed their hypothesis of genetically mediated impaired intrauterine growth and adult insulin resistance (12). In addition, metabolic programming continues after birth through early growth. Both catch-up and catch-down growth have an adverse impact on later cardiometabolic risk (13,14). The changes in metabolism caused by fetal programming and early growth are already visible in childhood and adolescence, although the clinical outcomes of cardiometabolic disease do not generally appear before adulthood (15).

Because the clinical outcomes of cardiometabolic disease are latent in mid-childhood, the future cardiometabolic risk needs to be evaluated indirectly. This can be done in prepubertal children by exploring the birth size, early childhood growth, current body size and composition, assessing blood pressure and carotid intima-media thickness (IMT), and through several biochemical characteristics such as lipids, glucose, insulin, and low-grade inflammation, which have all been found to affect adulthood cardiometabolic risk (15-17).

This study is based on a cohort strictly selected according to birth size. The aim of this thesis was to investigate the impact of birth size, especially large size, and early growth on various cardiometabolic characteristics in prepubertal children, some of which, to our knowledge, have not been reported earlier in LGA children.

2 REVIEW OF THE LITERATURE

2.1 INTRAUTERINE GROWTH

2.1.1 Intrauterine growth and its impact on later health

The guidelines for future health are already partly given in the uterus, as both small for gestational age (SGA) and LGA children have an increased risk for adverse metabolic outcomes. Intrauterine growth is a well-regulated cascade. Both genetic and environmental, epigenetic, factors have an influence on fetal growth and health, having an impact on birth and adult phenotypes and later risk of diseases (18-20).

The genetic influence on growth is strong. Maternal body size has an impact on intrauterine growth, as maternal height, but not paternal size, is associated significantly with birth weight. In addition, the birth weights of siblings tend to be within the same range (21). Sex also has an impact on size, as full-term male newborns are on average 100–150 g heavier than female ones. There is also ethnic diversity in fetal size (22).

2.1.2 Definitions of SGA, AGA, and LGA

Pregnancy between 37 and 42 weeks of gestation is considered full term (23). Birth weights and lengths of term newborns naturally vary and the normality of the birth size has to be assessed in relation to the gestational age.

SGA and LGA are most commonly defined as birth weight < 10th and > 90th percentiles, respectively. In Finland, SGA is defined as gender-specific birth weight or length ≤ −2.0 standard deviation scores (SDS) and LGA as birth weight or length ≥ +2.0 SDS, being equivalent to ≤ 2.3 and ≥ 97.7 percentiles, respectively (24). Children who are between these cut-off points are considered appropriate for gestational age (AGA). Macrosomia is most widely defined as a birth weight > 4000 g but there is no consensus agreement on the diagnostic threshold (21). Low birth weight, very low birth weight, and extremely low birth weight are defined as birth weight < 2500 g, < 1500 g, and < 1000 g, respectively (23).

IUGR is a state where the fetus cannot achieve its growth potential due to the underlying pathophysiological process. IUGR is not a synonym for SGA, although they are commonly used as synonyms. IUGR needs to be confirmed by several prenatal growth assessments, while SGA status is defined by anthropometrics at birth. Thus, being born SGA does not necessarily mean the presence of IUGR, and having IUGR may be independent from being born SGA (1).

In the recent renewal of the Finnish population-based references for birth weight, the proportions of full-term singleton boys born SGA or LGA according to birth weight were 2.7 % and 2.9 %, respectively (25). Similar data for girls were not reported.

2.1.3 Determinants for being born SGA and IUGR

If the optimal intrauterine environment is compromised, this is reflected in fetal growth. The numerous causes for impaired fetal growth are often classified as fetal, uteroplacental, and maternal, and some of those factors are presented in Table 1 (1,2,26). Still, the etiology of IUGR often remains unsolved.

Table 1. Factors associated with an increased incidence of infants being born SGA or with intrauterine growth restriction (modified from (1,2,26)).

Fetal	
	Multiple births
	Chromosomal abnormalities
	e.g. Turner syndrome or trisomy 21 (Down syndrome)
	Genetic diseases
	e.g. Silver-Russell syndrome
	Intrauterine infections
	e.g. cytomegalovirus or toxoplasmosis
Uteroplacental	
	Structural placental factors
	e.g. circumvallate placenta
	Reduced blood flow
	e.g. preeclampsia
	Placenta previa
	Placental abruption
Maternal	
	Medical conditions
	e.g. hypertension, severe chronic disease, malignancy
	Malnutrition
	Demographic factors
	Delivery at age <16 or >35 yrs.
	Maternal body size
	Low maternal height
	Low pre-pregnancy BMI
	Low pregnancy BMI with poor gestational weight gain
	Maternal and paternal race
	Parity
	Multiple gestation
	Previous delivery of an SGA infant
	Low socioeconomic status
	Substance use/abuse
	Smoking
	Alcohol
	Illicit drugs
	Therapeutic drugs

There are several genetic syndromes that affect intrauterine growth. Children with Silver-Russell syndrome, an epigenetic-genomic imprinting problem, have IUGR, impaired postnatal growth, dysmorphic facial features, and body asymmetry (27). Mulibrey nanism (MUL) is a monogenic disorder caused by mutations in the TRIM37 gene. Children with MUL are born SGA and they have dysmorphic features (28). Other embryogenic causes for IUGR include chromosomal abnormalities (e.g.

Trisomy 21 (Down syndrome) and 45,XO (Turner syndrome)) and many other genetic diseases (including osteochondrodysplasias).

A growing fetus is dependent on the placenta. This is an essential organ which provides nutrients and oxygen from mother to fetus and exports excess products derived from the fetal metabolism. It can synthetize and secrete hormones, growth factors, and cytokines (29). Disturbances in placental perfusion, structural abnormalities, and changes in placental implantation are involved in intrauterine growth restriction.

If the gestational weight gain is poor, the risk of SGA birth is higher (30). This was seen in 1944–45 in the Dutch Hunger Winter famine, where maternal malnutrition led to a decreased ponderal index (PI) of newborns (31). Several maternal diseases, including severe anemia and renal diseases, are associated with impaired fetal growth. Maternal smoking and alcohol consumption are related to poor fetal growth, as well as some pharmaceuticals and drugs. Anderson et al. showed that smoking during pregnancy decreases infant birth weight by 12.5 g/cigarette smoked daily. However, there were no differences in birth weights between infants whose mothers smoked before but not during pregnancy and whose mothers were non-smokers (32).

2.1.4 Determinants for being born LGA

Factors for being born LGA can be roughly divided into two: fetal and maternal factors (Table 2). Fetal factors are mostly genetic or chromosomal disorders (33). In Beckwith-Wiedemann syndrome, neonates are characterized by macrosomia due to large muscle mass and thick subcutaneous tissue. This syndrome is derived from dysregulation of the imprinted genes on chromosome 11p15.5 (34) that causes biallelic insulin-like growth factor (IGF)-2 gene expression. This demonstrates the importance of IGF-2 on fetal growth. However, studies show no correlation between cord blood levels of IGF-2 and birth weight, and higher cord blood levels of IGF-2 were identified in AGA infants compared to IUGR ones but not when comparing LGA and AGA infants (35).

Insulin is the only fetal hormone along with the IGF system that is related to intrauterine growth and serves as a growth hormone (GH) (36). Fetal insulin is derived from the fetus because maternal insulin does not transfer through the placental membrane. An inappropriate over-secretion of insulin due to hyperglycemia caused by poorly controlled maternal diabetes leads to an increased usage of glucose leading to excess adipose tissue in fetuses (37). Not only poorly controlled but also well controlled maternal diabetes causes fetal hyperinsulinemia by over-expressing the placental glucose transporter GLUT-1 and GLUT-3 genes. This hyperglycemia-hyperinsulinemia is the most common reason for fetal macrosomia, and the hypothesis was introduced by Jørgen Pedersen in 1952 (38).

The prevalences of gestational overweight and excess weight gain have increased in the last decades. LGA and macrosomia have been associated with maternal high pre-pregnancy body mass index (BMI) and excess gestational weight gain. Pre-pregnancy overweight is an independent risk factor for high birth weight, although,

gestational weight gain over the recommendations may have a stronger implication on high birth weight than pre-pregnancy BMI (39,40).

Table 2. Factors associated with an increased incidence of infants being born LGA (21,33,41).

Fetal	
	Genetic, racial, and ethnic factors
	Genetic or chromosomal disorders
	e.g. Beckwith-Wiedemann syndrome
	Congenital hyperinsulinemia
	Tumors
	Male fetus
	Gestational age >40 weeks
Maternal	
	Diabetes mellitus
	Type I
	Type II
	Gestational diabetes or maturity onset diabetes of the young (MODY)
	Maternal body size
	Maternal obesity before pregnancy
	Excess gestational weight gain
	Tall maternal height
	History of macrosomia
	Multiparity
	Maternal nonsmoking status

2.2 CHILDHOOD GROWTH

Normal human growth is mostly genetically derived. It is a complex process and environmental factors also have an impact on it. To achieve their full growth potential, children need to have proper nutritional and hormonal status during their growth (36). Notwithstanding the complexity of growth, children normally grow in a predictable manner, and deviation from this may indicate, for example, metabolic disorders and disease processes (24).

Postpartum growth can be divided into three phases: infancy, childhood, and adolescence. The velocity of growth is high in the first year of life and diminishing until the pubertal growth spurt, apart from the mild acceleration in growth in mid-childhood simultaneous with the adrenarche (24,42).

2.2.1 Karlberg's model of linear growth

The Swedish researcher Karlberg developed a mathematical approach to growth in the late 1980s (43). It consists of three components (infancy, childhood, puberty (ICP)) that can be analyzed separately, and are combined into one, partly superimposed curve (Figure 1). The ICP model provides a tool for detecting and intervening in disturbances in normal growth, as well as helping to monitor therapy.

At infancy (the first component of the ICP model) the velocity of growth is high, declining rapidly during the first year of life. After birth, the weight and height

velocities are approximately 11 kg/year and 45 cm/year, decreasing to approximately 3 kg/year and 15 cm/year at the age of one year, respectively (24). The first year is mainly the phase where catch-up or catch-down growth occurs. The infancy component lasts about until three years of age (44).

The second component is childhood growth, which begins at the age of 6–12 months with the infancy-childhood growth spurt and operates throughout adolescence (44,45). From the age of three years until the onset of the growth spurt in puberty (phase 3) human growth rate is rather constant, while the growth phase becomes complicated at puberty. Growth is derived only by the childhood component in prepubertal children, hence creating an advantageous period for studies.

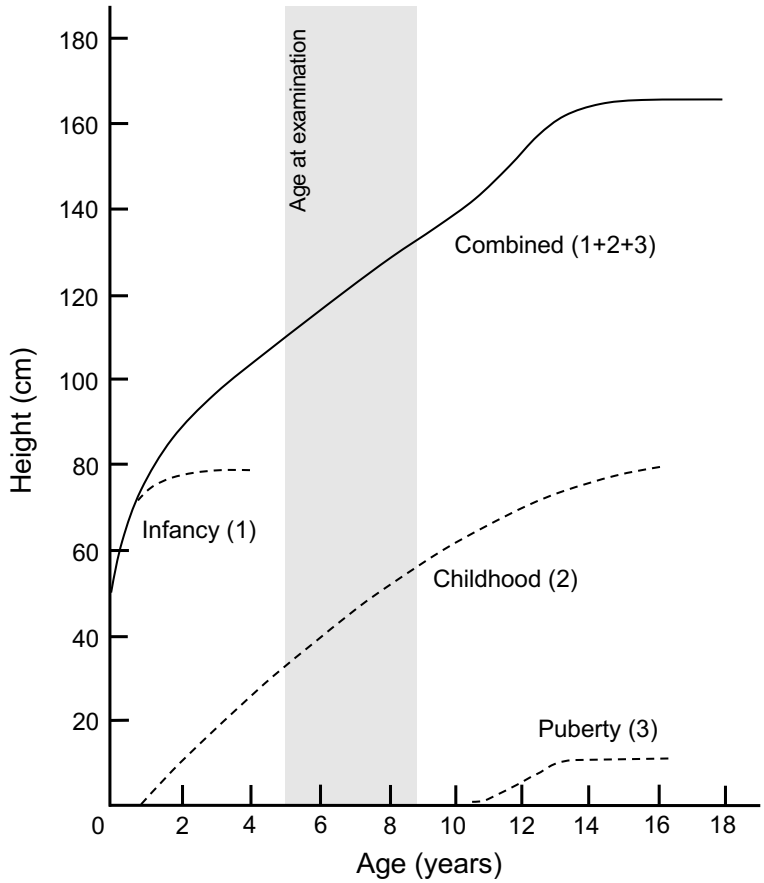

Figure 1. Mathematical growth model of average growth patterns for males during infancy (1), childhood (2), and puberty (3). The solid line (1+2+3) represents the sum growth. Modified from (43-45).

2.2.2 Regulation of growth

Growth in early childhood is strongly regulated by nutrition, and its disturbances have a major impact on an infant's growth. Breastfeeding, which has been associated with reduced risk of obesity in childhood (46), accelerates growth in the first months but decelerates growth in length at the age of six months if given as an exclusive nutriment. Growth is amended after nutrition is diversified. The importance of nutrition in a child's growth decreases in later childhood as hormonal changes play a more dominant role.

The thyroid hormone is vital for post partial growth at all ages. Childhood growth is regulated mainly by GH and IGF-1. The GH–IGF-1 axis has some impact on growth as early as in the first months, but it is crucial for normal growth after infancy. IGF-1, which is stimulated by GH to be produced from the liver, is a mediator in GH-conducted growth. In addition to its endocrine impact, IGF-1 has paracrine and intracrine effects, including a direct impact on the activity of chondrocytes in the growth plate. In the mid-childhood growth spurt, the adrenal androgens may affect the growth plate directly or by increasing the secretion of GH.

In puberty, the sex hormones conduct the growth spurt. Estrogens are needed in both boys and girls to accelerate the growth velocity, and androgens to develop other signs of puberty, including pubic hair and skin greasiness. The growth and sex hormones work together during puberty (47).

2.2.3 Catch-up and catch-down growth

The definition of catch-up growth varies in the literature, but the term refers to the change in the velocity of growth in weight or height in early life. The cut-off point for considerable change in growth can be noted as percentiles or SDS. There is no consistent definition for catch-up growth, but typically it is determined as an increase in weight or height SDS more than 0.67 during the first two years of life (48).

Catch-up growth is very common in children born SGA, as a clear majority of them have catch-up growth by the age of 2 years and most of this appears in first 6–12 months (13,49). The endocrine mechanisms behind catch-up growth are still incompletely understood. It has been suggested that catch-up growth in SGA children is due to delayed growth plate senescence (50).

Catch-up growth is a compensatory mechanism for restricted intrauterine growth and has both good and bad consequences. The positive effects of catch-up growth include increased adult height compared to those without catch-up growth and better cognitive function. However, the early weight gain increases the risk for childhood overweight and obesity, central and intra-abdominal fat, and insulin resistance (13,51). There is a narrow pathway between healthy and harmful catch-up growth.

Correspondingly, catch-down growth can be defined as a decrease in weight or height SDS more than 0.67 during the first two years of life (52). It is seen mostly in infants born LGA as they approach the average weight and height SDS, but SGA and

AGA children with familial short stature may also show catch-down growth (53). Catch-down growth in LGA children has been speculated to be the result of the departure from the energy-rich fetal environment (caused by, for example, maternal obesity or excessive gestational weight gain). Postnatally, without the influence of intrauterine stimuli, LGA children seek their natural genetic growth patterns (54).

2.3 EARLY ORIGIN OF CARDIOMETABOLIC DISEASE

The fetal programming hypothesis, known as the Barker hypothesis, was described in 1990 by David Barker, who observed the association between poor fetal growth due to fetal undernutrition and increased cardiovascular disease (CVD) risk in adulthood (11). Barker and Osmond had earlier noticed that ischemic heart diseases were more common in areas with poor living conditions, and they suggested that poor nutrition in early childhood increases the CVD risk (55). Fetal metabolic adaptation due to IUGR and poor early postnatal nutrition causes a thrifty phenotype, leading, both alone and combined with improved infant nutrition, to increased risk of metabolic disorders, hypertension, hyperlipidemia, and type 2 diabetes (T2D), in later life (56,57).

Alternatively, Hattersley and Tooke proposed that impaired intrauterine growth and adult insulin resistance are genetically mediated (Figure 2). This hypothesis suggests that small birth size is not caused by poor intrauterine nutrition but

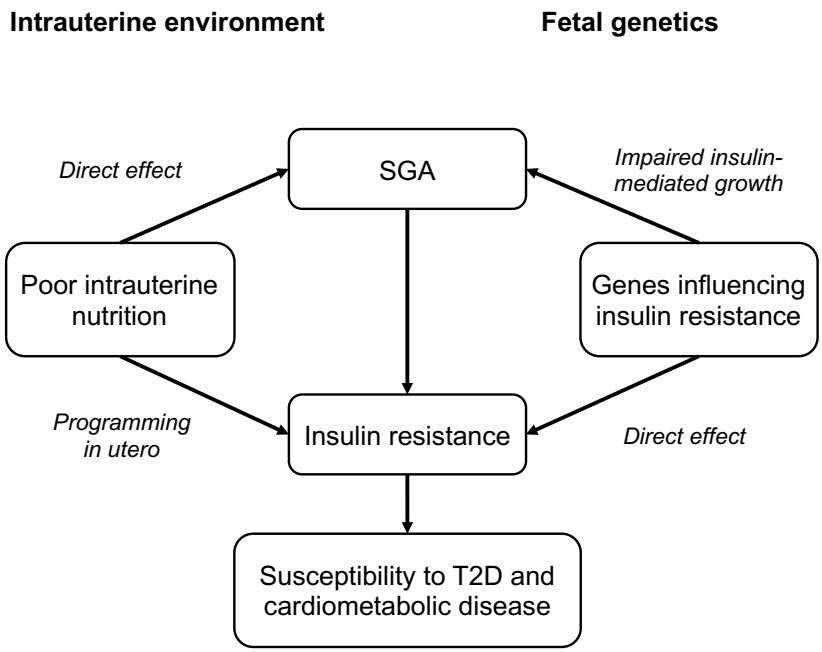

Figure 2. Intrauterine environment and fetal genetics as explanations for the association of SGA newborns with later insulin resistance and cardiometabolic disease. Modified from (12).

impaired insulin-mediated growth. They suggested that the insulin-resistant genotype is the reason for insulin-related phenotypes throughout life: poor fetal growth, hypertension, and insulin resistance and diabetes (12). The argument supporting the hypothesis is that genetic abnormalities affecting pancreatic glucose sensing, insulin secretion, or insulin resistance have a significant impact on birth weight. It is likely that both environmental and genetic factors have an impact on fetal growth and future risk of diseases.

However, previous studies have suggested the presence of a somewhat similar pathway in high birth weight, too (Figure 3). In 1980, Freinkel introduced the hypothesis of fuel-mediated teratogenesis that could lead to alterations in the organogenesis of fetuses of diabetic mothers, causing long-range metabolic changes (58). The hypothesis has been investigated particularly in Pima Indians, a population with a high prevalence of T2D and obesity (59).

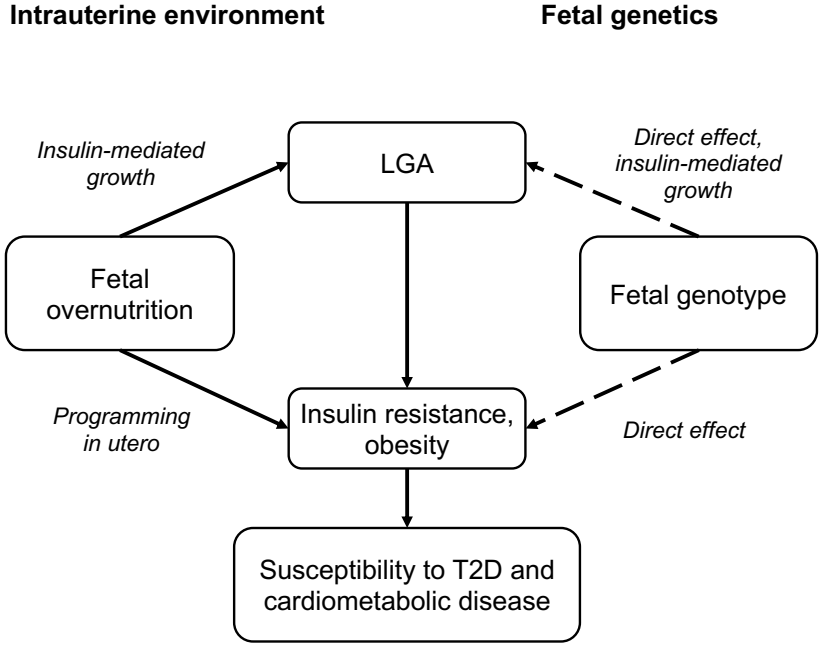

Figure 3. Intrauterine environment and fetal genetics as explanations for the association of LGA newborns with later insulin resistance and cardiometabolic disease (60,62).

This fetal programming could be seen as impaired glucose tolerance, increased insulin secretion, and β-cell hyperplasia in the offspring of diabetic mothers, and in obesity and related metabolic changes in the descendants of obese mothers, creating a vicious cycle through epigenetic changes (37,60). In the study by Dyer et al., insulin sensitivity was compromised in newborn LGA infants born to mothers without diabetes (61), indicating the involvement of a genetic compound in the development of altered insulin sensitivity. Even though the majority of the genetic correlations

between birth weight and T2D concern lower birth weight, some T2D risk alleles are associated with higher birth weight (62). In a recent study, Hughes et al. did not find an association between the fetal genetic score for birth weight and fetal insulin secretion, but the fetal genetic score was associated with newborn skinfold thickness (63). This could implicate a common genetic background for high birth weight and the possible long-term effects of newborn visceral fat. Still, the overall genetic mechanisms associating high birth weight and future risk of cardiometabolic disease remain unclear.

There is also evidence that not birth size but rapid catch-up growth in the early years could explain the adverse cardiometabolic outcomes. Systematic reviews have reported a clear association between early rapid growth and later overweight and obesity (48,64), and the association is independent of birth weight: both SGA and AGA children, if gaining weight rapidly in infancy, have similar risk for later obesity (65). A recent systematic review states that low birth weight increases the risk of adulthood cardiometabolic risk, and postnatal catch-up growth has an important role in that development (16).

2.4 BODY COMPOSITION

2.4.1 Body composition and its measurements

The human body consists of water, protein, fat, and minerals. Body composition can be divided into a fat component and a fat-free component. Body fat is composed of essential and storage fat, and its constituents vary most in the human body (66). Body composition varies between the sexes and changes remarkably at different ages, as early as in childhood. These changes must be taken into consideration when interpreting body composition in children of different ages (67,68).

Fetuses have little fat until 24 weeks of gestation. Two studies using maternal magnetic resonance imaging (MRI) showed that fetal fat content was significantly lower in women without diabetes compared to those with diabetes at 34/38–41 weeks of pregnancy: the average fetal body fat percentage (%BF) in non-diabetic mothers and diabetic mothers were 22.5/17.2 % and 40.4/27.4 %, respectively (69,70). No statistical difference was observed in the calculated fetal weights between non-diabetic and diabetic groups (69).

Neonates lose approximately 5–10 % of body weight (body water) during the first week after birth. Most fat is subcutaneous in newborns (71), and the fat-free mass increases and total water decreases during the first year of life (68). Infants have a larger proportion of extracellular water and organ mass than older children (72). The body fat percentage is approximately 25 % in both boys and girls at the age of two years (68).

In older children, the growth velocity is lower and changes in the body composition are less pronounced before puberty (72). Between 5 and 10 years of age, median %BF ascends in boys from 15.6 to 17.8 and in girls from 18.0 to 22.8 (73). The sex differences in body fat are visible through childhood, but the greater diversity in

body compositions occur at puberty, when boys are gaining more lean body mass than girls, and %BF declines in boys but not in girls (72,73).

Body composition can be evaluated in various ways, and there is no *in vivo* gold standard for measurement in children. PI (weight/length^3), first introduced by Rohrer in 1921, can be used for assessing the nutritional state and adiposity of the newborn (74). A traditional way to estimate subcutaneous fat is skinfold thickness measurement, but accuracy in obese children is poor. BMI is widely used but it does not separate lean and fat masses (57). Still, it is a simple way to detect children with increased risk for later metabolic syndrome (MetS), T2D, or high carotid IMT in adulthood (75). Waist circumference predicts central fatness and has been shown to associate with CVD risk factors in children (76). Waist-to-height ratio (waist circumference/height) has been shown to associate strongly with abdominal and total fat in children (77). In addition, bioelectric impedance analysis, dual-energy x-ray absorptiometry (DXA), densitometry, isotope dilution, and MRI can be used for obtaining body composition. DXA is quick and provides information on fat, lean, and bone mass, albeit having limitations in estimating soft tissue in the trunk area compared to the limbs (78).

2.4.2 Overweight and obesity in childhood regarding birth size

The prevalence of childhood overweight and obesity has increased during the past two to three decades in most developed countries and in urban areas of several low-income countries (79). It was estimated that in 2016, globally, 41 million children under the age of 5 years and over 340 million children and adolescents aged 5 to 19 years were overweight or obese (80). In Finland, approximately 25 % of boys and 16 % of girls aged 2 to 16 years were overweight in 2014–2015. At the same time the prevalence of obesity was 7 % in boys and 3 % in girls (81). The classification for overweight and obesity is not unanimous in children (79). Age- and sex-specific BMI is a widely used tool to monitor overweight and obesity in children. The International Obesity TaskForce (IOTF) references for overweight and obesity equate adult BMI values of 25 and 30 kg/m^2, respectively (82).

In addition to being independent risk factors for cardiometabolic disease (83), overweight and obesity have been associated with other adverse risk factors for CVD in childhood. Children who are overweight or obese have elevated systolic and diastolic blood pressure and dyslipidemia compared to children with normal weight, and obesity has been associated with elevated insulin resistance, higher levels of fasting glucose, and an increase in left ventricular (LV) mass (84). IMT, the predictor of cardiovascular risk, has been shown to increase already in obese children and adolescents (85). In addition, obesity has been associated with significant changes in myocardial geometry and function, including thicker LV walls and increased LV volume, and higher LV stroke volume and cardiac output (86). The risk for developing cardiovascular, metabolic, and hepatological disorders is increased in children with severe obesity compared to those with moderate obesity (87).

The relationship between birth size and later risk for obesity is suggested to be U-shaped. Children born LGA have an increased risk for childhood overweight/obesity and higher BMI SDS, especially if they have no catch-down growth (88-91). The trend is similar in adults. In a large Swedish cohort, LGA-born children had a higher risk for adulthood obesity, both in men and women (4). A large meta-analysis demonstrated the association between high birth weight and long-term risk of overweight in persons aged 6 months to 79 years (92). In the same study, low birth weight seemed to decrease the risk of later overweight. The increasing proportion of children born LGA partly explains the growing tendency to childhood obesity (7). SGA children are also acknowledged to have a higher risk of overweight and obesity in childhood, and the risk is augmented by early rapid weight development (1). Still, childhood obesity may not be visible at a young age but develop later (88).

Obesity tracks from childhood to adolescence (93) and adulthood (94), thus creating a risk of cardiometabolic disturbances later in life. This is seen both in LGA- and SGA-born adults. Juonala et al. showed that a risk for type 2 diabetes, hypertension, dyslipidemia, and increased carotid IMT was increased in persons who were obese from childhood to adulthood (95). In a recent meta-analysis, overweight or obesity in children aged 0–6 years was associated with a risk of MetS in adults (96).

2.4.3 The impact of birth size on bone metabolism and bone mineral density

In growing children, bone modeling is driven by osteoblasts and osteoclasts (97), and during the first two decades of life nearly maximal bone mass is achieved. Nutrition, especially calcium and vitamin D, and mechanical load affect the final bone accrual (98). Serum 25-hydroxyvitamin D (25(OH)D) concentrations are reported to be low in children (99). The (25(OH)D) levels should exceed 50 nmol/l (100). Overweight and low 25(OH)D concentrations are associated in children and adolescents (101).

Many hormones, growth factors and cytokines are involved in bone metabolism. The effect of GH on growth derives mostly from IGFs (IGF-1 and IGF-2). The circulating IGFs form complexes with IGF binding proteins (IGFBP)-1–6 and acid-labile subunits (ALS). These complexes lengthen the half-life of IGFs, and the IGF-1–IGFBP-3–ALS complex is the most common. IGF-1 levels are low in newborns but rise during childhood, reaching peak levels at puberty. IGF-1 is known to increase bone metabolism, both remodeling and resorption, while cytokine interleukin (IL)-1 stimulates osteoclast formation and accelerates resorption. These factors are also associated with cardiometabolic health. Obese hyperinsulinemic children have been reported to have an altered GH–IGF-1 axis (102).

Sex hormones have a crucial role in bone development and maintenance, but the effect is seen mainly in adolescence and adulthood, less in prepuberty. Dehydroepiandrosterone sulfate (DHEAS), a weak androgen, has been shown to correlate positively with total body bone mineral content (BMC) in prepubertal children (103) but negative associations have also been published (104). Finnish prepubertal children with premature adrenarche (PA) had higher bone mineral

density (BMD) than controls, but the association was explained mainly by the increased height of the PA subjects (105). This positive correlation seems to track to adulthood. A recent study by Park et al. demonstrated the positive correlation in adults between DHEAS and femur BMD (106).

It has been suggested that cardiometabolic risk factors may have a negative impact on bone in children and adolescents. Overweight prepubertal children with normal glucose levels had higher BMC than those with pre-diabetes (107). In older children, the trend was similar, as healthy overweight youths had higher BMC and areal BMD compared to overweight peers with cardiometabolic risk factors, and abnormal glucose regulation was suggested to have an impact on the growing skeleton (108).

Mechanical load is a major cause of higher bone mass. BMI and volumetric BMD are positively associated with bone mass in childhood. Studies imply that lean mass, not fat mass, is the determinant of bone mass in children. To the contrary, in children, there is increasing concern that obesity is associated with suboptimal bone growth leading to skeletal fractures and lower bone mass (109,110), but studies have also reported positive associations between body fat and bone mass in childhood (111,112).

The association between birth size and bone accrual in childhood is not well-established. Significant differences between the birth size groups appear in BMC, not in BMD (113,114), and the trend is similar in adulthood (64). Children born SGA (without catch-up growth) had lower and children born LGA (without catch-down growth) had higher BMC and BMD than children born AGA at the age of six years. If growth realignment were shown between 0 and 2 years of age, BMD and BMC were similar in all groups (113).

The association between birth weight and bone mass in adulthood is linear. The risk for poor accrual of adult bone mass is increased in SGA children, especially preterm, while higher birth weight leads to greater BMC (64,115,116). Catch-up growth is important for SGA children for achieving higher BMD in adulthood (117).

2.5 ADRENOCORTICAL FUNCTION AND ITS ASSOCIATION WITH BIRTH SIZE

The maturation of the adrenal glands in mid-childhood is called adrenarche. It is derived from the secreted precursors of androgens, primarily dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) from the adrenal cortex, where they are synthesized from cholesterol. These androgen precursors are transformed into biologically active androgens and estrogens in the peripheral tissues. DHEA and DHEAS, together with 11β-hydroxylated androstenedione and testosterone, are often regarded as adrenal androgens. Due to its long half-life, DHEAS is a stable and widely used serum biomarker of adrenal androgen secretion and adrenarche (118,119). Adrenarche is defined as premature (PA) when clinical signs appear in the presence of elevated serum DHEAS levels for age before the age

of 8 years in girls and 9 years in boys. Clinical signs of adrenarche are adult-type body odor, oily hair, acne or comedones, and the appearance of pubic or axillary hair. A serum DHEAS level above 1 μmol/l is regarded commonly as a biochemical cut-off level for adrenarche (120).

PA has a significant influence on growth and metabolism. The impact of small birth size on higher DHEAS concentrations in childhood is known (121,122), but studies on DHEAS concentrations in LGA children are rare. The ALSPAC (Avon Longitudinal Study of Parents and Children) study demonstrated the negative association between birth weight and DHEAS levels at prepuberty (123). Children with PA are at increased risk to develop obesity in childhood. In one study, prepubertal children with PA had higher BMI SDS and %BF than control children (105) and in another study 65 % of children with precocious pubarche were overweight or obese at the age of 7 years (124). A recent study by Mäntyselkä et al. showed that higher DHEAS is not associated with adverse cardiometabolic risk factor levels in mid-childhood apart from higher BMI SDS (125). Accelerated growth during the first two or three years of life is associated with PA (126) and higher DHEAS levels (123) in 7–8 year-old children. Prepubertal girls with PA have decreased insulin sensitivity and hyperinsulinemia compared to girls without PA (127,128). Girls with a history of premature pubarche have an adverse lipid profile in childhood and adolescence: higher serum triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and lower high-density lipoprotein cholesterol (HDL-C) concentrations (129).

2.6 BIRTH SIZE AND LOW-GRADE INFLAMMATION

Low-grade inflammation is known to strongly affect atherosclerosis and CVD risk (130,131), and markers of inflammation can be detected as early as in childhood (132). Several metabolic factors are involved in this process. Overweight is associated with increased low-grade inflammation (133), and this is seen already at prepuberty (134).

The adipose tissue that is excessively present in MetS and obesity produces inflammatory cytokines, such as IL-1 and tumor necrosis factor (TNF), into the systemic circulation. This cascade of inflammatory cytokines, including IL-1 and IL-6, increases the production of C-reactive protein (CRP) that is often used as a marker of an inflammatory state for clinical purposes. Elevated levels of CRP suggest the progression of atherosclerosis before any clinical signs appear (135), and increased CRP concentrations predict CVD in adults (136).

Birth size has an impact on later levels of inflammatory markers. Lower birth weight has been associated with elevated serum CRP concentrations in both children (137) and adults (138,139). In a study of Swedish children and adolescents, birth weight was negatively associated with fibrinogen and C4, but not with CRP (140). Elsewhere, macrosomic newborns of mothers with gestational diabetes had lower proinflammatory cytokine, TNF-α and IL-6 concentrations than control newborns

(141). Cetin et al. compared idiopathic LGA-born prepubertal children to AGA-born controls and found lower TNF-α and higher IL-6 concentrations in LGA-born children (142). In addition, these LGA children had higher homeostasis model assessment for insulin resistance (HOMA-IR) than AGA children, and TNF-α was negatively correlated with HOMA-IR, suggesting that decreased TNF-α levels may be associated with insulin resistance.

2.7 CARDIOMETABOLIC RISK FACTORS RELATED TO LOW AND HIGH BIRTH WEIGHT IN CHILDHOOD

2.7.1 Glucose and insulin

Low and high birth weights are known to be associated with elevated risk of T2D in adulthood (4,143). Even if the clinical outcomes of CVD do not appear until adulthood, the cardiometabolic risk factors can be detected already in childhood.

It has been demonstrated that excess body fat, especially central, is associated with hyperinsulinemia as early as in childhood (144,145). Lurbe et al. found a negative correlation between fasting glucose and insulin concentrations and current weight, but not birth weight, in 5-year-old children (146). Still, plasma glucose and insulin balances are compromised in children with abnormal birth size, independently of overweight. In one study, fasting glucose was higher and insulin sensitivity was lower in lean short SGA than AGA children after adjusting for age and BMI (147). In another study, being born SGA with catch-up growth indicated higher fasting insulin levels and HOMA-IR in non-obese prepubertal children. However, fasting glucose concentrations were lower in the SGA group compared to the AGA group (148).

Wei et al. studied schoolchildren with T2D and noticed a U-shaped association between birth weight and the risk of T2D (3). Prepubertal LGA children had higher HOMA-IR and fasting insulin levels than AGA children, but the fasting glucose concentrations did not differ between these groups (149).

2.7.2 Lipids

Both low and high birth weight have been associated with dyslipidemia in adulthood (4,150). Dyslipidemia is a risk factor for atherosclerosis and has an important influence on cardiometabolic health (151,152). In a Finnish study, 12-year-old SGA girls had significantly higher TG concentrations compared to SGA boys and AGA girls, and poor catch-up growth in SGA children predicted an increased risk for hypercholesterolemia (153). Lin et al. showed that LGA children aged 3–6 years had higher serum TC, LDL-C, and TC/HDL-C ratio than AGA children (154). However, the LGA children were significantly heavier than the AGA controls and the analyses were not adjusted for current weight. They also proposed that the observed lipid dysfunction in LGA-born children was explained by altered DNA methylation as early as at birth. In another study, LGA children were not reported to have elevated

serum TC or TG, but had lower lipoprotein(a) concentrations compared to AGA children (149). A recent study of 11-year-old children showed that TG and VLDL-C levels were higher in overweight or obese SGA children compared to overweight or obese AGA and LGA children (155).

2.7.3 Blood pressure

Elevated blood pressure is a significant risk factor for CVDs in adulthood (156). It is associated with atherosclerotic vascular changes, including high carotid IMT (157). Angiotensin II, which is closely related to hypertension, transforms endothelial cells into proinflammatory ones (158). These mechanical and metabolic factors accelerate the inflammation of the arterial wall. If blood pressure is elevated in childhood, the risk that it will track to adulthood and cause adverse remodeling of the cardiac and arterial system arises (159). This risk can be reduced by early intervention (160).

In Finland, blood pressure is measured in every child at the age of 4 or 5 years during a scheduled visit to a child health clinic. Blood pressure should be interpreted in age-, sex-, and height-specific percentiles. In children aged 3–11 years, blood pressure is considered elevated when exceeding the 95th percentile. If two or more abnormally high blood pressure measurements are observed in childhood, it may predict adult hypertension (161).

Current weight is a strong determinant of hypertension in childhood, as well as birth weight having an impact on weight in childhood. Still, some studies show that there is a negative causal effect of birth weight on systolic blood pressure in children when the confounding factors, such as current weight and child health behavior, are considered (162,163).

Huxley et al. reviewed the role of birth size and catch-up growth in systolic blood pressure. An inverse association was found between birth weight and systolic blood pressure in children, adolescents, and adults (164). In addition to low birth weight, rapid postnatal growth, also as an independent factor, was associated with elevated systolic blood pressure in children and adolescents (164,165).

There is also evidence that high birth weight or being born LGA are associated with elevated blood pressure in adolescents, and the association between high birth weight or being LGA and hypertension was also significant when odd ratios were adjusted for age, sex, and BMI (166). In a recent study, 7-year-old LGA children without catch-down growth had an increased risk of high blood pressure, but those with catch-down growth did not (90).

3 AIMS OF THE STUDY

The purpose of this study was to evaluate the impact of birth size, especially large, on overweight and obesity, and cardiometabolic risk factors in mid-childhood. The main hypothesis was that overweight would be more common in LGA than AGA children at this age. Another aim was to investigate if the early childhood growth pattern affects these risk factors.

The specific aims were:

1. To evaluate associations between birth size and mid-childhood overweight and obesity.
2. To study the differences in biochemical markers of cardiometabolic risk between the birth size groups at prepuberty.
3. To determine the possible differences in body composition between the study groups in prepubertal children.
4. To investigate the impact of catch-up and catch-down growth on overweight and cardiometabolic risk at prepuberty.

4 GROWTH AND CARDIOVASCULAR RISK FACTORS IN PREPUBERTAL CHILDREN BORN LARGE OR SMALL FOR GESTATIONAL AGE

ABSTRACT

Background: Both large and small birth size are associated with an increased risk of developing cardiovascular and metabolic problems later in life. We studied whether such association can be observed at prepubertal age.

Methods: A cohort of forty-nine large (LGA), 56 appropriate (AGA), and 23 small for gestational age (SGA)-born children (age range 5–8 years) were studied. Being born SGA, AGA or LGA was the exposure, and overweight at prepubertal age was the main outcome. Blood pressure measurements, laboratory parameters, and whole body dual-energy x-ray absorptiometry were secondary outcomes.

Results: The LGA-born children were significantly taller than the AGA controls ($p=0.03$), and the SGA children were lighter and shorter compared to the AGA ($p=0.002/0.001$) and LGA children ($p<0.001$). The mean plasma glucose was higher in the LGA than in the SGA group ($p=0.006$). Being born LGA (OR 3.82) and the ponderal index Z-score at birth (OR 4.24) were strong predictors for being overweight or obese in childhood.

Conclusion: The children born LGA remained taller and heavier than those born AGA or SGA in mid-childhood, and they had higher BMI and body fat percentage than the SGA-born children. The differences in other cardiometabolic risk factors were minimal between the birth size groups.

4.1 INTRODUCTION

Small birth size has a well-known effect on childhood growth and metabolism, and children born small for gestational age (SGA) have an increased risk to develop cardiovascular and metabolic problems later in life (e.g. obesity, hypertension, type 2 diabetes, and dyslipidemia) (1). It has also been suggested that the risk for later disturbances associated with birth size may be U-shaped (143) and some recent studies have shown an association between large birth size and later childhood obesity (6,88), the metabolic syndrome, type 2 diabetes (4,149), and hypertension (165). Furthermore, as obesity tracks from childhood to adulthood (94), childhood obesity is a predictor of hypertension, dyslipidemia, and type 2 diabetes in adulthood (95) thus creating a major global health risk.

The main aim of our study was to explore whether large birth size, compared with appropriate or small birth size is associated with overweight, hypertension or metabolic disturbances in children at prepubertal age. We also studied if the preceding growth pattern during the first two years of life associates with overweight in later prepubertal childhood.

4.2 SUBJECTS AND METHODS

4.2.1 Study population

We studied 128 children (67 boys) born singleton at term between 2004 and 2007 at Kuopio University Hospital, Eastern Finland. The study design was a cohort study and the children were studied once at the age of 5 to 8 years, median (interquartile range (IQR)) age 6.97 (6.30, 7.69) years.

Standard deviation scores (SDS) for birth weight, length, and head circumference had been created for an earlier study (167) using the Kuopio University Hospital's obstetric register data of 47613 newborns. Children were enrolled in this study according to the birth size. SGA was defined as gender-specific birth weight ≤ −2.0 SDS, large for gestational age (LGA) as birth weight ≥ +2.0 SDS, and appropriate for gestational age (AGA) for this study as birth weight and length being between −1.0 and +1.0 SDS.

An invitation letter was sent to parents to participate in this study. The study entry percentages were 17.8%, 25.0% and 10.0% of the invitations in the SGA (n=23 final participants), LGA (n=49) and AGA (n=56) groups, respectively. Sex distribution, birth length SDS, ponderal index, maternal pre-pregnancy BMI, and the proportion of gestational diabetes were similar in the non-participating families to the participants within the three study groups. Median birth weight SDS was slighty higher in the participating LGA children (median (IQR) 2.46 (2.24, 2.87) than in the non-participating LGA children 2.34 (2.14, 2.60; p=0.04).

Exclusion criteria were any continuous medication, a significant developmental delay or any chronic disease other than atopic eczema, allergic rhinitis, or mild asthma requiring no continuous medication. Children with maternal gestational

diabetes were excluded from the AGA group but not from the LGA or SGA groups. Ten mothers in the LGA group had gestational diabetes and nineteen mothers had pre-pregnancy BMI > 25; 7/19 overweight mothers had also gestational diabetes. One mother in the SGA group had epilepsy and a bipolar disorder. All mothers in the AGA group were healthy.

We also divided the whole study population of 128 children to three groups by early childhood (0–2 years) weight development (based on data recorded at child health clinics). An increase or decrease in weight SDS more than 0.67 was considered as catch-up or catch-down growth, respectively (48). Weight data of one AGA boy and one LGA girl at the age of two years were missing.

An information letter was sent to every participating family and a written informed consent was received from all participants. The Committee on Research Ethics of the Hospital District of Northern Savo approved the study protocol.

4.2.2 Methods

Perinatal data were obtained from the hospital's obstetric register. In the morning of the study visit after an overnight (≥ 10h) fast, anthropometric measurements were performed by a trained nurse. Height was measured with a calibrated Harpenden stadiometer (Holtain Ltd, Crymych, UK) to the nearest millimeter and recorded as the mean of three measurements. Weight was measured with a calibrated digital scale (Seca, Vogel & Halke, Hamburg, Germany) to the nearest 0.1 kg while the participants were wearing light indoor clothes without shoes.

Body mass index (BMI) was calculated as the body weight divided by the square of the height (kg/m^2). Sex- and age-specific SDS for height and BMI were calculated according to the recently published Finnish growth reference (168). The following BMI SDS cut-off points for overweight and obesity were used corresponding to BMI of 25 and 30 kg/m^2 at the age of 18 years: for boys 0.78, 1.70, and for girls 1.16, 2.11, respectively (168).

Blood samples were collected from the antecubital vein in the morning after an overnight fast. Plasma glucose concentration was determined by the hexokinase method (Roche Diagnostics GmbH, Mannheim, Germany). Plasma concentrations of total cholesterol (TC) and triglycerides (TG) were analyzed with colorimetric enzymatic assays, and those of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) with homogeneous colorimetric enzymatic assays (both Roche Diagnostics GmbH). The kinetic method according to International Federation of Clinical Chemistry was used for plasma alanine transaminase (ALT) concentration measurements (Roche Diagnostics GmbH). Serum insulin concentration was analyzed using electrochemiluminescence immunoassay (Roche Diagnostics GmbH). Serum high sensitivity C-reactive protein (hs-CRP) was measured by immuno-turbidimetric assay (Roche Diagnostics GmbH).

Insulin resistance was evaluated by using homeostasis model assessment for insulin resistance (HOMA-IR) as (insulin, mU/l × glucose, mmol/l) / 22.5 (169).

Fat percentage and muscle mass was assessed by whole body dual-energy x-ray absorptiometry (DXA), using Lunar device (Lunar Prodigy Advance; GE-Medical Systems, Madison, WI, USA). DXA measurements were performed in the morning with an empty bladder, after an overnight fast. Muscle index was calculated as the muscle mass divided by the square of the height (kg/m^2).

Blood pressure was measured using mercury sphygmomanometer three times in a supine position after 15 minutes rest with 1–2 minutes intervals between the measurements. The proper-sized cuff was placed on the right arm. The mean of the lowest two values was recorded.

One child refused to provide the blood sample and one sampling did not succeed (both SGA children). One child (LGA) refused from the DXA measurement. Blood pressure results of two children (AGA and LGA) were rejected due to the problems with the cuff. Children having any acute infection 0–14 days before the examination day (n=9, 4 boys) or hs-CRP value over 10 mg/l (1 girl) were excluded from the hs-CRP analysis.

4.2.3 Statistical methods

Data were analyzed using SPSS statistical software (version 19; SPSS, Chicago, IL, USA). All data are presented as median and IQR, unless stated otherwise. A p value of <0.05 was considered statistically significant.

Mann-Whitney U –test was used to analyze differences between two study groups. Blood pressure was adjusted for height SDS, sex, and age. TC, HDL-C, LDL-C, TG, ALT, hs-CRP, glucose, insulin, and HOMA-IR values were adjusted for BMI SDS, and the differences between the study groups were analyzed using the analysis of covariance (ANCOVA). A logarithmic transformation was performed for every variable used in parametric tests, except HDL-C.

Logistic regression analysis was performed to evaluate predictors for childhood overweight and obesity. Two models contained three independent variables each {model 1: sex, birth size group [SGA, AGA (reference), LGA], and the change in weight SDS from birth to the age of two years; model 2: sex, ponderal index Z-score at birth, and the change in weight SDS from birth to the age of two years}.

One sample T-test was used to assess the difference of the mean BMI SDS of each study group on the examination day from the mean BMI SDS (0) of the Finnish growth reference (168).

4.3 RESULTS

The LGA children were significantly taller than the SGA and AGA children, and heavier than the SGA children at the examination. BMI SDS did not differ significantly between the LGA and AGA groups. The observed small difference in BMI SDS would have required 550 participants in each group to be significant (α 0.05, power 0.80). BMI SDS was significantly lower in the SGA than LGA and AGA groups (Table 3). BMI SDS on the examination day differed significantly from the test value

zero (the national reference) in all groups: the SGA children were lighter (−0.88 SDS, p=0.018), and the AGA and LGA children were heavier (0.31 SDS, p=0.025; 0.48 SDS, p=0.002, respectively). When the AGA boys and girls were analyzed separately, the AGA boys did not differ significantly from zero, but the AGA girls were significantly heavier than the Finnish reference (0.42 SDS, p=0.017).

The SGA children had significantly higher hs-CRP values than the AGA and LGA children (Table 3). The plasma glucose concentration adjusted for BMI SDS was significantly higher in the LGA than SGA group (Table 3). The serum insulin concentrations and HOMA-IR were significantly lower in the LGA than AGA girls. ALT was significantly higher among the LGA than AGA boys (Table 4). Lipid and glucose levels did not differ significantly between the LGA and AGA groups (Tables 3 and 4).

The SGA children had significantly lower body fat percentage compared to the LGA and AGA children, and the LGA and AGA children had higher muscle mass index than the SGA children (Table 3). The children with later catch-up growth were smallest and the children with later catch-down growth were largest at birth (Table 5). At the current examination, the children with previous catch-down growth were still taller than the ones with early stable growth, but no other significant differences in anthropometrics were found between the groups. Hs-CRP was significantly higher in the children with previous catch-up growth compared to those with catch-down growth (Table 5).

The blood pressure levels did not differ significantly between the SGA, LGA, and AGA groups (Table 3). The diastolic blood pressure (DBP) was significantly higher in the catch-down than in the stable growth group when adjusted for height SDS (Table 5). The subgroup of tall LGA children, whose birth weight and length were >2.0 SDS (n=15, 10 boys), had median (IQR) systolic blood pressure (SBP) 103 (99,106) mmHg and DBP 64 (60, 70) mmHg, which were significantly higher than in the AGA group (p=0.049 and 0.043, respectively; ANCOVA analysis adjusted for height SDS, sex and age).

The LGA children with birth weight > 3 SDS (n=9) had higher BMI SDS [median 1.90 (IQR 1.09, 2.27) vs. 0.28 (−0.41, 0.95); p<0.001], body fat percentage [27.6 (22.8, 36.3) vs. 19.0 (15.2, 26.1), p=0.01], muscle mass [13.3 kg (12.5, 13.8) vs. 12.2 kg (11.6, 13.3); p=0.02], and hs-CRP [0.47 mg/l (0.15, 1.45) vs. 0.15 (0.06, 0.36); p=0.02] than the LGA children with birth weight ≤ 3 SDS (n=40).

In model 1 of logistic regression, the strongest predictor for being overweight (n=22) or obese (n=14) at examination was being born LGA, recording an odds ratio (OR) of 3.82. Being born SGA reduced the risk of overweight (OR 0.07) (Table 6). In model 2, the strongest predictor was the Z-score of ponderal index at birth, recording an OR of 4.24. In both models the change in weight SDS from birth to the age of two years had a statistically significant contribution to the model, recording OR of 2.00 in model 1 and 2.13 in model 2 (Table 6).

Table 3. Anthropometric, biochemical, and clinical characteristics of the study participants.

	LGA	AGA	SGA	*p	†p	**p	††p	***p	†††p
n	49	56	23						
Boys	25	29	13						
Girls	24	27	10						
At birth									
Gestational age (w)	40.0 (39.2, 40.6)	40.0 (38.9, 40.7)	39.9 (38.4, 40.9)	0.70		0.47		0.80	
Weight (g)	4730 (4553, 4833)	3540 (3370, 3790)	2440 (2290, 2760)	<0.001		<0.001		<0.001	
Weight (SDS)	2.46 (2.24, 2.87)	−0.02 (−0.44, 0.46)	−2.33 (−2.63, −2.08)	<0.001		<0.001		<0.001	
Length (cm)	53.0 (52.0, 54.0)	50.0 (49.0, 51.0)	46.0 (45.0, 48.0)	<0.001		<0.001		<0.001	
Length (SDS)	1.54 (1.24, 2.11)	−0.10 (−0.44, 0.13)	−1.99 (−2.28, −1.72)	<0.001		<0.001		<0.001	
Head circumference (cm)	37.0 (36.0, 38.0)	35.5 (34.0, 36.0)	33.0 (32.0, 34.3)	<0.001		<0.001		<0.001	
Head circumference (SDS)	1.64 (0.97, 2.34)	0.33 (−0.46, 0.80)	−1.55 (−2.26, −0.62)	<0.001		<0.001		<0.001	
Ponderal index (kg/m^3)	3.16 (3.03, 3.33)	2.85 (2.71, 2.99)	2.50 (2.33, 2.64)	<0.001		<0.001		<0.001	
At examination									
Age (y)	7.06 (6.04, 7.67)	6.99 (6.46, 7.85)	6.59 (6.18, 7.49)	0.36		0.06			
Weight (kg)	28.0 (24.7, 30.3)	26.1 (22.6, 30.9)	20.4 (19.3, 24.0)	0.31		<0.001		<0.001	
BMI (SDS)	0.48 (−0.03, 1.38)	0.31 (−0.41, 1.31)	−0.88 (−1.29, 0.09)	0.31		0.002		<0.001	
Height (cm)	127.5 (122.2, 130.6)	125.2 (119.7, 130.5)	118.6 (115.2, 124.3)	0.52		0.001		0.001	
Height (SDS)	0.44 (0.20, 0.97)	0.15 (−0.47, 0.69)	−0.55 (−1.14, −0.04)	0.03		0.001		<0.001	
Systolic BP (mmHg)	99 (95, 104)	98 (93, 103)	97 (93, 105)	0.12	0.08	0.66	0.22	0.59	0.87
Diastolic BP (mmHg)	63 (58, 68)	60 (57, 64)	61 (59, 64)	0.19	0.09	0.50	0.81	0.49	0.65
Cholesterol (mmol/l)	4.4 (4.0, 4.8)	4.3 (3.6, 4.7)	4.4 (4.0, 4.6)	0.40	0.55	0.81	0.68	0.48	0.40
HDL-C (mmol/l)	1.68 (1.47, 1.92)	1.70 (1.43, 1.91)	1.74 (1.56. 1.98)	0.94	0.73	0.16	0.36	0.20	0.39
LDL-C (mmol/l)	2.5 (2.2, 2.9)	2.3 (1.9, 2.9)	2.2 (1.9, 2.7)	0.29	0.27	0.50	0.81	0.12	0.09
Triglycerides (mmol/l)	0.60 (0.48, 0.69)	0.60 (0.44, 0.69)	0.48 (0.44, 0.64)	0.68	0.98	0.20	0.44	0.10	0.47
ALT (U/l)	17.0 (13.5, 22.0)	16.0 (14.0, 19.8)	19.0 (13.5, 23.0)	0.49	0.50	0.30	0.08	0.70	0.13
hs-CRP (mg/l)	0.19 (0.08, 0.49)	0.20 (0.07, 0.66)	0.55 (0.14, 0.91)	0.88	0.50	0.04	<0.001	0.03	0.003
Glucose (mmol/l)	4.9 (4.8, 5.1)	4.9 (4.7, 5.1)	4.9 (4.6, 5.0)	0.45	0.34	0.55	0.36	0.28	0.006
Insulin (mU/l)	4.79 (3.64, 6.41)	4.74 (3.91, 7.44)	3.86 (3.29, 5.59)	0.51	0.35	0.04	0.86	0.12	0.69
HOMA-IR	1.06 (0.79, 1.40)	1.05 (0.81, 1.56)	0.85 (0.69, 1.19)	0.67	0.47	0.07	0.81	0.13	0.94
Body fat (%)	22.0 (15.7, 27.3)	21.2 (15.0, 29.5)	15.1 (13.5, 20.6)	0.94		0.01		0.003	
Muscle mass (kg)	20.4 (18.7, 22.4)	20.1 (17.1, 21.5)	16.7 (16.0, 18.9)	0.27		<0.001		<0.001	
Muscle mass index (kg/m^2)	12.45 (11.80, 13.38)	12.44 (11.80, 13.02)	11.84 (11.49, 12.48)	0.52		0.03		0.01	

Data are presented as median (interquartile range)

Mann-Whitney test between *LGA and AGA, **SGA and AGA, ***SGA and LGA groups

Analysis of covariance between †LGA and AGA, ††SGA and AGA, †††SGA and LGA groups, adjusted for BMI SDS, except blood pressure for height SDS, sex, and age

Table 4. Anthropometric, biochemical, and clinical characteristics of the boys and girls of the LGA and AGA groups.

	Boys		*p	†p	Girls		*p	†p
	LGA	**AGA**			**LGA**	**AGA**		
n	25	29			24	27		
At examination								
Age (y)	7.25 (6.93, 7.71)	7.04 (6.53, 7.88)	0.95		6.65 (5.94, 7.54)	6.96 (6.20, 7.79)	0.17	
Weight (kg)	28.1 (26.7, 30.9)	26.1 (22.3, 32.1)	0.13		26.8 (22.2, 30.2)	25.3 (22.7, 31.0)	0.96	
BMI (SDS)	0.48 (0.00, 1.49)	−0.12 (−0.53, 1.24)	0.09		0.50 (−0.44, 1.13)	0.42 (−0.11, 1.33)	0.93	
Height (cm)	128.1 (125.5, 132.1)	126.3 (122.4, 132.4)	0.45		124.9 (118.9, 129.4)	125.1 (119.1, 129.3)	0.87	
Height (SDS)	0.41 (0.07, 0.78)	0.07 (−0.32, 0.60)	0.17		0.57 (0.26, 1.24)	0.19 (−0.71, 0.82)	0.08	
Systolic BP (mmHg)	100 (95, 106)	99 (91, 103)	0.15	0.28	98 (95, 104)	97 (94, 103)	0.43	0.16
Diastolic BP (mmHg)	64 (57, 69)	60 (57, 64)	0.21	0.35	62 (58, 67)	61 (57, 65)	0.65	0.14
Cholesterol (mmol/l)	4.3 (3.8, 4.9)	4.2 (3.7, 4.6)	0.63	0.53	4.6 (4.0, 4.8)	4.4 (3.6, 4.9)	0.77	0.94
HDL-C (mmol/l)	1.70 (1.46, 1.91)	1.81 (1.49, 2.05)	0.39	0.52	1.67 (1.46, 1.94)	1.53 (1.33, 1.84)	0.33	0.33
LDL-C (mmol/l)	2.5 (2.1, 3.0)	2.4 (1.9, 2.9)	0.34	0.29	2.6 (2.2, 2.9)	2.3 (2.0, 3.0)	0.62	0.64
Triglycerides (mmol/l)	0.54 (0.43, 0.69)	0.55 (0.41, 0.63)	0.63	0.50	0.64 (0.52, 0.69)	0.64 (0.47, 1.01)	0.94	0.46
ALT (U/l)	21.0 (15.0, 25.0)	15.0 (13.5, 18.5)	0.02	0.047	16.0 (13.0, 18.8)	18.0 (14.0, 21.0)	0.17	0.25
hs-CRP (mg/l)	0.09 (0.05, 0.28)	0.12 (0.05, 0.24)	0.78	0.40	0.36 (0.15, 0.69)	0.51 (0.20, 0.89)	0.50	0.62
Glucose (mmol/l)	4.9 (4.8, 5.2)	4.9 (4.7, 5.1)	0.21	0.19	4.8 (4.6, 5.1)	4.9 (4.6, 5.1)	0.97	0.84
Insulin (mU/l)	5.19 (4.09, 6.29)	4.37 (3.45, 5.52)	0.15	0.26	4.13 (2.79, 6.61)	5.65 (4.36, 9.03)	0.03	0.04
HOMA-IR	1.11 (0.97, 1.28)	0.96 (0.72, 1.22)	0.11	0.21	0.90 (0.60, 1.47)	1.37 (0.90, 1.91)	0.04	0.049
Body fat (%)	18.5 (14.5, 26.6)	16.9 (13.1, 28.3)	0.55		23.5 (17.6, 29.0)	23.2 (19.8, 32.1)	0.56	
Muscle mass (kg)	21.5 (20.0, 23.2)	20.6 (18.7, 22.0)	0.19		19.5 (17.2, 20.9)	17.8 (16.2, 21.2)	0.71	
Muscle mass index (kg/m^2)	12.79 (12.30, 13.61)	12.48 (12.06, 13.24)	0.35		12.07 (11.56, 12.55)	12.16 (11.33, 12.93)	0.90	

Data are presented as median (interquartile range)

*Mann-Whitney test

†Analysis of covariance, adjusted for BMI SDS, except blood pressure for height SDS and age

Table 5. Anthropometric, biochemical, and clinical characteristics of the study participants divided by early childhood weight development.

	Catch-up	No catch-up/down	Catch-down	*p	†p	**p	††p	***p	†††p
n	36	28	62						
Boys	20	18	28						
Girls	16	10	34						
At birth									
Gestational age (w)	40.1 (38.9, 40.9)	40.1 (38.8, 40.7)	39.9 (39.3, 40.5)	0.65		0.94		0.40	
Weight (g)	3010 (2425, 3480)	3590 (3220, 3858)	4640 (3978, 4803)	0.001		<0.001		<0.001	
Weight (SDS)	−0.92 (−2.32, −0.42)	−0.00 (−0.44, 0.52)	2.36 (0.85, 2.82)	<0.001		<0.001		<0.001	
Length (cm)	48.5 (47.0, 50.0)	50.0 (48.0, 51.0)	52.0 (51.0, 54.0)	0.08		<0.001		<0.001	
Length (SDS)	−0.85 (−1.98, −0.20)	−0.23 (−0.85, 0.13)	1.31 (0.30, 1.92)	0.03		<0.001		<0.001	
Head circumference (cm)	34.0 (32.9, 36.0)	35.4 (34.4, 36.8)	37.0 (35.9, 38.0)	0.02		0.001		<0.001	
Head circumference (SDS)	−0.69 (−1.61, 0.41)	0.28 (−0.68, 1.09)	1.14 (0.47, 1.95)	0.009		0.001		<0.001	
Ponderal index (kg/m^3)	2.65 (2.40, 2.77)	2.88 (2.69, 3.01)	3.07 (2.97, 3.23)	<0.001		<0.001		<0.001	
At examination									
Age (y)	6.90 (6.31, 7.71)	7.04 (6.45, 7.91)	6.99 (6.18, 7.63)	0.33		0.27		0.95	
Weight (kg)	24.8 (21.3, 31.1)	26.9 (21.5, 30.9)	26.7 (22.2, 29.8)	0.75		0.77		0.85	
BMI (SDS)	0.24 (−0.88, 1.21)	−0.11 (−0.71, 1.33)	0.29 (−0.60, 1.02)	0.94		0.79		0.82	
Height (cm)	125.1 (118.9, 130.5)	125.1 (118.5, 129.9)	125.5 (119.1, 130.0)	0.71		0.72		0.87	
Height (SDS)	0.32 (−0.43, 1.00)	−0.18 (−0.94, 0.53)	0.29 (−0.28, 0.85)	0.10		0.03		0.92	
Systolic BP (mmHg)	98 (93, 108)	98 (93, 101)	99 (95, 104)	0.64	0.53	0.29	0.11	0.72	0.88
Diastolic BP (mmHg)	61 (58, 67)	60 (57, 63)	62 (58, 67)	0.11	0.28	0.05	0.02	0.68	0.56
Cholesterol (mmol/l)	4.2 (3.7, 4.6)	4.4 (4.0, 4.7)	4.4 (3.8, 4.7)	0.25	0.31	0.97	0.93	0.25	0.26
HDL-C (mmol/l)	1.67 (1.47, 1.89)	1.76 (1.44, 2.09)	1.70 (1.47, 1.93)	0.29	0.16	0.55	0.40	0.55	0.40
LDL-C (mmol/l)	2.3 (1.9, 2.8)	2.5 (1.9, 3.0)	2.4 (2.0, 2.7)	0.43	0.39	0.90	0.72	0.34	0.17
Triglycerides (mmol/l)	0.60 (0.47, 0.70)	0.49 (0.39, 0.64)	0.59 (0.47, 0.68)	0.13	0.41	0.11	0.44	1.00	0.81
ALT (U/l)	17.0 (13.8, 22.3)	16.0 (13.3, 19.8)	17.0 (14.0, 21.3)	0.52	0.53	0.47	0.52	0.99	0.98
hs-CRP (mg/l)	0.34 (0.11, 0.80)	0.17 (0.08, 0.61)	0.21 (0.07, 0.51)	0.13	0.08	0.89	0.95	0.04	0.02
Glucose (mmol/l)	4.9 (4.7, 5.1)	4.8 (4.6, 5.1)	4.9 (4.7, 5.1)	0.45	0.71	0.42	0.56	0.97	0.92
Insulin (mU/l)	5.44 (3.73, 8.28)	4.29 (3.04, 5.60)	4.62 (3.67, 6.14)	0.10	0.06	0.41	0.38	0.15	0.06
HOMA-IR	1.20 (0.85, 1.69)	0.91 (0.65, 1.22)	1.00 (0.78, 1.31)	0.08	0.06	0.37	0.37	0.11	0.08
Body fat (%)	20.8 (14.3, 28.4)	19.1 (15.9, 31.9)	20.9 (15.1, 26.6)	0.74		0.69		0.95	
Muscle mass (kg)	19.3 (16.2, 21.5)	20.2 (16.9, 21.3)	19.7 (17.1, 21.6)	0.99		0.82		0.88	
Muscle mass index (kg/m^2)	12.27 (11.83, 13.03)	12.20 (11.63, 13.09)	12.32 (11.66, 12.93)	0.96		0.94		0.88	

Data are presented as median (interquartile range)

Mann-Whitney test between *catch-up and no catch-up/down, **catch-down and no catch-up/down, ***catch-up and catch-down growth groups

Analysis of covariance between †catch-up and no catch-up/down, ††catch-down and no catch-up/down, ††† catch-up and catch-down growth groups, adjusted for BMI SDS, except blood pressure for height SDS, sex, and age

Table 6. Logistic regression predicting likelihood of being overweight or obese in childhood.

n=126	Odds Ratio (95% CI)	p
Model 1		
Sex	1.04 (0.45–2.40)	0.92
Group		0.003
SGA group	0.07 (0.01–0.38)	0.002
LGA group	3.82 (1.05–13.88)	0.04
Δ weight SDS	2.00 (1.28–3.10)	0.002
Model 2		
Sex	0.72 (0.30–1.72)	0.46
Ponderal index Z-score	4.24 (2.05–8.76)	<0.001
Δ weight SDS	2.13 (1.40–3.25)	<0.001
(Model 1: Nagelkerke R^2=0.19, p=0.002, Model 2: Nagelkerke R^2=0.22, p<0.001)		

4.4 DISCUSSION

High birth weight and ponderal index seemed to increase the risk of childhood overweight. Otherwise, our study suggested that being born LGA does not have major effects on other cardiometabolic risk factors at prepubertal age.

The SGA children were smaller at the age of 5 to 8 years compared to the AGA and LGA children in our study. Though their body weight and height SDS had ascended from birth, they remained below those of the AGA children. Approximately 90 % of the children born SGA are known to have catch-up growth by the age of two years (49). In our study, 21/23 children (91.3%) presented with some catch-up (range 0.37–2.92 SDS) in linear growth during the first two years though catch-up of > 0.67 SDS was seen in 78.3% of the SGA children. Thus the early growth of our SGA children was similar to that reported earlier in the literature.

Our data suggest low-grade inflammation in the SGA children indicated by higher hs-CRP in the SGA than AGA and LGA groups. This finding agrees with previous reports on children (137) and young adults (138,139). High hs-CRP together with low birth weight may indicate an increased risk of cardiovascular disease in adulthood (136,170). However, our SGA children had normal weight and if they stay lean also later, this may be strongly protective from any cardiovascular events (170).

Fasting plasma lipid concentrations did not differ between the birth size groups. However, fasting plasma glucose concentrations adjusted for BMI SDS were higher in the LGA than SGA children. Also, serum insulin concentrations were significantly lower and there was a trend for lower HOMA-IR in the SGA than AGA children, which were explained by their lower BMI. However, there are other studies showing higher fasting insulin levels also in those SGA children who are thinner than their controls (148). Interestingly, HOMA-IR was also significantly lower in the LGA than AGA girls. The combination of low birth weight with early catch-up growth has been

shown to associate with reduced insulin sensitivity later in childhood in several previous studies (171,172). Also in our study, children with catch-up growth (in weight) had somewhat (though not significantly) higher HOMA-IR than the children without catch-up/down growth.

Most LGA children had catch-down growth, but they were still taller and heavier than the AGA controls though no significant difference could be found in BMI SDS. This may be due to our small sample size or by the fact that especially our AGA girls had both height and weight above 0 SD at examination. Very high birth weight (> 3 SDS) LGA children were significantly heavier at examination than those with smaller birth weight. The number of these children was very small in our study, but special attention should be paid to these very large babies in the future.

Elevated blood pressure in childhood is an established risk factor for elevated blood pressure later in adulthood (173). Our data showed no significant differences in blood pressure between the SGA, AGA and LGA groups. However, there was a trend for higher blood pressure in the LGA compared to the AGA group, and the combination of high birth weight and length associated with higher blood pressure in mid-childhood compared to the controls.

The strengths of our study include the detailed data regarding pregnancy, birth, and early childhood growth. We also studied the children thoroughly anthropometrically, by metabolic laboratory measurements, and by whole body dual-energy x-ray absorptiometry. We also selected the AGA group to represent children with their birth weight within one SDS above or below the mean. The most important weakness of our study is the relatively small sample size reducing the statistical power of the study. Also the fact that the AGA (control) children were more overweight than the Finnish children on average, had an impact on our results. The Finnish growth reference (168) is recent and we do not believe that this finding is explained by a secular trend in weight. It is most likely due to a coincidence and small study sample.

In conclusion, being born LGA seems to be a risk factor for childhood overweight, but as regards to other cardiometabolic risk factors, it does not seem to cause a major effect in mid-childhood. Children born SGA had evidence on low-grade inflammation, but their insulin sensitivity was not compromised. Since there is some evidence (including this study) that LGA children have a higher risk for overweight and its adverse effects, more research on this topic is needed.

5 BIRTH SIZE, BODY COMPOSITION, AND ADRENAL ANDROGENS AS DETERMINANTS OF BONE MINERAL DENSITY IN MID-CHILDHOOD

ABSTRACT

Background: Birth weight has an impact on adult bone mass. Higher birth weight is associated with greater bone mineral content (BMC) and children born small for gestational age (SGA) are at increased risk for impaired accrual of bone mass. Our aim was to study if the impact of birth size or early childhood growth on bone mass is visible already in mid-childhood.

Methods: We studied 49 children born large for gestational age (LGA), 56 children born appropriate for gestational age (AGA), and 23 children born SGA at 5.0–8.7 years of age. Body composition was assessed by whole-body dual-energy X-ray absorptiometry. Fasting blood samples and anthropometric data were collected.

Results: The children born SGA had lower bone mineral density (BMD) Z-score ($P<0.001$) and age- and sex-adjusted BMD ($P<0.005$) than the LGA and AGA children. Adjusted BMC, muscle mass, and body fat percentage (%BF) did not differ between the study groups. Muscle mass, BMI SD score (SDS), %BF, and serum dehydroepiandrosterone sulfate (DHEAS) concentration were the strongest predictors of high BMD in mid-childhood.

Conclusion: SGA-born children had lower BMD in mid-childhood compared to AGA- and LGA-born ones. Muscle mass or BMI SDS, %BF, and DHEAS were significant predictors of childhood BMD.

5.1 INTRODUCTION

Birth weight affects bone mass in adulthood, as higher birth weight is associated with greater bone mineral content (BMC) (64). Intrauterine growth restriction and programming are acknowledged to have an influence on cardiometabolic health in childhood and adulthood (1,10), and children born small for gestational age (SGA), especially preterm, are at increased risk for impaired accrual of adult bone mass (64,115,116). Children born SGA without catch-up growth have lower total body bone mineral density (BMD) in early adulthood compared to those with catch-up growth (117).

Almost maximal bone mass is achieved during the first two decades of life (174). Nutrition, especially calcium and vitamin D, and mechanical load affect the final accrual (98). The association between BMI and volumetric BMD in children may mostly be determined by lean mass (LM) (175), not body fat mass that has been reported to have a negative association with bone mass in childhood (176,177).

Vitamin D is essential for bone metabolism (178). Although serum 25-hydroxyvitamin D (25(OH)D) concentrations are recommended to exceed 50 nmol/l in children (100), there is evidence that low 25(OH)D status is common in children (99). The association between birth size and 25(OH)D concentrations has not been widely studied. No differences in serum 25(OH)D concentrations were detected between newborn infants born SGA, appropriate (AGA), and large for gestational age (LGA) (179), but it is unclear if the status is similar also in older children. In adults higher BMI leads to lower 25(OH)D (180) and the association of overweight with low 25(OH)D is seen also in children and adolescents (101).

The purpose of our study was to investigate whether the impact of birth size or early childhood growth on bone mass is visible already in prepubertal children.

5.2 METHODS

The study cohort included 128 Caucasian children (67 boys) born singleton at term between 2004 and 2007 in Eastern Finland (181,182). In brief, the children were enrolled according to their birth size and studied at 5.0–8.7 years of age [mean (95% CI, 6.9 (6.8–7.1) years] (Table 7). SGA was defined as gender-specific birth weight ≤ −2.0 SD score (SDS), LGA as birth weight ≥ +2.0 SDS, and AGA as birth weight and length being between −1.0 and +1.0 SDS. Anthropometric data at birth, at the age of two years, and at examination were recorded.

BMI was calculated as the body weight divided by the square of the height (kg/m^2). Sex- and age-specific SDS for weight, height and BMI were calculated according to the recently published Finnish growth reference (168). Catch-up or catch-down growth was determined as an increase or decrease in weight or height SDS more than 0.67 during the first two years of life, respectively (48).

Areal BMD and BMC, body fat percentage (%BF), and muscle mass were assessed by whole-body dual-energy X-ray absorptiometry (DXA), using the Lunar device

(Lunar Prodigy Advance; GE-Medical Systems, Madison, WI). BMD Z-scores were calculated using the recently published data by Crabtree et al. (183). LM was defined as a sum of muscle mass and BMC. Total body less head (TBLH) parameters were used for the analyses.

Fasting blood samples were collected for serum analyses of 25(OH)D, ionized calcium, dehydroepiandrosterone sulfate (DHEAS), and IGF-1 concentrations, and plasma analysis of alkaline phosphatase (ALP) concentrations. DHEAS Z-scores were created using recently published reference data on Caucasian children (184). Serum 25(OH)D concentrations were assessed using chemiluminescence immunoassay (DiaSorin Inc., Stillwater, MN). Serum ionized calcium and plasma ALP concentrations were determined with routine automated methods (ion-selective electrode and photometric (The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommendation), respectively) in the laboratory of Kuopio University Hospital. Serum DHEAS concentrations were analyzed using electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). Serum IGF-1 concentrations were determined using an ELISA kit (Mediagnost, Reutlingen, Germany).

A written informed consent was obtained from all parents and participating children aged ≥ 6 years. The study protocol was approved by the Committee on Research Ethics of the Hospital District of Northern Savo.

5.2.1 Statistical analyses

Data are presented as mean (95% CI). Analyses were conducted using SPSS statistical software (version 24; SPSS, IBM Corp., Armonk, NY). A significance level of 0.05 was used in all analyses. Skewed data were either logarithm or square root transformed before parametric analyses, and power transformed to geometric means for presentation. ANOVA was used for comparisons between the study groups on anthropometric measures and BMD Z-scores. ANCOVA was used for comparisons between the study groups on metabolic and imaging parameters. Following factors were used for adjusting ANCOVA (vary between analyses): month of the blood sampling, age, sex, BMI SDS, weight, and height. Obtained estimated means are presented in Table 1. Linear regression was used to analyze factors predicting bone mineral density. The regression coefficients are expressed as standardized betas. Each model contained sex, age, 25(OH)D, ionized calcium, ALP, DHEAS, and IGF-1, and additional predictors were: Model 1: birth weight SDS, muscle mass, %BF; Model 2: birth length SDS, muscle mass, %BF; Model 3: the change in weight SDS from birth to the age of 2 years, muscle mass, %BF; Model 4: the change in height SDS from birth to the age of 2 years, muscle mass, %BF; Model 5: birth size group, muscle mass, %BF; Model 6: birth weight SDS, BMI SDS.

5.3 RESULTS

Subject characteristics for the three birth weight groups are shown in Table 7. The SGA children had significantly lower age- and sex-adjusted BMD and BMD Z-scores compared to the LGA and AGA groups (Table 7). The boys in the whole study population had lower BMD than the girls [adjusted for age and height, P=0.028, mean (95% CI) 0.69 (0.68–0.70) and 0.70 (0.69–0.71) g/cm^2, respectively]. The boys had higher muscle mass [P=0.006, mean (95% CI) 16.8 (16.5–17.1) kg] and LM [P=0.011, mean (95% CI) 17.4 (17.0–17.7) kg] than the girls [16.1 (15.8–16.5) and 16.7 (16.4–17.1) kg, respectively]. The mean %BF of the boys was lower [P<0.001, mean (95% CI) 17.7 (16.0–19.5) than that of the girls 23.8 (21.5–26.5)] when adjusted for age and height. There were no statistical differences between the birth weight groups in BMC, muscle mass, LM, or %BF (Table 7). A significant difference was seen in plasma ALP concentrations between the groups (Table 7), but not between the sexes. The girls had significantly higher serum ionized calcium concentrations than the boys [P=0.001, mean (95% CI) 1.27 (1.26–1.28) and 1.25 (1.25–1.26) mmol/l, respectively]. A trend toward lower 25(OH)D concentrations (adjusted for the month of the blood sampling time, age, and BMI SDS) was seen in the LGA children compared to the AGA ones (Table 7, the post hoc test (Sidak correction) P=0.086).

Muscle mass or BMI SDS were the strongest weight-related predictors of higher BMD in the whole study population. Also, %BF was a significant predictor in the whole study population (Table 8). In the boys, being born SGA predicted lower BMD in mid-childhood (beta −0.27, P<0.001). Higher DHEAS concentrations predicted higher BMD in all models in the whole study population (Table 8, Figure 4) and among the boys (beta 0.22–0.26, P=0.001–0.006), but the association between BMD and DHEAS in girls remained weaker (beta 0.05–0.19, P=0.053–0.548). The other biochemical parameters (25(OH)D, ionized calcium, ALP, IGF-1) did not significantly associate with BMD (Table 8).

5.4 DISCUSSION

In this study, we evaluated the effect of birth size on BMD in prepubertal children. Being born SGA predicted lower BMD in prepubertal boys, but not in girls. Being born LGA had no significant impact on BMD. Current weight, especially muscle mass, was the strongest predictor of BMD in mid-childhood, but also birth weight SDS and serum DHEAS concentrations were positively associated with BMD.

There are not many studies on birth size and bone mass in childhood. In a recent cohort study, six-year-old SGA-born children had lower and LGA-born children higher BMC, but not BMD, compared to AGA-born ones (113). Biosca et al. showed a significant difference in age-, sex-, and weight-adjusted total body BMC between SGA (lowest mean), AGA, and LGA (highest mean) children at the age of 8 years, but when adjusted additionally for height the difference turned non-significant. No

Table 7. Anthropometric, biochemical, and imaging characteristics of the study groups.

	LGA	AGA	SGA	P
Total number (boys)	49 (25)	56 (29)	23 (13)	
At birth				
Gestational age, weeks	39.8 (39.5–40.1)	39.9 (39.6–40.2)	39.7 (39.2–40.3)	0.810
Weight (g)	4722 (4631–4812)	3561 (3484–3637)	2476 (2345–2607)	<0.001
Weight (SDS)	2.63 (2.46–2.79)	−0.02 (−0.16–0.12)	−2.39 (−2.53–−2.25)	<0.001
Length (cm)	53.0 (52.6–53.4)	50.0 (49.7–50.4)	46.2 (45.5–46.9)	<0.001
Length (SDS)	1.58 (1.40–1.76)	−0.11 (−0.24–0.03)	−2.16 (−2.43–−1.88)	<0.001
At the age of 2 years				
Weight (SDS)	0.65 (0.41–0.90)	0.16 (−0.14–0.45)	−0.95 (−1.37–−0.53)	<0.001
Height (SDS)	0.40 (0.17–0.63)	−0.05 (−0.34–0.24)	−0.98 (−1.33–−0.63)	<0.001
At examination				
Age (years)	6.89 (6.62–7.16)	7.09 (6.86–7.33)	6.65 (6.22–7.07)	0.130
Weight (kg)	27.6 (26.2–29.0)	27.5 (25.7–29.4)	21.8 (19.8–23.7)	<0.001
Weight (SDS)	0.68 (0.38–0.97)	0.39 (0.11–0.67)	−0.80 (−1.26–−0.33)	<0.001
Height (cm)	126.1 (124.0–128.3)	125.7 (123.8–127.7)	119.0 (115.6–122.4)	<0.001
Height (SDS)	0.54 (0.30–0.78)	0.20 (−0.07–0.46)	−0.64 (−1.01–−0.27)	<0.001
BMI (SDS)	0.56 (0.22–0.89)	0.36 (0.05–0.67)	−0.65 (−1.18–−0.12)	<0.001
25(OH)D (nmol/l)[a]	72.4 (68.0–77.2)	78.6 (73.9–83.7)	76.8 (70.3–83.9)	0.121
25(OH)D (nmol/l)[b]	73.5 (68.9–78.4)	80.5 (75.4–86.0)	74.5 (67.9–81.7)	0.082
Ionized calcium (mmol/l)[c]	1.27 (1.26–1.28)	1.26 (1.25–1.27)	1.27 (1.25–1.28)	0.217
ALP (U/l)[c]	230 (217–243)	251 (239–263)	228 (208–248)	0.038
DHEAS (µmol/l)[d]	0.49 (0.38–0.62)	0.67 (0.54–0.81)	0.83 (0.60–1.09)	0.028[d]
BMD (g/cm^2)[e]	0.70 (0.69–0.71)	0.70 (0.69–0.71)	0.66 (0.64–0.68)	0.002[e]
BMD (g/cm^2)[f]	0.69 (0.68–0.70)	0.70 (0.69–0.71)	0.68 (0.67–0.70)	0.242
BMD (g/cm^2)[g]	0.69 (0.68–0.70)	0.70 (0.69–0.71)	0.68 (0.67–0.70)	0.320
BMD (g/cm^2)[h]	0.70 (0.69–0.71)	0.70 (0.69–0.71)	0.68 (0.66–0.69)	0.068
BMD (Z-score)[i]	0.43 (0.13–0.74)	0.36 (0.08–0.63)	−0.65 (−1.15–−0.14)	<0.001[i]
BMC (g)[f]	589 (567–611)	599 (578–621)	561 (529–594)	0.163
Muscle mass (kg)[f]	16.7 (16.3–17.1)	16.4 (16.1–16.8)	16.0 (15.4–16.6)	0.154
Lean mass (kg)[f]	17.3 (16.9–17.7)	17.0 (16.7–17.4)	16.6 (16.0–17.2)	0.165
Body fat (%)[f]	21.0 (18.6–23.5)	21.1 (18.9–23.6)	18.6 (15.6–22.1)	0.454

Data are presented as mean (95% CI), except 25(OH)D, ionized calcium, DHEAS, BMC, and percent of body fat (geometric mean (95% CI)).

ANCOVA between the three study groups, except anthropometric data and BMD Z-score (ANOVA).

[a]Adjusted for the month of blood sampling.

[b]Adjusted for the month of blood sampling, age, and BMI SDS at examination.

[c]Adjusted for age and sex.

[d]Adjusted for age, sex, and BMI SDS.

[e]Adjusted for age and sex. The post hoc test (Sidak correction) between SGA and LGA/AGA P<0.005.

[f]Adjusted for age, sex, and height.

[g]Adjusted for age, sex, and weight.

[h]Adjusted for age, sex, and BMI.

[i]The post hoc test (Sidak correction) between SGA and LGA/AGA P<0.001.

LGA, large for gestational age; AGA, appropriate for gestational age; SGA, small for gestational age; SDS, standard deviation score; BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; DHEAS, dehydroepiandrosterone sulfate; BMD, bone mineral density; BMC, bone mineral content; ANCOVA, analysis of covariance; ANOVA, analysis of variance

Table 8. Determinants of bone mineral density (total body less head) in the whole study population at examination (linear regression analysis).

	Model 1		**Model 2**		**Model 3**		**Model 4**		**Model 5**		**Model 6**	
P (Model)	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
R square	0.78		0.78		0.79		0.79		0.79		0.70	
N	117		117		115		115		117		117	
	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*
Female sex	0.10	0.071	0.11	0.065	0.11	0.049	0.13	0.026	0.10	0.088	0.02	0.679
SGA-born	-	-	-	-	-	-	-	-	−0.10	0.069	-	-
LGA-born	-	-	-	-	-	-	-	-	−0.04	0.501	-	-
Birth weight SDS	0.04	0.504	-	-	-	-	-	-			0.12	0.045
Birth length SDS	-	-	0.03	0.583	-	-	-	-	-	-	-	-
Δ Weight SDS 0–2 years	-	-	-	-	−0.07	0.133			-	-	-	-
Δ Length SDS 0–2 years	-	-	-	-	-	-	−0.08	0.086	-	-	-	-
Age	0.18	0.009	0.18	0.009	0.17	0.012	0.17	0.013	0.17	0.011	0.53	<0.001
Muscle mass	0.61	<0.001	0.61	<0.001	0.63	<0.001	0.63	<0.001	0.60	<0.001	-	-
Body fat percentage	0.18	<0.001	0.19	<0.001	0.19	<0.001	0.18	0.001	0.18	0.001	-	-
BMI SDS (at examination)	-	-	-	-	-	-	-	-	-	-	0.40	<0.001
25(OH)D	0.04	0.400	0.04	0.427	0.05	0.299	0.05	0.310	0.02	0.637	0.08	0.175
Ionized calcium	0.00	0.947	0.00	0.936	0.00	0.968	0.00	0.943	0.02	0.756	0.00	0.969
ALP	−0.03	0.489	−0.04	0.456	−0.03	0.508	−0.03	0.554	−0.05	0.300	−0.02	0.757
DHEAS	0.17	0.002	0.17	0.002	0.19	<0.001	0.18	<0.001	0.17	0.002	0.24	<0.001
IGF-1	0.05	0.389	0.05	0.390	0.05	0.394	0.05	0.396	0.04	0.416	0.11	0.083

SGA, small for gestational age; LGA, large for gestational age; SDS, standard deviation score; BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; DHEAS, dehydroepiandrosterone sulfate; IGF-1, insulin-like growth factor 1

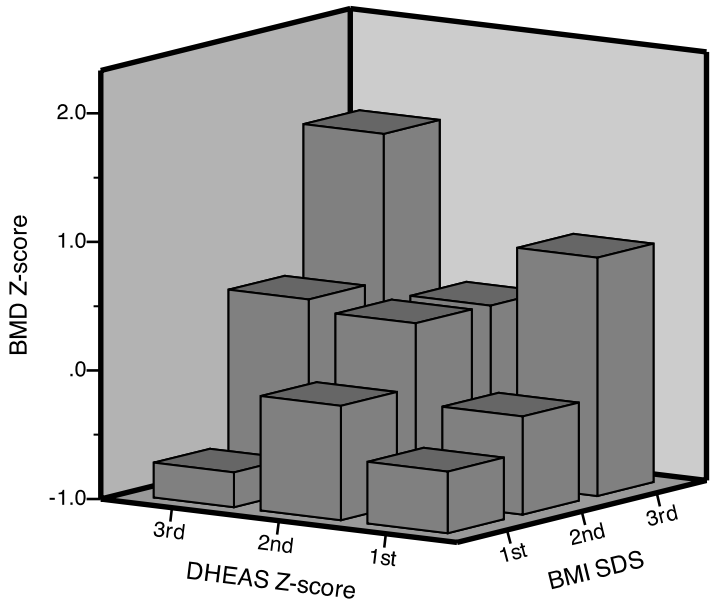

Figure 4. Bone mineral density (BMD) mean Z-score (183) by tertile groups of dehydroepiandrosterone sulfate (DHEAS) Z-score (184) and body mass index SD score (BMI SDS) (168) of 120 prepubertal children.

differences between the birth size groups were found in total body BMD (114). In a previous study on children aged 3–12 years, lumbar spine and femoral neck BMD were lower in SGA than AGA children (185). In our study, the SGA children had the lowest BMD among the study groups and lower birth weight SDS in the whole study population and being born SGA in the boys predicted lower BMD in mid-childhood. A positive association between birth weight and adult BMC, but not BMD, at the lumbar spine and hip has been reported previously (64). Children born SGA, especially preterm, are at increased risk for impaired accrual of adult bone mass (64,115,116).

Not only birth size, but also early growth has an impact on future bone mass. Catch-up growth especially during the first two years of life reduced the adverse effect of small birth size on childhood bone mass (113). SGA-born children had lower lumbar spine BMD Z-scores than AGA-born children when there was no catch-up growth (185). Children born SGA with no catch-up growth had lower total body BMD in early adulthood compared to children born SGA with catch-up growth (117). Weight at the age of 1 year had a positive association with adult bone mass (64), and catch-up growth in weight but not in height predicted higher BMD in adulthood (117). Our data did not show any significant impact of early catch-up or catch-down growth in weight or height on BMD in mid-childhood.

The association between BMI and volumetric BMD in children may mostly be mediated by LM. It has been debated if fat mass is protective against fractures in childhood as it is in adults (110). Body fat mass is reported to have both positive and negative associations with bone mass in childhood (112,176,177). Our results did not show any differences in muscle mass, LM, or %BF between the birth size groups when adjusted for age, sex, and height. In linear regression analysis both high muscle mass and %BF predicted higher BMD in the whole study population.

Vitamin D is vital for bone metabolism by regulating calcium homeostasis, but it has also a positive effect on cardiometabolism (186), as serum 25(OH)D deficiency associates with cardiovascular disease (187), diabetes (188), and hypertension (189). Interestingly, vitamin D did not have a significant impact on BMD in our study cohort. Though, the LGA-born children did have a trend toward lower 25(OH)D concentrations than the AGA-born children. Other studies have showed an association between low vitamin D concentrations and low bone density in children and adolescents (190). In this study vitamin D concentrations were adequate in all groups, which may explain our result. Serum 25(OH)D concentrations are recommended to exceed 50 nmol/l in children for health benefits (100).

DHEAS is an adrenal androgen precursor and its concentrations increase individually through childhood (118). Children with premature adrenarche had higher areal BMD than their controls, but the differences were non-significant after adjusting for height SDS (105). We demonstrated recently that LGA children had lowest and SGA children highest DHEAS concentrations in mid-childhood (182). Linear regression analysis in the current study showed that DHEAS concentrations had a positive association with BMD in the whole study population and separately in boys but not in girls. DHEAS is metabolized to a more potent androgen testosterone and to estrone (191). There is evidence that both androgens and estrogens have a positive effect on bone mass accrual (191,192). Our recent study showed a positive association between DHEAS and IGF-1 concentrations, but no differences in IGF-1 concentration were found between the birth size groups (182). IGF-1 has a significant impact on bone mineral accrual and it has been positively associated with BMC in prepubertal children (103,193). In this study IGF-1 did not have any impact on BMD. This is in agreement with a previous report showing that IGF-I is a determinant of cortical bone mass but not cortical bone density (103).

We acknowledge several limitations in this study. First, the sample size was relatively small thus affecting the power of the analyses. Second, the AGA children were heavier than the Finnish children on average at examination. This might impact on the results, and that is why our analyses were adjusted also for body size. Third, the BMD was not measured as volumetric but areal. The International Society for Clinical Densitometry (ISCD) recommends TBLH DXA measurement as one of the methods for performing BMC and areal BMD measurements in pediatric subjects (194). The strengths of our study include the detailed data from birth, early childhood growth, and examination. The data at examination included anthropometric, biochemical, and imaging data. In addition, the study participants were enrolled

strictly according to the birth size, and the AGA group was selected to represent the children close to the mean birth weight and length.

In conclusion, children born SGA had lower BMD in mid-childhood compared to children born AGA and LGA. Muscle mass or BMI SDS were the strongest weight-related predictors of childhood BMD, while %BF and serum DHEAS as a marker of adrenal androgen secretion were also associated positively with BMD.

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Disclosure

The authors declare no conflict of interest.

6 PREPUBERTAL CHILDREN BORN LARGE FOR GESTATIONAL AGE HAVE LOWER SERUM DHEAS CONCENTRATIONS THAN THOSE WITH A LOWER BIRTH WEIGHT

ABSTRACT

Background: Children born small for gestational age (SGA) have higher serum dehydroepiandrosterone sulfate (DHEAS) concentrations than children born appropriate for gestational age (AGA). The overall metabolic risk associated with birth weight is U-shaped, but it is not known if children born large for gestational age (LGA) have elevated serum DHEAS levels.

Methods: A cohort of 49 LGA, 56 AGA, and 23 SGA children were studied at 5–8 years of age. Anthropometric data at birth, at the age of two years, and at examination were recorded. Fasting blood samples were collected for serum analyses of DHEAS, insulin-like growth factor 1 (IGF-1), and insulin concentrations.

Results: The LGA children had lower serum DHEAS levels adjusted for BMI SDS (SD score) and age than the rest of the children. Lower birth weight SDS and higher weight gain during the first two years of life predicted higher serum DHEAS levels. Higher serum IGF-1 was also associated with higher prevalence of adrenarchal DHEAS levels.

Conclusion: Being born LGA associated with lower DHEAS levels, whereas small birth size and early catch-up growth predicted higher levels. This suggests that genetic or early epigenetic factors have an impact on adrenarche. IGF-1 may be a mediator in this process.

6.1 INTRODUCTION

Children born small for gestational age (SGA) have higher serum dehydroepiandrosterone sulfate (DHEAS) concentrations than children born appropriate for gestational age (AGA) (121,122). High prepubertal DHEAS levels are related to premature adrenarche (PA), defined as androgenic clinical signs appearing before the age of 8 years in girls and 9 years in boys in the presence of elevated serum DHEAS levels for age (reviewed in (118,120,195)). PA has been associated with several metabolic disturbances including hyperinsulinemia/decreased insulin sensitivity (127,128), adverse lipid profile (129), and increased fat mass and body fat percentage (105).

It is also well known, that both SGA and large for gestational age (LGA) children have an increased cardiometabolic disease risk (143,196). They may develop obesity, type 2 diabetes, the metabolic syndrome, and hypertension later in life (1,4,88,143,149,165). However, it has not been studied, if LGA children have elevated serum DHEAS levels in childhood and/or an increased prevalence of PA.

PA has been associated with increased body weight (105,124) and PA girls have accelerated statural growth already during the first two years of life (126,197). Early rapid weight gain of children with normal birth weight predicts higher DHEAS levels at the age of eight years (123).

The purpose of this study was to investigate the influence of large birth size on serum DHEAS levels and the prevalence of adrenarche in prepubertal children.

6.2 METHODS

A cohort of 128 Caucasian children (67 boys) born singleton at term between 2004 and 2007 in Eastern Finland was studied (182). In brief, the children were enrolled according to their birth size and studied at 5.0–8.7 years of age (mean (95% CI), 6.9 (6.8–7.1) years) (Table 9). SGA was defined as gender-specific birth weight ≤ −2.0 SDS (SD score), LGA as birth weight ≥ +2.0 SDS, and AGA as birth weight and length being between −1.0 and +1.0 SDS. Anthropometric data at birth, at the age of two years, and at examination were recorded (Table 9).

BMI was calculated as the body weight divided by the square of the height (kg/m^2). Sex- and age-specific SDS for height and BMI were calculated according to the recently published Finnish growth reference (168). The following BMI SDS cutoff points for overweight and obesity were used corresponding to BMI of 25 and 30 at the age of 18 years: for boys 0.78 and 1.70 and for girls 1.16 and 2.11, respectively (168). Catch-up or catch-down growth was defined as an increase or decrease in weight SDS more than 0.67 during the first two years of life, respectively (48).

Clinical signs of adrenarche (adult type body odor, oily hair, acne or comedones, appearance of pubic and axillary hair) and pubertal status (breast development in girls, testicular size in boys, and pubic hair in both sexes) were recorded. Children

were defined prepubertal when girls had no palpable breast tissue or boys had a testicular volume ≤ 3 mL.

Fasting blood samples were collected for serum analyses of DHEAS, insulin-like growth factor 1 (IGF-1), and insulin concentrations. DHEAS level of 1.0 μmol/L (37 μg/dL) was referred as a cutoff for biochemical adrenarche (198,199). Serum DHEAS and insulin concentrations were analyzed using electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). Serum IGF-1 concentrations were determined using an ELISA kit (Mediagnost, Reutlingen, Germany).

A written informed consent was obtained from all the parents and from participating children aged ≥ 6 years. The study protocol was approved by the Committee on Research Ethics of the Hospital District of Northern Savo.

6.2.1 Statistical analyses

Data are presented as mean (95 % CI). Analyses were performed using SPSS statistical software (version 22; SPSS, IBM Corp., Armonk, NY). A significance level of 0.05 was used in all analyses. ANOVA was used for comparisons between groups on anthropometric measures. Differences in serum DHEAS, IGF-1 and insulin concentrations between the three groups were analyzed by the BMI SDS and age -adjusted ANCOVA and predictors of serum DHEAS levels (model 1: weight SDS at birth; model 2: the change in weight SDS from birth to the age of 2 years; both models: BMI SDS at examination, serum IGF-1, serum insulin, and age at examination) were explored by linear regression analysis. Skewed data were either logarithm or square root transformed before parametric analyses. Obtained estimated means (BMI SDS and age -adjusted) were power transformed to geometric means for presentation. Association of insulin or IGF-1 levels (tertiles) with the absence/presence of biochemical adrenarche (blood samples obtained at the same age) [DHEAS < 37 μg/dL (1.0 μmol/L); DHEAS ≥ 37 μg/dL (1.0 μmol/L)] were analyzed using the χ^2 test.

6.3 RESULTS

All girls had prepubertal breast stage (Tanner B1), all boys prepubertal genital stage (Tanner G1), and no child had pubic hair. Nine girls (prevalence 14.8%) and 2 boys (3.0%) had some clinical sign of PA (6 girls and 2 boys adult type body odor, 2 girls oily hair and 1 comedones). Thirty-two children [25%, 17 boys; 8 LGA, 18 AGA, and 6 SGA (P=0.17, the $\chi 2$ test between the groups)] had DHEAS level ≥ 37 μg/dL (1.0 μmol/L). Three girls and 1 boy (3%) had both clinical signs of PA and DHEAS level ≥ 37 μg/dL (1.0 μmol/L).

Serum DHEAS levels did not differ between the sexes (P=0.50). There was a significant difference in serum DHEAS levels between the three study groups (Table 9). The post hoc test (Sidak correction) showed significantly lower serum DHEAS levels in the LGA than SGA group (Table 9). A significant difference was also found

Table 9. Anthropometric and biochemical characteristics of the study groups.

	LGA	AGA	SGA	P
Total number (boys)	49 (25)	56 (29)	23 (13)	
At birth				
Gestational age, weeks	39.8 (39.5–40.1)	39.9 (39.6–40.2)	39.7 (39.2–40.3)	0.81
Weight, g	4722 (4631–4812)	3561 (3484–3637)	2476 (2345–2607)	<0.001
Weight, SDS	2.63 (2.46–2.79)	−0.02 (−0.16–0.12)	−2.39 (−2.53–−2.25)	<0.001
Length, cm	53.0 (52.6–53.4)	50.0 (49.7–50.4)	46.2 (45.5–46.9)	<0.001
Length, SDS	1.58 (1.40–1.76)	−0.11 (−0.24–0.03)	−2.16 (−2.43–−1.88)	<0.001
At the age of 2 years				
Weight, SDS	0.65 (0.41–0.90)	0.16 (−0.14–0.45)	−0.95 (−1.37–−0.53)	<0.001*
Height, SDS	0.40 (0.17–0.63)	−0.05 (−0.34 –0.24)	−0.98 (−1.33–−0.63)	<0.001*
At examination				
Age, years	6.89 (6.62–7.16)	7.09 (6.86–7.33)	6.65 (6.22–7.07)	0.13
Weight, kg	27.6 (26.2–29.0)	27.5 (25.7–29.4)	21.8 (19.8–23.7)	<0.001
Weight, SDS	0.68 (0.38–0.97)	0.39 (0.11–0.67)	−0.80 (−1.26–−0.33)	<0.001
Height, cm	126.1 (124.0–128.3)	125.7 (123.8–127.7)	119.0 (115.6–122.4)	<0.001
Height, SDS	0.54 (0.30–0.78)	0.20 (−0.07–0.46)	−0.64 (−1.01–−0.27)	<0.001
BMI, SDS	0.56 (0.22–0.89)	0.36 (0.05–0.67)	−0.65 (−1.18–−0.12)	<0.001
DHEAS, µg/dL	18.3 (14.1–23.0)	24.7 (20.2–29.8)	30.5 (22.2–40.2)	0.028**
IGF-1, ng/mL	196.3 (179.1–214.8)	198.6 (182.4–216.3)	190.1 (165.2–218.8)	0.87
Insulin, µIU/mL	4.47 (3.92–5.09)	4.79 (4.24–5.40)	4.84 (3.94–5.93)	0.70

Data are presented as mean (95% CI), except DHEAS, IGF-1, and insulin (geometric mean (95% CI)).

ANOVA between the three study groups, except DHEAS, IGF-1, and insulin (BMI SDS and age -adjusted ANCOVA).

* The post hoc test (Sidak correction) P<0.001 between SGA and AGA / LGA groups; P<0.05 between LGA and AGA groups.

**The post hoc test (Sidak correction) P=0.041 between the LGA and SGA groups.

in BMI SDS and age -adjusted serum DHEAS levels between the LGA and the rest of the study population (P=0.015; mean (95% CI) 18.4 (14.2–23.1); 26.2 (22.2–30.6), respectively). A trend toward lower DHEAS levels adjusted for BMI SDS and age was seen in the LGA children compared to the AGA children but the difference was not statistically significant (P=0.06) (Table 9). There were no significant differences in serum IGF-1 and insulin concentrations between the study groups (Table 9).

Lower birth weight SDS (model 9) and higher weight gain during the first two years of life (model 2) predicted higher serum DHEAS concentrations in linear regression analyses (Table 10). The same trend was also seen when the children were arranged by their birth size or weight gain during the first two years of life and their weight SDS at examination (Figure 5). A significant association was found between biochemical adrenarche and IGF-1 (P=0.007) but not insulin levels (P=0.57) (Table 11).

Table 10. Determinants of serum DHEAS levels (linear regression analysis) in the whole study population at examination. Adjusted for age at examination.

	Independent variables	**Standardized B**	***P* (variables)**	***P* (model)**	**R Square**
Model 1	Weight SDS (at birth)	−0.27	0.002	<0.001	0.27
n=125	BMI SDS	0.11	0.22		
	Serum IGF-1	0.16	0.09		
	Serum insulin	0.03	0.73		
Model 2	Δ Weight SDS 0–2 years	0.26	0.001	<0.001	0.28
n=123	BMI SDS	0.02	0.78		
	Serum IGF-1	0.14	0.12		
	Serum insulin	0.03	0.78		

Table 11. Association of biochemical adrenarche with IGF-1 and insulin levels at examination.

Biochemical adrenarche	**IGF-1 tertiles**					
	1		2		3	
	n	%	n	%	n	%
Yes	7	21.9	7	21.9	18	56.3
No	34	36.6	35	37.6	24	25.8
	Insulin tertiles					
	1		2		3	
	n	%	n	%	n	%
Yes	9	28.1	10	31.3	13	40.6
No	33	34.7	33	34.7	29	30.5

The χ^2 test between IGF-1 tertiles P=0.007, and insulin tertiles P=0.57.

Biochemical adrenarche: serum DHEAS ≥ 37 µg/dL (≥ 1 µmol/L).

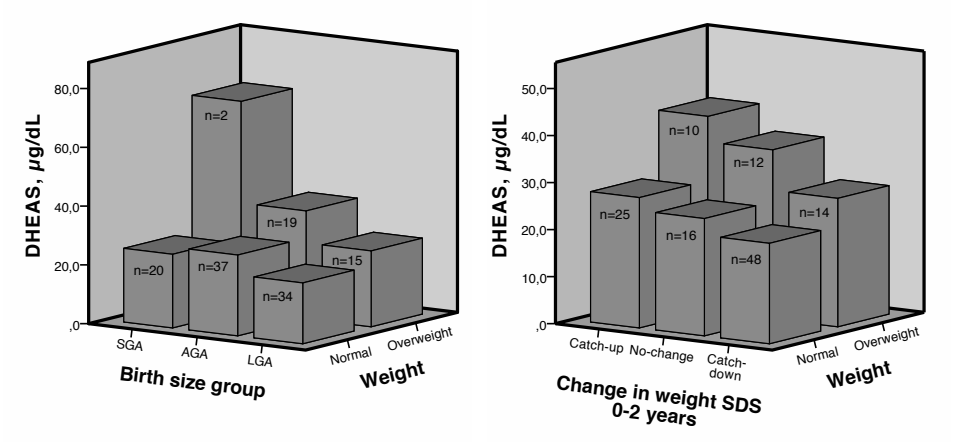

Figure 5. DHEAS levels (mean) at prepuberty, by birth size/early childhood weight development and current weight. Normal and overweight defined as BMI SDS corresponding to adult BMI < 25 and ≥ 25, respectively (168).

6.4 DISCUSSION

As far as we know, there are no previously published reports on DHEAS levels or early adrenarche in LGA-born children. In this study the prepubertal LGA children had lower serum DHEAS levels compared to the SGA children or SGA and AGA children combined. Low birth weight SDS and early weight SDS change (0–2 years) were associated with DHEAS levels, and the prevalence of biochemical adrenarche was highest among the children with the highest IGF-1 levels. There was no difference in the DHEAS levels between the sexes.

Previous studies have shown an association between low birth size and increased serum DHEAS levels in later childhood (121,122,200). In addition, the ALSPAC study with a large population-based sample of children showed that the negative relationship between birth weight and later prepubertal serum DHEAS levels is continuous throughout the normal birth weight range (123). Our study shows that the trend towards low prepubertal DHEAS levels extends to the LGA-born children. Consequently, LGA children are not prone to develop PA suggested to increase later metabolic risk (105,127,128,201). Adrenal androgen levels do not have the U-shaped association with birth size as some other metabolic risks and outcomes may have (143,196). As no follow-up studies exist, the later significance of lower DHEAS levels in LGA children remains unknown.

Metabolic programming during fetal (e.g. intrauterine growth restriction) and early postnatal development, as well as increased IGF-1 and insulin levels in SGA-born children with catch-up growth, have been linked to increased prepubertal adrenal androgen secretion (123). These factors could at least partly explain the negative association between birth weight and later serum DHEAS levels as the majority of the SGA- and LGA-born children experience catch-up and catch-down

growth, respectively. This might indicate a greater impact of the early childhood growth pattern than the birth size itself on later adrenal androgen production and its consequences.

Our data did not show difference in the DHEAS levels between the sexes. In a previous study girls had higher DHEAS than boys, but in that study DHEAS was not adjusted for BMI or age (202). When these factors are taken into account, no difference in serum DHEAS between the sexes is expected (199).

In our study the SGA and AGA children did not have a significant difference in their DHEAS levels, but birth weight was negatively associated with prepubertal DHEAS levels in the whole study population supporting the previously described association (121,122). One reason for the relatively high DHEAS levels in our AGA children may be their BMI SDS being above the population mean (182) at the examination. Early catch-up growth and weight in childhood seem to have a strong impact on DHEAS levels in prepuberty (123,203), which was noticeable also in our study.

No child in this study had pubic or axillary hair, which is permissible as the appearance of the clinical signs of PA is related to the level of androgen effect (ascending order: adult-type body odor, oily hair, comedones, pubic or axillary hair) (199), although variation may occur due to ethnicity. The prevalence of children with some clinical sign of PA and of girls with both clinical signs of PA and DHEAS level ≥ 37 μg/dL was lower in our study than in the previous Finnish study of larger population (198). Participants being younger in our study could explain the difference. In addition, the proportion of children with biochemical adrenarche was higher in our study compared to data of Mäntyselkä et al. (198). Increased body weight is associated with PA (105,124), and the LGA and AGA groups were somewhat heavier in our study than the children in the previous study (198). Our findings are thus well coherent with previously published Finnish data, although some differences could originate from the relatively small sample size in the current study.

Increased IGF-1 concentrations were previously demonstrated in prepubertal girls (126,204) and boys (202) with PA compared to age-matched controls. IGF-1 stimulates steroidogenesis in adrenocortical cells and its serum concentrations increase with overweight and hyperinsulinism (reviewed in (118,195)). In our study, linear regression analysis showed a trend between serum IGF-1 and DHEAS levels, and the highest prevalence of biochemical adrenarche was detected in the children with the highest IGF-1 serum levels. Hyperinsulinism has also been suggested to contribute to PA (118). However, our study showed no association of insulin with DHEAS. In our previous study, prepubertal girls with PA had slightly higher oral glucose tolerance test-stimulated serum insulin concentrations than control girls, but basal insulin concentrations were similar (127).

The strengths of this study include the detailed physical examination including the clinical signs of adrenarche and the pubertal stage. In addition, the study participants were enrolled strictly according to the birth size and the AGA group was

selected to represent the children close to the mean birth weight and length. Furthermore, to reduce the influence of confounding factors we adjusted our analyses for BMI SDS and age. The main limitation of this study is the relatively small sample size, affecting the statistical power of the study.

In conclusion, being born LGA associated with lower prepubertal DHEAS levels, whereas small birth size and early catch-up growth predicted increased DHEAS levels. This suggests that genetic or early epigenetic factors have an impact on adrenal androgen secretion and adrenarche. IGF-1 may be a mediator in this process.

7 PLASMA IL-1 RECEPTOR ANTAGONIST CONCENTRATION HAS AN INVERSE ASSOCIATION WITH BIRTH WEIGHT IN PREPUBERTAL CHILDREN

ABSTRACT

Context: Birth size has an impact on later cardiometabolic risk that is strongly related to low-grade inflammation.

Objective: To evaluate plasma IL-1 receptor antagonist (IL-1ra) concentrations in relation to birth size and cardiometabolic and inflammatory markers in prepubertal children.

Design: A cohort study. Anthropometric data were recorded. Fasting blood samples were collected for plasma analyses of IL-1ra, alanine transaminase, total cholesterol, high- and low-density lipoprotein cholesterols, triglyceride, glucose, and serum analyses of 25-hydroxyvitamin D and high-sensitivity C-reactive protein (hs-CRP) concentrations.

Participants: Forty-nine large (LGA), 56 appropriate (AGA), and 23 small for gestational age (SGA) children at 5–8 years of age were examined.

Main Outcome Measures: Differences in IL-1ra concentrations between the birth size groups and associations between IL-1ra and other metabolic markers were assessed.

Results: BMI SDS -adjusted plasma IL-1ra concentrations were highest in the SGA- and lowest in the LGA-born children ($P=0.015$). Age- and sex- adjusted IL-1ra concentrations had strongest associations with BMI SDS ($P<0.001$) and hs-CRP ($P<0.001$, also when further adjusted for BMI SDS).

Conclusions: Prepubertal children born SGA had highest and those born LGA lowest IL-1ra concentrations in this study cohort. Most associations found between IL-1ra and the studied metabolic parameters were weight-related, but the association with hs-CRP remained strong after adjustment for BMI. It seems that at prepuberty, SGA children have a stronger inflammatory state than LGA children and may thus be at a greater risk for later metabolic disturbances.

7.1 INTRODUCTION

Birth size affects the cardiovascular risk in adulthood through prenatal programming (the leading hypothesis), and indicators of this risk can already be seen in childhood and adolescence (16). Children born small or large for gestational age (SGA and LGA, respectively) have an increased risk for childhood obesity, adverse serum glucose and lipid concentrations, elevated blood pressure, and metabolic syndrome (1,149,165). Also, early growth during first years of life has been suggested to impact future metabolism and cardiometabolic risk (13,14,16).

Chronic low-grade inflammation has a strong relationship with atherogenic changes leading to later cardiovascular disease (CVD) (131). IL-1β, one of the proinflammatory cytokines of the IL-1 family, contributes to the risk of atherosclerosis and cardiovascular events (205). The use of IL-1β analysis in clinical assessment is difficult, because the circulating concentrations of IL-1β are extremely low (206). Instead, an anti-inflammatory cytokine IL-1 receptor antagonist (IL-1ra) expressed in white adipose tissue (207) is a counter-regulator for IL-1β (208) and its circulating concentrations can be measured accurately (206). Elevated IL-1ra concentrations reflect higher IL-1β secretion (209) and have been suggested for a marker of an inflammatory process (210). Though IL-1ra is anti-inflammatory by itself, its elevated concentrations are associated with obesity in children (211) and with obesity (212), insulin resistance (213) and an increased risk of type 2 diabetes (T2D) (209) in adults, increasing the overall CVD risk as reported in a recent meta-analysis (208).

Several studies suggest that low birth size increases low-grade inflammation in children and young adults (137,139,182), but it has not been examined how birth size affects circulating IL-1ra concentrations in children. Our aim was to investigate if plasma IL-1ra concentrations differ between birth size groups (SGA, LGA, AGA) and how they associate with other metabolic parameters reflecting later cardiovascular risk in prepubertal children.

7.2 METHODS

We examined a cross-sectional cohort of 128 Caucasian children (67 boys) born singleton at term between 2004 and 2007 in Eastern Finland (182). In brief, the children were enrolled according to their birth size from the Kuopio University Hospital birth registry and all SGA and LGA children born between those years, and randomly selected sex- and age-matched AGA controls were invited to participate. The children were studied at 5.0–8.7 years of age [mean (95% confidence interval (CI)), 6.9 (6.8–7.1) years] (Table 1). SGA was defined as gender-specific birth weight ≤ −2.0 SD score (SDS), LGA as birth weight ≥ +2.0 SDS, and AGA as birth weight and length being between −1.0 and +1.0 SDS. Anthropometric data at birth, at the age of two years, and at examination were recorded. The enrolled children did not have any chronic diseases other than atopic eczema, allergic rhinitis, or mild asthma requiring

no continuous medication, or systemic medication that might have affected a possible inflammatory state. No child in this study had been previously treated with growth hormone.

Body mass index (BMI) was calculated as the body weight divided by the square of the height (kg/m^2). Sex- and age-specific SDS for weight, height and BMI were calculated according to the recently published Finnish growth reference (168). Catch-up or catch-down growth was determined as an increase or decrease in weight SDS more than 0.67 during the first two years of life, respectively (48). Waist circumference was measured midway between the top of the iliac crest and the lowest rib at the end of a normal expiration using a flexible metal tape to the nearest 1 mm. Waist-to-height ratio (WHtR) was calculated as the waist circumference (cm) divided by the height (cm). Atherogenic index (AI) that has been validated also for use in children (214) was calculated as plasma triglyceride (TG) concentrations divided by high-density lipoprotein cholesterol (HDL-C) concentrations. Insulin resistance was determined by using the homeostasis model assessment for insulin resistance (HOMA-IR) as (insulin, mU/L × glucose, mmol/L)/22.5 (169).

Fasting blood samples were collected for plasma and serum analyses. Plasma IL-1ra concentrations were analyzed using enzyme-linked immuno-sorbent assay (R&D Systems, Minneapolis, MN). The intra- and inter-assay coefficients of variation (CVs) were 3.59% and 5.68%, respectively. Plasma glucose concentrations were determined by the hexokinase method (Roche Diagnostics GmbH, Mannheim, Germany). Plasma concentrations of total cholesterol and TG were analyzed with colorimetric enzymatic assays, and those of HDL-C and low-density lipoprotein cholesterol (LDL-C) with homogeneous colorimetric enzymatic assays (both Roche Diagnostics GmbH). The kinetic method according to the International Federation of Clinical Chemistry was used for obtaining plasma alanine transaminase (ALT) concentrations (Roche Diagnostics GmbH). Serum 25-hydroxyvitamin D (25(OH)D) concentrations were assessed using chemiluminescence immunoassay (LIAISON® 25 OH Vitamin D TOTAL Assay, DiaSorin Inc., Stillwater, MN) with an automatic immunoanalyzer (LIAISON®, DiaSorin S.p.A., Saluggia, Italy). Total variation (including intra- and inter-assay variation) was 8.2–11.0% in the concentration range of 21–123 nmol/L. Serum high-sensitivity C-reactive protein (hs-CRP) was measured by immunoturbidimetric assay (Roche Diagnostics GmbH).

Blood pressure was measured three times in a supine position using mercury sphygmomanometer and a proper-sized cuff on the right arm after a 15-min rest and with intervals of 1–2 min between the measurements. The mean of the lowest two values was recorded.

To eliminate the impact of acute infections on hs-CRP concentrations, values exceeding 10 mg/L (1 girl) and children reported to have any acute infection 0–14 days before the examination day (n=9; 4 boys) were excluded from the hs-CRP analysis.

A written informed consent was obtained from all parents and participating children aged ≥ 6 years. The study protocol was approved by the Committee on Research Ethics of the Hospital District of Northern Savo.

7.2.1 Statistical analyses

Data are presented as mean (95% CI). Analyses were conducted using SPSS statistical software (version 24; SPSS, IBM Corp., Armonk, NY). A significance level of 0.05 was used in all analyses. Skewed data were either logarithm or square-root transformed before parametric analyses, and power transformed to geometric means for presentation. ANOVA was used for comparisons between the study groups on anthropometric measures. Analysis of covariance (ANCOVA) was used for comparisons between the study groups on IL-1ra and hs-CRP concentrations. The obtained estimated means of IL-1ra concentrations are presented in Table 1. Sidak correction was used for post hoc tests. General linear model (GLM) was used for estimating associations of IL-1ra concentrations with BMI SDS, WHtR, the weight development before and after two years of age, total cholesterol, HDL-C, LDL-C, TG, AI, ALT, glucose, insulin, HOMA-IR, hs-CRP, 25(OH)D, and systolic and diastolic blood pressures (SBP and DBP, respectively). In GLM analyses the results were reported as standardized beta-values and all P-values were corrected using the false discovery rate (FDR) method. The correlation between BMI SDS and WHtR was estimated by the Pearson correlation coefficient.

7.3 RESULTS

The SGA children had highest and the LGA children lowest age-, sex-, and BMI SDS-adjusted plasma IL-1ra concentrations, but when adjusted for age, sex, and WHtR the differences turned non-significant (Table 12). The correlation coefficients (r) between BMI SDS and WHtR ($P<0.001$) were 0.81 in all children, 0.83 in LGA, 0.85 in AGA, and 0.84 in SGA children. When adjusted for age and sex, IL-1ra concentrations had strong associations with BMI SDS and hs-CRP concentrations, and the association with hs-CRP concentrations remained strong after further adjustment for BMI SDS (Table 13). Age- and sex-adjusted IL-1ra concentrations associated positively with the weight development (changes in weight SDS) both before and after two years of age. IL-1ra concentrations adjusted for age and sex had negative associations with HDL-C and 25(OH)D concentrations and positive associations with TG and insulin concentrations, but these associations turned non-significant when adjusted also for BMI SDS (Table 13). Both AI and HOMA-IR associated positively with IL-1ra concentrations when adjusted for age and sex but not when adjusted further for BMI SDS (Table 13). The other measured biochemical parameters or blood pressure did not associate with IL-1ra concentrations.

We also looked at associations of IL-1ra with metabolic risk factors separately in three birth weight groups. In the SGA group, no significant associations were found.

Table 12. Anthropometric and biochemical characteristics of the study groups.

	LGA	AGA	SGA	P
Total number (boys)	49 (25)	56 (29)	23 (13)	
At birth				
Gestational age, weeks	39.8 (39.5–40.1)	39.9 (39.6–40.2)	39.7 (39.2–40.3)	0.81
Weight (g)	4722 (4631–4812)	3561 (3484–3637)	2476 (2345–2607)	<0.001
Weight (SDS)	2.63 (2.46–2.79)	−0.02 (−0.16–0.12)	−2.39 (−2.53–−2.25)	<0.001
Length (cm)	53.0 (52.6–53.4)	50.0 (49.7–50.4)	46.2 (45.5–46.9)	<0.001
Length (SDS)	1.58 (1.40–1.76)	−0.11 (−0.24–0.03)	−2.16 (−2.43–−1.88)	<0.001
At the age of 2 years				
Weight (SDS)	0.65 (0.41–0.90)	0.16 (−0.14–0.45)	−0.95 (−1.37–−0.53)	<0.001
Height (SDS)	0.40 (0.17–0.63)	−0.05 (−0.34–0.24)	−0.98 (−1.33–−0.63)	<0.001
At examination				
Age (years)	6.89 (6.62–7.16)	7.09 (6.86–7.33)	6.65 (6.22–7.07)	0.13
Weight (kg)	27.6 (26.2–29.0)	27.5 (25.7–29.4)	21.8 (19.8–23.7)	<0.001
Weight (SDS)	0.68 (0.38–0.97)	0.39 (0.11–0.67)	−0.80 (−1.26–−0.33)	<0.001
Height (cm)	126.1 (124.0–128.3)	125.7 (123.8–127.7)	119.0 (115.6–122.4)	<0.001
Height (SDS)	0.54 (0.30–0.78)	0.20 (−0.07–0.46)	−0.64 (−1.01–−0.27)	<0.001
Waist-to-height ratio	0.46 (0.45–0.47)	0.46 (0.45–0.48)	0.45 (0.43–0.46)	0.469
BMI (SDS)	0.56 (0.22–0.89)	0.36 (0.05–0.67)	−0.65 (−1.18–−0.12)	<0.001
IL-1ra (pg/mL)[a]	217.9 (196.3–241.8)	253.3 (229.9–279.2)	290.8 (246.0–343.8)	0.011[b]
IL-1ra (pg/mL)[c]	230.5 (209.3–253.9)	252.7 (231.0–276.5)	260.7 (224.8–302.4)	0.257
hs-CRP (mg/L)[a]	0.19 (0.14–0.26)	0.22 (0.17–0.30)	0.71 (0.44–1.15)	<0.001[d]

Data are presented as mean (95% CI), except IL-1ra and hs-CRP (geometric mean (95% CI)).

ANOVA between the three study groups, except IL-1ra and hs-CRP (ANCOVA).

[a]Adjusted for age, sex, and BMI SDS at examination.

[b]Post hoc test (Sidak correction) between the SGA and LGA groups P=0.015.

[c]Adjusted for age, sex, and waist-to-height ratio.

[d]Post hoc test (Sidak correction) between the SGA and LGA/AGA groups P<0.001.

LGA, large for gestational age; AGA, appropriate for gestational age; SGA, small for gestational age; SDS, SD score; BMI, body mass index; IL-1ra, IL-1 receptor antagonist; hs-CRP, high-sensitivity C-reactive protein

Table 13. Associations between plasma IL-1 receptor antagonist concentrations and metabolic variables.

	n	beta[a]	P[b]	beta[c]	P[d]
BMI SDS	126	0.50	<0.001[e,f]	n/a	n/a
WHtR	125	0.63	<0.001[e,f]	n/a	n/a
Δ weight SDS (0–2 yr)	124	0.19	0.047	n/a	n/a
Δ weight SDS (2 yr –)	124	0.23	0.024	n/a	n/a
Cholesterol	126	0.08	0.466	0.14	0.413
HDL-C	126	−0.23	0.022[f]	−0.12	0.447
LDL-C	126	0.18	0.066[f]	0.20	0.197
TG	126	0.25	0.018[f]	0.19	0.181
AI	126	0.28	0.007[f]	0.19	0.257
ALT	126	0.14	0.167	0.05	0.840
Glucose	125	−0.04	0.678	0.02	0.857
Insulin	126	0.24	0.019[f]	0.04	0.769
HOMA-IR	125	0.22	0.022[f]	0.04	0.706
hs-CRP	116	0.51	<0.001[e,f]	0.43	<0.001
25(OH)D	120	−0.24	0.021	−0.24	0.135
SBP	124	−0.01	0.869	−0.09	0.591
DBP	124	−0.03	0.433	−0.04	0.516

[a]General linear model adjusted for sex and age.

[b]False discovery rate -corrected P-values for general linear model adjusted for sex and age.

[c]General linear model adjusted for sex, age, and BMI SDS at examination.

[d]False discovery rate -corrected P-values for general linear model adjusted for sex, age, and BMI SDS at examination.

[e]The association is significant in the LGA group.

[f]The association is significant in the AGA group.

BMI SDS, body mass index SD score; n/a, not applicable; WHtR, weight-to-height ratio; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; AI, atherogenic index; ALT, alanine transaminase; HOMA-IR, homeostasis model assessment for insulin resistance; hs-CRP, high-sensitivity C-reactive protein; 25(OH)D, 25-hydroxyvitamin D; SBP, systolic blood pressure; DBP, diastolic blood pressure

In the AGA and LGA groups, age- and sex-adjusted IL-1ra concentrations were associated with BMI SDS (LGA: beta=0.49, P=0.004; AGA: beta=0.71, P<0.001), WHtR (LGA: beta=0.68, P<0.001; AGA: beta=0.69, P<0.001), and hs-CRP (LGA: beta=0.58, P=0.003; AGA: beta=0.53, P<0.001). The association of IL-1ra with hs-CRP was not significant in any separate birth size group when adjusted further for BMI SDS (Table 13).

GLM analyses were also conducted between the groups formed by early weight development [catch-up n=34 (19 boys), no change n=28 (18 boys), and catch-down n=62 (28 boys)]. IL-1ra concentrations associated with hs-CRP concentrations when adjusted for both age and sex, and further for BMI SDS in the catch-up and catch-down groups (beta=0.59/0.54, P<0.001 and beta=0.55/0.40, P<0.001/P=0.015,

respectively), but not in the no change group. IL-1ra concentrations had a significant association with BMI SDS (beta=0.45–0.57) and WHtR (beta=0.60–0.71) in all these groups.

7.4 DISCUSSION

We found a clear association between birth size and plasma IL-1ra concentrations in prepubertal children: the children born SGA had the highest and the children born LGA the lowest BMI SDS-adjusted concentrations. IL-1ra concentrations associated strongest with BMI SDS and hs-CRP.

Previous studies have shown the association between elevated IL-1ra concentrations and childhood obesity (211). This study confirms this, as BMI SDS had a strong positive association with IL-1ra concentrations. To our knowledge, this is the first study to compare birth size and plasma IL-1ra concentrations in mid-childhood. Interestingly, the children born SGA had the highest and the children born LGA the lowest IL-1ra concentrations even though BMI SDS appeared the opposite. This suggests that prepubertal SGA children have low-grade inflammation independent of their current weight. Other associations of IL-1ra concentrations were also strongly weight-related, hence the majority of these turned non-significant after further adjustment for BMI SDS. When IL-1ra concentrations were adjusted for WHtR the differences between the study groups were non-significant. WHtR is age-dependent in prepubertal children, which could explain partly the differences in results after BMI SDS and WHtR adjustments (215).

Chronic low-grade inflammation is associated with obesity and CVD risk factors in youth (216). Though being anti-inflammatory itself, endogenous IL-1ra concentrations reflect an ongoing inflammatory state (217). The association between plasma IL-1ra concentrations and hs-CRP was clear in our current study. In a recent study, Bugge et al. did not find any correlation between CRP and IL-1ra concentrations in adolescents (216), but in adults the positive correlation has been reported (218). Also, the correlation between IL-1ra concentrations and the CVD risk factor profile remained non-significant in Danish adolescents, even though other inflammation markers had significant associations with the profile (216).

It is unclear if elevated IL-1ra concentrations only indicate higher IL-1 activity or if they also suppress the inflammatory response by reducing IL-1 signaling (217). Increased IL-1ra concentrations have been suggested to precede T2D (209), even if the experimental use of recombinant IL-1ra to block IL-1 receptor type 1 and decrease IL-1 bioactivity has been shown to protect β-cells from glucose-induced apoptosis and improve IL-1β-mediated impaired β-cell function in human cells (219). Both HOMA-IR and insulin concentrations had positive associations with IL-1ra concentrations in our study when adjusted for age and sex but not when further adjusted for BMI SDS.

An adverse lipid profile is a risk factor for future CVD (152). AI is a simple tool for detecting the risk of the metabolic syndrome and cardiovascular disease in adults

(220) and children (214,221). In a previous study, non-obese LGA-born children had higher AIs compared to non-obese AGA-born children (222). In this study, we demonstrated a positive but weight-related association between IL-1ra and AI. Also, TG associated positively and HDL-C negatively with IL-1ra concentrations when examined independently. These findings may suggest a relationship between an adverse lipid profile and low-grade inflammation as reviewed previously (223).

The strengths of this study include detailed anthropometric data since birth allowing to determine the early weight development. The study participants were enrolled strictly according to the birth size, and examined thoroughly before puberty. The major weakness is the relatively small sample size affecting the power in the analyses. We have adjusted the analyses for the most important confounding factors to reduce that effect. Another limitation of this study is that the nutritional status of the children was not described. There is a possibility of some bias in the study population, which we tried to minimize by recruiting only children who were not followed or did not require any special medical attention at the hospital. Accordingly, the invitations were sent to home, not given at the hospital.

Even though IL-1ra is only one indicator of low-grade inflammation and future CVD risk, our findings suggest that the relationship between birth size and CVD risk would be rather linear than U-shaped as previously suggested (143). Accordingly, we have also demonstrated in this study population that LGA children had lower serum dehydroepiandrosterone sulfate (DHEAS) concentrations than SGA and AGA children (181), and along with body weight, DHEAS was positively associated with bone mineral density (224). Fetal metabolic programming has been hypothesized to contribute to the increased CVD risk in SGA children. The adverse effects of large birth size in later life could be partly mediated by overweight that LGA children are predisposed to, rather than by the birth size itself. LGA children may have a combined environmental and genetic susceptibility to metabolic disturbances which do not emerge if the children do not become significantly overweight. Our finding is preliminary and warrants additional studies in larger study populations to confirm the significance of IL-1ra as a CVD risk marker in children.

In conclusion, the children born SGA had the highest and those born LGA the lowest IL-1ra concentrations in this study cohort. Most associations found between IL-1ra and the studied metabolic parameters were weight-related, but the relationship between IL-1ra and hs-CRP remained strong after adjustment for BMI SDS. Our results indicate that at prepuberty, SGA-born children have a stronger inflammatory state than LGA-born ones and may thus be at a greater risk for later metabolic disturbances.

8 GENERAL DISCUSSION

8.1 SUMMARY

The main finding of this study was that the cardiometabolic outcomes, such as inflammatory markers, detected in the SGA children were mostly adverse, but in the LGA children, the outcomes were both positive and negative at prepuberty.

There is evidence that even if being born SGA increases the risk of being overweight or obese in later life, this is not visible in young SGA children, who remain lean at prepuberty, but may develop overweight or obesity in the future (88). The early weight development strengthens the effect of birth size but also acts as an independent factor in the risk for later overweight. Catch-up and catch-down growth also increases and decreases the risk of childhood overweight in children born AGA, respectively (88,225). Our findings in this thesis were in accordance with previous results.

As part of body composition, BMD differed significantly between the birth size groups in our study cohort. A few studies regarding birth size and bone mass in children (113,185) and adults (64) showed a positive linear association between birth size and bone mass. It is also noticeable that early growth is critical for decent bone accrual in SGA children and SGA-born adults. Bone accrual seems to track to adulthood, therefore it is important to pay attention to children with lower bone mass before puberty: bone health can be improved by attending to adequate calcium, vitamin D, and nutritional intake and increasing the level of exercise (226). As with cardiometabolic programming in pre- and postnatal periods, bone health is also derived from the same time period, and could be seen as the trajectory of overall metabolic programming (226).

Similarly to our study, an association between low birth size and increased serum DHEAS levels in later childhood has been shown in previous studies (121,122,200). The negative relationship between birth weight and later prepubertal serum DHEAS levels has previously been demonstrated through the normal birth weight range (123), and our results suggest this to continue in LGA children who had the lowest DHEAS levels in mid-childhood. In addition, along with small birth size, early catch-up growth predicted increased DHEAS levels.

Our results did not support the U-shaped association between birth weight and cardiometabolic risk factors. Low-grade inflammation was strongest in the SGA children by both BMI SDS-adjusted hs-CRP and IL-1ra concentrations, and lowest in the LGA children (BMI SDS-adjusted IL-1ra concentrations). Stansfield et al. showed the U-shaped relationship between birth weight and low-grade inflammation in adolescents using leptin as a marker of low-grade inflammation. Interestingly, similar to our results, CRP was inversely related to birth weight in their study (227).

8.2 STRENGTHS AND LIMITATIONS

The strengths of this study include the study cohort enrolled strictly according to birth size, detailed growth information in early childhood, and thorough examination at prepuberty. We also acknowledge limitations of this study that may have had an impact on the results. The sample size was relatively small, reducing the statistical power of the study. In addition, the children in the control group were heavier than Finnish children on average. Therefore, the analyses were adjusted for the necessary variables to reduce the influence of the confounding factors.

This study was conducted as a cross-sectional study. In a cross-sectional study, it is possible to collect a comprehensive amount of data for analyses from a certain time point, but the study design has certain weaknesses itself. It does not reveal changes in the same study population in the future as a longitudinal study would do. Still, thanks to the Finnish comprehensive child health clinic system, we were able to include early growth data in our study design to demonstrate the effect of different growth patterns on cardiometabolic health markers.

8.3 FUTURE PERSPECTIVES

In this thesis, we have used traditional methods to investigate the association of birth weight and cardiometabolic risk. In future, it would be informative and beneficial to study the influence of epigenetic changes as part of the explanation to the adverse, but also somewhat beneficial, changes detected between the birth size groups. These heritable changes are independent of changes to the DNA sequence, and are suggested to be mediators of inflammation and cardiovascular disease, together with environmental factors and genetic susceptibility (228).

Studies of these underlying mechanisms have been published in recent years, and activity in this field is also increasing. In one study, birth weight for gestational age was presented as associating with DNA methylation at birth and partly in mid-childhood (229), but elsewhere, LGA infants did not have epigenetic changes compared to AGA infants at birth (54). Studying epigenetic changes could give a wider view of the reasons behind these changes associated with birth weight seen as early as at prepuberty.

Many of the observations demonstrated in this thesis are known to track to adulthood. Hence, it is not unimportant how we manage to improve health in later life. There are factors we are not able to change after birth, such as epigenetic changes originating from the fetal environment, but there are also factors we can affect through changes in lifestyle, e.g. obesity. Therefore, it is crucial to recognize the risk of low and high birth weight on cardiometabolic health in childhood, detect these adverse changes, and act to influence them beneficially, because ideal cardiovascular health can be restored if disturbances are treated before adulthood (95,230).

9 CONCLUSIONS

In conclusion, the impact of both low and high birth weight on growth and cardiometabolism is seen as early as in mid-childhood. Being born LGA seems to increase the risk for childhood obesity, and children born SGA had lower BMD compared with children born LGA and AGA. In addition, low-grade inflammation was higher in SGA compared with LGA children.

The association between birth weight and serum DHEAS concentrations appeared to be inversely linear; children born LGA had the lowest DHEAS concentrations. Low birth weight and accelerated early growth predicted higher DHEAS concentrations.

Our results suggest that children born SGA and LGA have an increased risk for later cardiometabolic disturbances already at prepuberty, but in LGA children, retaining normal weight could reduce these adverse outcomes in the future, and large birth size could even be beneficial to an extent.

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In this thesis, we investigated the impact of birth size and early growth on various cardiometabolic characteristics in prepubertal children. Our results suggest that both small (SGA) and large for gestational age (LGA) children have an increased risk for development of cardiometabolic disturbances at prepuberty. In SGA children, cardiometabolic disturbances seem to be independent from overweight, whereas in LGA children, retaining normal weight could reduce these adverse outcomes in future.

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