Relationship between Birth Weight, Early Growth Rate, and Body Composition in 5- to 7-Year-Old Children

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Abstract

Background: Programing of body composition during intrauterine growth may contribute to the higher risk for cardiometabolic disease in individuals born small or large for gestational age (SGA, LGA). Compensations of intrauterine growth by catch-up or catch-down postnatal growth may lead to adverse consequences like a thin-fat phenotype. ***Methods:*** The impact of (i) birth weight as well as (ii) the interaction between birth weight and catch-up or catch-down growth during the first 2 years of life on fat-free mass index (FFMI) and fat mass index (FMI) in 3,204 5–7-year-old children were investigated using Hattori's body composition chart. Body composition results were compared to appropriate for gestational age (AGA) birth weight with the same body mass index (BMI). ***Results:*** In total, 299 children at age 5–7 years were categorized as SGA, 2,583 as AGA, and 322 as LGA. When compared to AGA-children, BMI at 5–7 years of age was higher in LGA-children (15.5 vs. 16.2 kg/m^2; $p <$ 0.001) but not different in SGA-children. Compared to AGA with the same BMI, LGA was associated with higher FMI and a lower FFMI in 5–7-year-old girls. This phenotype was also seen for both sexes with catch-down growth during the first 2 years of life whereas catch-up growth prevented the higher FMI and lower FFMI per BMI. By contrast, SGA was associated with a higher FFMI and lower FMI in 5–7-year-old boys compared to AGA boys with the same BMI. This phenotype was also seen with catch-down growth in both genders whereas catch-up growth in girls led to more gain in FMI per BMI. ***Conclusion:*** LGA with a compensatory catch-down postnatal growth may be a risk factor for the development of disproportionate gain in fat over lean mass whereas SGA with a catch-down postnatal growth seems to favor the subsequent accretion of lean over fat mass. A higher propensity of lean mass accretion during postnatal growth in boys compared to girls explains sex differences in these phenotypes.

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Published by S. Karger AG, Basel

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Introduction

According to the "thrifty phenotype hypothesis," fetal malnutrition that results in a small for gestational age (SGA) birth weight increases the susceptibility to noncommunicable diseases in later life [1]. As a proposed underlying mechanism, body composition is "programmed" by early growth because energy restriction in utero leads to a preferential development of vital organs (e.g., brain and heart) at the expense of other tissues, such as muscle and the endocrine pancreas [1, 2]. In addition, early accretion of fat mass (FM) over fat-free mass (FFM) may contribute to impaired insulin-mediated glucose uptake, inflammation, and frailty throughout the life course. Birth weight was, however, shown to be strongly predictive of later lean mass and has a much weaker association with later fatness [3]. Intriguingly, not only a low birth weight but also a large for gestational age (LGA) birth weight is associated with adverse health outcomes during adulthood [4–6].

The contribution of body composition to this conundrum remains largely unknown. Since a high body mass index (BMI) is tantamount to a high FM and FFM and a low BMI is accompanied by low FM as well as FFM, the hypothesis of a higher prevalence of thin-fat phenotypes in children who were born SGA or LGA can only be investigated by comparing FFM and FM of these children with a reference population that has a similar BMI. A simultaneous evaluation of FM and FFM each normalized by height^2 (FM index [FMI] and FFM index [FFMI]) is provided by the Hattori chart method [7] that is therefore ideal to evaluate body composition in children with differences in height and similar BMI.

The "thrifty phenotype hypothesis" was complemented by the "predictive adaptive response hypothesis" [8]. According to this hypothesis, a low birth weight that is associated with characteristics like a reduced muscle mass and reduced nephron number provides an adaptation and thus a survival advantage in environments with food scarcity, whereas the program becomes maladaptive at the abundance of food in affluent societies leading to insulin resistance and the metabolic syndrome [8, 9]. In addition to birth weight itself, weight gain in the first 2 years of life may thus further add to the risk of obesity and metabolic disease later in life [10–13].

The interaction between birth weight and early growth is of great importance because approximately 80% of SGA infants show a "catch-up growth phenomenon" [14, 15] whereas in infants born LGA a "catch-down growth phenomenon" may occur [16]. According to the "predictive adaptive response" hypothesis [8], these compensations of intrauterine growth by early postnatal growth present a higher risk for adverse consequences like a thin-fat phenotype with a higher metabolic risk and should therefore be prevented. In line with this hypothesis, children who were small at birth and gained weight rapidly during early infancy had high abdominal fat in later childhood and adulthood [14, 17]. Systematic analyses of the interaction of intrauterine and postnatal growth are, however, lacking. The aim of this study was (i) to investigate the impact of birth weight (stratified into SGA, appropriate for gestational age [AGA], LGA groups) on body composition in 5–7-year-old children using Hattori's body composition chart and (ii) to examine the interaction between birth weight groups and early growth (catch-up or catch-down) on body composition in 5–7-year-old children.

Methods

Study Population

Cross-sectional data were collected as part of the Kiel Obesity Prevention Study (KOPS), which is an ongoing study starting in 1996 in Kiel (Northern Germany) with over 15,500 children and adolescents who were recruited in randomly sampled schools in different neighborhoods of Kiel. KOPS is composed of 3 cohorts: 1st graders, 4th graders, and 8th graders. KOPS aims to characterize the determinants of childhood overweight and the effect of preventive measures within schools and families. Participation was voluntary and without any eligibility criteria except the willingness to participate and written informed consent from the parents. The study was approved by the local Ethical Committee of the Medical Faculty of the Christian-Albrechts University (Kiel, Germany). Parents and children voluntarily participated in KOPS, and written consent was obtained from all parents. Details of the aims, study design, and recruitment procedure are described elsewhere [18, 19].

For the present analysis, the 1st-grader cohort was used (4,997 children, 41% of all 5–7-year-old children in Kiel between 1996 and 2001). A subpopulation ($n = 3,204$) of this cohort was selected based on those who responded to a questionnaire on weight, length, and gestational age at birth. Nonresponders to this questionnaire were more frequently people with overweight and obesity when compared with responders and belonged more often to low SES families [20]. The study population of the present study was stratified into three groups according to their birth weight as SGA, AGA, and LGA.

Birth Weight for Gestational Age

Gestational age, birth weight, and size (length) were assessed using data from maternity records. Based on German reference values for newborns [21], all subjects were classified into three length-related birth weight categories: (i) SGA (<10th percentile for gestational age and sex), (ii) AGA (10th–90th percentile for gestational age and sex), and (iii) LGA (>90th percentile for gestational age and sex).

Weight Status and Body Composition

Anthropometric measurements of height and weight at the age of 5–7 years were performed by trained observers from the Insti-

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tute of Human Nutrition and Food Science, Christian-Albrechts University in Kiel following standard procedures. Body weight was measured to the nearest 0.1 kg using a calibrated digital scale (model 861; seca GmbH, Hamburg, Germany) with subjects in underwear. Body height was assessed to the nearest 0.1 cm using a portable stadiometer (model 214, seca GmbH). BMI was calculated from weight and height as kg/m^2. Body composition was assessed by bioelectrical impedance analysis (BIA), using a tetrapolar BIA device with hand-to-foot electrodes (BIA 2000-C; Data Input GmbH, Darmstadt, Germany). FFM was calculated using a BIA-algorithm generated and cross-validated for children and adolescents in our lab using air displacement plethysmography as a reference: FFM (kg) = 0.66 × (height^2 [cm^2]/resistance [Ω]) + 0.196 × weight (kg) + 0.157 × reactance (Ω) + 0.348 × age (years) − 12.083 [22]. FM was calculated from the difference between body weight and FFM. FM and FFM were normalized by height^2 to FMI and FFMI. Medians of FMI and FFMI were calculated for boys and girls born SGA, AGA, and LGA and plotted on Hattori body composition charts.

Body Composition Charts

In order to graphically evaluate body composition in children with different birth weight groups and similar BMI at the age of 5–7 years, a Hattori chart based on FFMI (FFM/height^2) and FMI (FM/height^2), was applied (see online suppl. Fig. 1 for an introduction in the principles of the Hattori chart; for all online suppl. material, see www.karger.com/doi/10.1159/000522509). The *x*-axis represents FFMI (kg/m^2) and the *y*-axis FMI (kg/m^2). Since the sum of FMI and FFMI equals the BMI (BMI = FMI + FFMI), isolines of BMI (grey) shown as diagonal lines were added across the chart. Detailed information on the Hattori body composition chart is described elsewhere [7, 23].

Since FMI and FFMI can vary despite the same BMI, the application of the chart provides the opportunity to compare FMI and FFMI of children with different birth weights who have the same BMI. Therefore, medians of FFMI and FMI for each birth weight group were plotted in the body composition chart. AGA-children were defined as a reference population with normal FMI and FFMI for a given BMI. To graphically present the reference population in the Hattori chart, AGA-children were divided into BMI quartiles with equal distribution of age in both sexes. For evaluation of individual results from different birth weight groups, a trajectory of FMI and FFMI from AGA-children was used with continuous lines for boys (blue) and girls (red), which represent BMI values of 5–7-year-old AGA-children.

Early Growth Rate

To assess whether a gain in BMI within the first 2 years of life influences body composition at the age of 5–7 years, changes in BMI standard deviation score (SDS) between birth and 2 years were calculated (scores at 2 years minus scores at birth). Anthropometric measurements of height and weight at birth and at the age of 2 years were collected from maternity records. BMI was calculated from weight and height as kg/m^2 and converted into SDS using age- and sex-specific reference percentiles and the following equation:

$$SDS_{LMS} = \frac{\left[\frac{X}{M(t)}\right]^{L(t)} - 1}{L(t) \times S(t)},$$

where *X* represents the individual value of BMI, *L* is the power transformation, *M* is the median value, and *S* is the coefficient of variation value. Longitudinal data showed that from early childhood onward, the majority of children tend to track along a given centile and do not cross up or down through the centiles, indicating that growth is self-regulating and target-seeking [24]. Therefore, regardless of whether a child is large or small, centile crossing gives an indication of a clinical growth abnormality. Therefore, a gain in BMI-SDS >0.67 was taken to indicate catch-up growth, as 0.67 SDS represents the width of each percentile band on standard growth charts [25]. A BMI-SDS <−0.67 indicated catch-down growth. A BMI-SDS between ≥−0.67 and ≤0.67 was taken to indicate no change in growth. SGA- and LGA-children were categorized into 4 different groups, including (i) SGA catch-down/no change, (ii) SGA catch-up, (iii) LGA catch-up/no change, and (iv) LGA catch-down.

Statistical Analysis

Statistical analyses were performed with IBM® SPSS® Statistics for Windows (version 26.0; Somers, NY, USA). Descriptive statistics of the study population, stratified by sex and birth weight groups are presented as median and interquartile range or percentage of numbers (%). Mann-Whitney-U test was done to determine significant differences between boys and girls. χ^2 test and nonparametric Kruskal-Wallis test followed by Bonferroni post hoc test were performed to analyze differences between SGA-, AGA-, and LGA-children. The level of significance was set at *p* < 0.05 (two-sided).

Results

Association between Birth Weight Groups and Body Composition in Children

Characteristics of 5–7-year-old children stratified by birth weight groups and sex are shown in Table 1. In the overall sample, half of the children were boys (1,608 boys and 1,596 girls). The prevalence of obesity was similar between boys and girls (4.3% vs. 4.6%), whereas the prevalence of overweight was higher in girls when compared to boys (8.0% vs. 5.5%). Overall, 9.3% and 10.0% of the children were SGA and LGA, respectively, with no within-group sex differences. When compared to AGA-children, BMI at 5–7 years of age was higher in LGA-children (15.5 vs. 16.2 kg/m^2; *p* < 0.001) but not different in SGA-children or in subgroups of boys and girls. When compared with LGA, SGA-children had a lower prevalence of overweight and obesity (boys, 9.5% vs. 13.7%; girls 7.1% vs. 21.6%), while there were no differences in BMI-SDS, FMI, and FFMI. SGA-children were breastfed for shorter periods when compared with AGA- and LGA-children.

Hattori chart analysis allows an independent evaluation of both FFM and FM normalized for body height between birth weight groups (Fig. 1a1, a2) and between

Table 1. Characteristics of the study population of 5–7-year-old children stratified by birth weight for gestational age and sex (median and IQR)

	Boys			Girls		
	SGA	AGA	LGA	SGA	AGA	LGA
n	158	1,290	160	141	1,293	162
5–7 years old						
Age,[#] years	6.3 (5.9–6.5)	6.3 (6.0–6.5)	6.2 (6.0–6.6)	6.2 (6.0–6.5)	6.2 (5.9–6.5)	6.2 (5.9–6.5)
Weight,[#] kg	21.4 (19.5–24.0)[a]	22.5 (21.0–25.0)[b]	23.5 (22.0–27.0)[c]	21.3 (19.9–24.0)[a]	22.0 (20.0–24.5)[a]	24.0 (21.7–26.6)[b]
Height,[#] m	1.18 (1.15–1.22)[a]	1.21 (1.17–1.24)[b]	1.22 (1.18–1.26)[b]	1.18 (1.14–1.22)[a]	1.19 (1.16–1.23)[b]	1.21 (1.2–1.3)[c]
BMI-SDS[1,#]	−0.2 (−0.5 to 0.4)	0.0 (−0.5 to 0.6)	0.4 (−0.3 to 1.0)	0.0 (−0.5 to 0.6)	0.0 (−0.6 to 0.7)	0.4 (−0.1 to 1.1)
FMI,[#] kg/m²	2.87 (2.23–3.62)	3.25 (2.56–4.07)	3.62 (2.84–4.56)	3.21 (2.24–4.06)	3.30 (2.43–4.25)	3.83 (3.17–5.03)
FFMI,[#] kg/m²	12.47 (11.96–13.13)	12.36 (11.77–12.95)	12.52 (11.87–13.12)	12.34 (11.81–12.75)	12.33 (11.73–12.93)	12.40 (11.77–13.09)
Overweight (FM/FFM >90th P, %)[2]	40.0	52.9	36.4	50.0	51.3	57.1
Birth						
Birth weight,[#] g	2,820 (2,550–2,993)[a]	3,520 (3,270–3,800)[b]	4,320 (4,123–4,508)[c]	2,680 (2,305–2,840)[a]	3,400 (3,130–3,640)[b]	4,100 (3,950–4,290)[c]
Birth height,[#] cm	49 (48–51)[a]	52 (50–54)[b]	54 (53–55)[c]	49 (47–50)[a]	51 (50–53)[b]	53 (51–54)[c]
Gestational age,[#] weeks	40 (39–40)	40 (39–40)	40 (39–40)	40 (39–40)	40 (39–40)	40 (39–40)
Breastfeeding,[#] months	3 (0–7)[a]	5 (2–8)[b]	6 (2–8)[b]	3 (1–6)[a]	5 (2–8)[b]	5 (1–8)[b]
Infancy (0–2 years)						
Weight gain,* %						
Catch-down	6.3[a]	25.7[b]	63.8[c]	5.0[a]	28.6[b]	72.8[c]
No change	28.5	42.4	32.5	24.8	45.9	24.7
Catch-up	65.2[a]	31.9[b]	3.8[c]	70.2[a]	25.5[b]	2.5[c]

n = 3,204. SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; BMI, body mass index; FMI, fat mass index; FFMI, fat-free mass index; SDS, standard deviation score; IQR, interquartile range. [1] According to Kromeyer-Hauschild et al. [25]: catch-down, BMI-SDS <−0.67; no change, BMI-SDS ≥−0.67 and ≤0.67; catch-up, BMI-SDS >0.67. [2] According to Gätjens et al. [30]; significant differences between SGA-, AGA-, LGA-children by [#] Kruskal-Wallis test and [*] χ^2 test. [a, b, c] Medians/percentages not sharing a common superscript letter are significantly different within sex; $p < 0.05$.

Fig. 1. a–c Body composition chart for median FMI (kg/m²) and FFMI (kg/m²) in 5–7-year-old boys and girls categorized according to their birth weight for gestational age (**a1** + **a2**) and in SGA boys (**b1**) and SGA girls (**b2**) and LGA boys (**c1**) and LGA girls (**c2**) categorized according to their birth weight for gestational age and weight gain between birth and second year of life. SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; BMI, body mass index; FMI, fat mass index; FFMI, fat-free mass index; catch-down, gain in BMI-SDS <−0.67; no change, gain in BMI-SDS between ≥−0.67 and ≤0.67, catch-up, gain in BMI-SDS >0.67; continuous blue or red lines represent BMI values of 5–7-year-old AGA-children divided into quartiles and with equal distribution of age groups between quartiles of BMI in both sexes; dotted lines represent same BMI values at different FMI/FFMI ratios; colored areas with arrows represent differences in FFMI and FMI for SGA or LGA-children compared to AGA-children with the same BMI.

(For figure see next page.)

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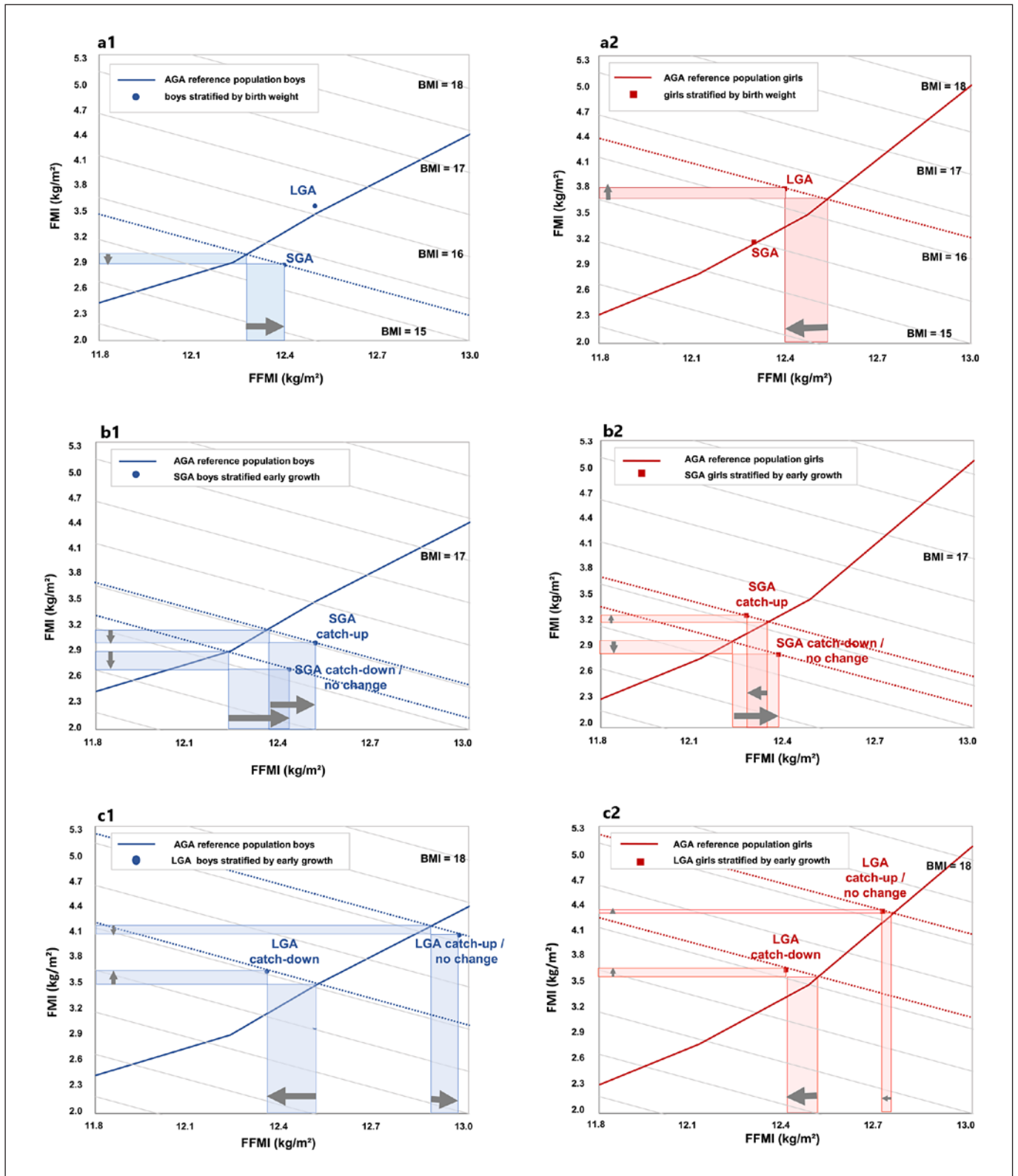
groups categorized by birth weight and change in BMI within the first 2 years of life (Fig. 1b1, b2, c1, c2). Normal values for FMI and FFMI in 5–7-year-old girls and boys stratified according to quartiles of BMI are plotted using data of AGA-children. These continuous reference lines gradually move upward with increasing BMI.

Compared to AGA birth weight groups with the same BMI, LGA birth weight was associated with higher FMI and a lower FFMI in 5–7-year-old girls (Fig. 1a2). This phenotype was also seen for both sexes with catch-down growth during the first 2 years of life whereas rapid catch-up growth prevented the higher FMI and lower FFMI per BMI especially in boys and to a lesser extent in girls (Fig. 1c1, c2). By contrast, SGA birth weight was associated with a higher FFMI and lower FMI in 5–7-year-old boys compared to boys born AGA with the same BMI (Fig. 1a1). This phenotype was also seen with slow catch-down growth in both genders whereas catch-up growth in girls led to more gain in FMI per BMI (Fig. 1b1, b2). No differences in FFMI or FMI were observed between groups categorized by change in BMI in the first 2 years of life and the reference population with the same BMI at the age of 5–7 years (online suppl. Fig. S2).

Discussion

During childhood and adolescence, the body becomes bigger while some "structural decisions" that impact body composition associated disease vulnerability have already been made during fetal and early postnatal growth [26]. The present study investigated the impact of birth weight and its interaction with postnatal growth during the first 2 years of life on the contribution of FMI and FFMI to BMI of 5–7-year-old children.

Low birth weight predisposes individuals to high metabolic risk [3]. This may be due to a thin-fat phenotype with a low lean mass and a high percentage of FM [3]. Many studies have shown that birth weight is positively correlated with FFM but not with FM in infants and adults [27–29]. These data suggest that birth weight determines FFM in later life. Absolute FFM in kg or FFMI do, however, increase with increasing body mass and thus BMI. Evaluation of divergent energy partitioning into fat and lean mass must therefore consider both compartments simultaneously and thus the mass of the body. In our study, a disproportionately high or low FFM or FM in 5–7-year-old children with SGA or LGA birth weights was therefore evaluated by comparison with AGA-children of the same BMI using the Hattori chart. The assessment of energy partitioning specific for weight status revealed a different picture compared to previous studies. Our major findings are:

- SGA was associated with a higher FFMI and lower FMI per BMI in 5–7-year-old boys and in both sexes after catch-down growth during the first 2 years of life.
- LGA increased the risk of a low FFMI and a high FMI per BMI in 5–7-year-old girls and in both sexes after catch-down growth during the first 2 years of life.
- Catch-up growth during the first 2 years of life is associated with a higher FMI gain in girls and a higher FFMI gain in boys.

The differences in FFMI or FMI >0.2 kg/m^2 that we found between SGA or LGA-children and AGA-children with the same BMI are biologically meaningful because in the age group of 5–7-year-old children only 1 kg/m^2 is separating the 10th from the 50th FFMI-percentile, or the 50th from the 90th FFMI-percentile; and differences between FMI-percentiles are only slightly larger with 1.5 kg/m^2 separating the 10th from the 50th FMI-percentile and 2–2.5 kg/m^2 separating the 50th from the 90th FMI-percentile [30]. Since we found no adverse effect of SGA birth weight on partitioning of fat and lean mass at the age of 5–7 years, the well-established association between SGA and type 2 diabetes [31–35] could be due to changes in body fat distribution [36] or changes in metabolic or mitochondrial function [37] unrelated to childhood body composition. Potential interacting mediators or mechanisms underlying developmental programing are, however, manifold and do not all lead to persistent changes in energy partitioning (e.g., epigenetic influences, maternal diet composition, chemical exposures like cigarette smoke, and metabolic features like insulin resistance or inflammation as well as the gut microbiome) [37].

Interaction between Birth Weight and Early Postnatal Growth

According to the "predictive adaptive response hypothesis" growth in utero presents an adaptation to postnatal environmental conditions [8]. In case of a mismatch between prenatal and postnatal conditions in utero, developmental programing should therefore be a disadvantage. Most studies that investigated the impact of SGA followed by catch-up growth on body composition in children or adults indeed found a higher absolute or percentage of FM [38, 39] with only a few studies reporting a normal or low FM [16, 40].

By contrast, in the present study, no adverse consequences on partitioning of FM and FFM were found in

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5–7-year-old children who had an SGA and a subsequent catch-up growth when compared to AGA-children with the same BMI (Fig. 1b1, b2). The higher lean mass that we found for the SGA-phenotype was maintained under conditions of catch-up growth in boys, whereas in SGA-girls catch-up growth increased the contribution of FMI to BMI resulting in normal body composition compared to AGA-children with the same BMI.

On the other hand, catch-down growth did not normalize the phenotype with a higher FMI and a lower FFMI in LGA girls, but may even further aggravate this adverse effect on partitioning that is seen in both sexes after catch-down growth (Fig. 1c1, c2). LGA followed by a rapid growth rate during the first 2 years of life resulted in a high increase in BMI with a disproportionate increase in FFM and thus a normalization of partitioning in boys only (Fig. 1c1).

In summary, our results do not support the "predictive adaptive response hypothesis." Correspondingly, a study in rodents has found that adequate fetal growth followed by postnatal caloric restriction and slower growth increased longevity [41]. This result shows that even a mismatch between prenatal and postnatal conditions can be "beneficial" for health. As an intriguing alternative concept, the "maternal capital hypothesis" proposed by Wells [42, 43] states that ecological exposures across maternal or grand-maternal development shape the phenotype of the fetus because the mother is able to buffer the fetus from current environmental conditions.

Sex differences are already evident for the effect of birth weight on partitioning with higher FFMI for BMI in SGA boys and higher FMI for BMI in LGA girls (Fig. 1a1, a2). During catch-up growth in the first 2 years of life, sexual dimorphism is also evident from a higher propensity of lean mass accretion in boys and a higher accretion of FM in girls (Fig. 1b1, b2, c1, c2). Previous studies support this observation and show that sex differences in the gain of FFMI in relationship to FMI occur early on as revealed by Hattori chart analysis of the reference child [44]: Despite a lower body weight and BMI until 8 years, the reference girl has higher FMI and higher BMI by 10 years than the boy. This difference was largely attributed to the girl's FMI decreasing less in early childhood, and beginning to increase again earlier compared to the reference boy so that girls have a greater FMI from 3 years of age. In a Brazilian cohort, the effect of weight gain on lean mass was also greater for male than for female infants, and vice versa the effect on FM was greater for females than males [45].

Strengths and Limitations of the Study

Our study was retrospective and does therefore not allow a causal interpretation of the observed associations. In addition, birth weight is only a marker for different causes of accelerated or impaired prenatal growth (e.g., maternal BMI and nutrition, gestational diabetes, placental insufficiency, smoking) that were not considered. Since groups of SGA- and LGA-children are rather small, the results of the study should be interpreted with caution, and further studies are needed to confirm the findings. A strength of the study is the comparison of body composition between risk groups with extreme birth weight with or without compensatory growth during the first 2 years of life and AGA-children with the same BMI. In contrast to previous publications, this analysis allows the evaluation of partitioning for a specific weight status (e.g., is the amount of FM or FFM normal for the BMI of the child). Beyond FM and FFM, data on the plasticity of adipose tissue as well as the composition of FFM (e.g., organ and tissue masses like kidney, pancreas, or left ventricular mass) could add substantially to the understanding of causes and consequences of developmental programing and should therefore be obtained in future studies.

Conclusions

We have shown that catch-down growth during the first 2 years of life in LGA-children leads to a disproportionate gain in FM although it leads to a much lower BMI at the age of 5–7 years compared to rapid postnatal growth. In SGA-children, catch-up growth had no adverse effects on partitioning of FM and FFM, whereas slow or normal growth maintained the higher lean mass per BMI but also maintained a low absolute lean mass due to a lower body mass.

Statement of Ethics

Parents of the subjects provided their written informed consent. The study was approved by the local Ethical Committee of the Medical Faculty of the Christian-Albrechts University (Kiel, Germany; AZ: A 36/95).

Conflict of Interest Statement

Manfred James Müller is Associate Editor of the journal.

Funding Sources

Author Contributions

A.B.-W. developed the aim of the study; I.G. and M.H. did the statistical analyses; I.G., A.B.-W., S.F., and M.J.M. interpreted the data; A.B.-W. and M.J.M. wrote the final draft of the paper. All authors discussed the data and approved the final version of the paper. A.B.-W. will act as guarantor for the paper.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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