Selective fetal growth restriction in identical twins: from womb to adolescence

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Chapter 10

Fetal growth restriction inhibits childhood growth despite catch-up in discordant identical twins.

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Abstract

Background and objectives. Research suggests that postnatal catch-up growth after fetal growth restriction (FGR) occurs frequently and is completed within two years. Yet, postnatal growth in singletons may be influenced by multiple factors. Identical twins with discordant prenatal growth, termed *selective* FGR (sFGR), can be regarded as a natural experiment eliminating these sources of bias.

Methods. Monochorionic twins with sFGR born in our center between 2002-2017 were eligible for inclusion. Growth measurements (height, weight, head circumference) were performed at follow-up. Detailed growth curves as documented by a systematic primary care system in the Netherlands were retrospectively collected. A mixed-effects model was used to assess within-pair standard deviation score (SDS) difference and individual height SDS relative to target height SDS.

Results. Forty-seven twin pairs (94 children) were included at a median age of 11 (8-13) years. At the time of the last measurement, the smaller twin at birth had a lower height SDS (-0.6 vs. -0.3, $p < 0.001$, median difference 0.5 (95% CI 0.4-0.7)), lower weight SDS (-0.5 vs. -0.1, $p < 0.001$, median difference 0.8 (95% CI 0.5-1.0)) and lower head circumference SDS (-0.5 vs 0.2, $p < 0.001$, median difference 0.6 (95% CI 0.6-0.9)) compared to larger twins. These differences persisted at least until the age of seventeen. Smaller twins catch-up to a height within their target range between 8-11 years.

Conclusions. Identical twins with discordant prenatal growth maintain a modest but significant difference in height, weight and head circumference until, indicating a persistent, inhibitory effect of an adverse intrauterine environment on childhood growth.

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Introduction

Fetal growth restriction (FGR) is a condition in which the fetus is unable to reach its intrinsic growth potential due to unfavorable intrauterine circumstances[1]. A period of accelerated growth usually follows after birth as compensation, termed catch-up growth. This is regarded as completed when height is within normal range. Multiple definitions of completed catch-up growth can be identified in literature, including height above -2 standard deviation score (SDS) on population growth curves, or height within target height (TH) range, based on parental height[2]. The former is useful for tracking childhood growth in a clinical setting, to evaluate whether height deviates substantially from the norm and an intervention may be necessary. The latter also explores growth in relation to an individuals' actual intrinsic growth potential. Children born small for gestational age (SGA) generally complete catch-up growth within two years after birth and approximately 90% has reached a normal height, i.e., above -2 SDS at eight years[3,4]. At twelve years, the mean height of children born after FGR falls within 0.5 SDS of the population mean and only 5% had a height below TH range[5]. Yet, comparisons of childhood growth measurements of appropriately-grown singletons cannot control for known and unknown factors that influence postnatal growth, including maternal, obstetrical, genetic factors, and postnatal family environment. The study of monochorionic (MC) twin pairs affected by selective fetal growth restriction (sFGR) provides a direct opportunity to circumvent these limitations.

MC twins are monozygotic twins, who share a single placenta in utero. This placenta is unequally shared in 10-15% of pregnancies which is thought to cause a disproportionate oxygen and nutrient supply resulting in a growth discrepancy. When the difference in birth weight of the twins is more than 20%, this is defined as sFGR[6-8]. Within such twin pairs a growth-restricted twin can be compared with a larger co-twin who is genetically identical and who shared similar maternal and obstetric factors as well as postnatal family environment. Therefore, the study of sFGR twins results in a robust estimate of the long-term effect on growth of FGR due to an adverse intrauterine environment.

At present, research on catch-up growth in birth weight discordant monozygotic twins is scarce (Table 1)[9-14]. In the available studies sample sizes are often limited, chorionicity is largely unknown and neither BMI nor pubertal status were recorded. Additionally, the timing and number of growth measurement varied substantially and importantly, multiple definitions of catch-up growth have been used. Therefore,

detailed analysis of catch-up growth patterns in MC twins with sFGR is unavailable at present. Hence, the aim of this study is to assess the childhood growth patterns of MC twins with sFGR to evaluate to what extent catch-up growth (i.e., height within TH range) occurs in the smaller twin, using comprehensive growth measurements from birth up to seventeen years of age. Our definitions of catch-up growth thereby differs from previous studies focusing on population growth curves and allows for the analysis of more subtle differences in growth.

Table 1. An overview of available literature on catch-up growth in monozygotic twins.

Authors (year)	Study population	Follow-up	Findings
Babson et al. (1973)	9 discordant MZ twin pairs of which 3 MC	Three measurements between: 7.5-11.5 yrs, 12-16 yrs, 18-22 yrs	Smaller twin 5.6-6.8 cm shorter than larger twin at each follow-up moment.
Buckler et al. (2009)	38 discordant MZ twin pairs	One measurement between 2-9 yrs	Smaller twin 0.5 SDS shorter and 0.8 SDS lighter than larger twin.
Henrichsen et al. (1986)	14 discordant MZ twin pairs	One measurement between 9-17 yrs	Smaller twin 0-8 cm shorter and 0-1.5 kg lighter than larger twin.
Keet et al. (1986)	14 discordant MZ twin pairs	Nine measurements from birth until 6 yrs	Within-pair percentage difference at 6 years of age was 0.2% for height, 8.0% for weight and 1.0% for head circumference.
Schulte et al. (2016)	16 discordant MC twin pairs after TTTS	Three measurements at a mean age of 2, 4 and 10 yrs	Smaller twin 0.53 SDS shorter than larger twin at age 14.6 yrs.
Wilson (1978)	10 discordant MZ twin pairs	One measurement at 6 yrs	Smaller twin was 1.85 cm shorter and 2.19 kg lighter than larger twin at 6 years of age.

MZ: monozygotic, MC: monochorionic, TTTS: twin-twin transfusion syndrome.
Outcomes are presented as median (interquartile range (IQR)) or n (%).

Methods

This study is part of the LEMON study (Long-term Effects of selective fetal growth restriction in MONochorionic twins, International Clinical Trial Registry Platform ID NL9833), a longitudinal cohort study including all MC twins with sFGR born in the Leiden University Medical Center (LUMC) in the age range of 3-17 years with available growth measurements from birth onwards[15]. The LUMC is the national referral center for complicated MC twins in the Netherlands, so data of a large cohort of MC twins is available. The LEMON study was reviewed and approved by the ethics committee of the LUMC (P20.089). All parents and/or children ≥ 12 years of age have provided written informed consent. The neurodevelopmental outcomes, including cognitive test scores, of the twins included in the LEMON study have previously been described[15].

All MC twins with sFGR born in the LUMC between 2002-2017 were eligible for this study, with sFGR defined as a birth weight discordance ≥ 20% (calculated as (birth weight larger twin – birth weight smaller twin)/birth weight larger twin x 100)[8]. Cases with twin-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence or monoamnionicity were excluded, as well as cases complicated by perinatal mortality in one or both twins before inclusion, since this would preclude within-pair analyses[16,17]. Cases with twin reversed arterial perfusion (TRAP) or other congenital abnormalities were excluded as well.

The following maternal, obstetrical and neonatal baseline characteristics were collected from digital patient files: maternal age, gravidity, parity, Gratacós type based on umbilical artery (UA) Doppler flow patterns in the smaller twin (type I positive end-diastolic flow, type II persistent absent/reversed end-diastolic flow, type III intermittent absent/reversed end-diastolic flow[18], gestational age at birth, sex, delivery mode and birth weight from which birth weight discordance and small for gestational age (SGA) (birth weight < 10th centile) were derived.

After informed consent was obtained, a follow-up examination was scheduled in which standardized growth measurements (height, weight, body mass index (BMI), head circumference, arm span and sitting height) were obtained of each twin. Parents were asked to bring the childhood growth curves as documented by the primary care system, to the examination. The primary care system in the Netherlands consists of regular follow-up appointments for every child, including height, weight and head circumference measurements at standard time points (3 months, 5-6 months, 10-12

months, 12-15 months, 22-26 months, 22-29 months and 42-48 months). If twins were simultaneously followed up in a local hospital in case of prematurity or dysmaturity, these growth measurements were retrieved as well. Only measurements of both twins on the same day were used for further analysis. Prior to the follow-up examination, both parents were asked to report their own height and weight in a questionnaire. Children ≥ 8 years of age were asked to fill out the Pubertal Development Scale, a standardized and validated self-assessment on pubertal status in children, classifying them on an ordinal scale from 1 = prepubertal, 2 = early pubertal, 3 = mid pubertal, 4 = late pubertal to 5 = post pubertal[19].

All growth measurements throughout childhood were plotted in Dutch growth curves, generating appropriate standard deviation scores (SDS)[20]. No correction for gestational age was applied, as this is not generally performed in clinical practice. BMI was regarded as an absolute value in line with clinical practice and as appropriate Dutch SDS are currently unavailable. Within-pair differences in height SDS, weight SDS and BMI were calculated as SDS or BMI larger twin – SDS or BMI smaller twin. TH was calculated according to the Dutch guidelines taking ethnicity into account and plotted in the growth curves as well[21]. TH range was defined as -0.8 to +0.8 SDS. Subsequently, catch-up growth was defined as growth into TH range[2].

Statistical analyses were performed using IBM Statistics Version 25.0 (SPSS, Inc. an IBM company, Chicago, IL, USA) and RStudio Version 2021.9.2.382 (RStudio, PBC, Boston, MA, USA). Data are presented as median (interquartile range (IQR)), n/N (%) or n (%). To test for association between FGR and the growth measurements/pubertal status at follow-up examination, a Wilcoxon signed-rank test was used (non-parametric data). This analysis takes into account that observations between co-twins are not independent. A *p*-value of < 0.05 was considered statistically significant. Multiple mixed-effects models were compared and tested (Supplement). Ultimately, mixed-effects models using a third-degree natural cubic spline to fit the curves were used to assess 1) within-pair difference in height SDS, BMI and head circumference SDS in relation to age to evaluate catch-up growth relative to the larger twin and 2) individual height SDS minus TH SDS in relation to age (a negative value indicates height below TH), to evaluate catch-up growth of both twins to their TH range. These models included a twin-specific random effect (second degree spline).

Results

Between 2002-2017, 73 twin pairs were eligible for inclusion. Of these twin pairs, 12 (16%) did not want to participate in the study and 13 (18%) were lost to follow-up (5 twin pairs moved abroad and 8 could not be reached for inclusion). Ultimately, 47 twin pairs were included.

Table 2. Maternal, obstetrical and characteristics for the 47 included sFGR twin pairs.

Characteristics	**MC twins (n=94; 47 pregnancies)**
Maternal age at delivery – *years*	32 (29-35)
Gravidity	2 (1-2)
Parity	0 (0-1)
Gratacós type	
Type I	24 (51)
Type II	10 (21)
Type III	13 (28)
Gestational age at birth – *weeks*	33.9 (31.3-36.0)
Female	48 (51)
Caesarean	54 (57)
Birth weight discordance – *%*	30.1 (26.1-33.4)
Birth weight – *grams*	1744 (1219-2184)
Smaller twin	1400 (1111-1875)
Larger twin	2003 (1600-2680)
Small for gestational age	57 (61)
Smaller twin	46 (98)
Larger twin	11 (23)

MC: monochorionic.

Outcomes are presented as median (interquartile range (IQR)) or n (%).

Baseline characteristics are presented in Table 2. Two smaller twins had an indication to start with recombinant growth hormone therapy. One of them (age 5 years) was scheduled to start recombinant growth hormone therapy after the follow-up examination, so all growth measurements could still be included in this study. The other one (age 11 years) had started recombinant growth hormone therapy at age four, so only growth measurements up to this point of both the smaller and larger twin were included in the analysis. Moreover, in one twin pair growth measurements at follow-up examination could not be performed due to severe cognitive impairment and subsequent resistance to anthropometric measurements in the smaller twin.

The SDS scores of the growth measurements at the follow-up examination are shown in Table 3. All SDS scores differed significantly between the smaller and the larger

twin, with persistently lower SDS for the smaller twin for all three main outcome measurements (height, weight and head circumference). The smaller twin had a 0.3 lower SDS in height as opposed to the larger twin (-0.6 vs. -0.3, $p < 0.0001$; median difference 0.5 (95% CI 0.4-0.7)); weight was 0.4 SDS lower (-0.5 vs. -0.1, $p < 0.0001$; median difference 0.8 (95% CI 0.5-1.0)) and head circumference was 0.7 SDS lower (-0.5 vs. 0.2, $p < 0.0001$; median difference 0.8 (95% CI 0.6-0.9)). Median BMI was 16.0 (IQR 14.9-19.4) kg/m^2 for the smaller twin and 17.2 (IQR 16.0-20.3) kg/m^2 for the larger twin ($p < 0.0001$). Pubertal status did not differ between the smaller and larger twin ($p = 0.915$). In the majority of twin pairs, the smaller twin was smaller (91% (41/45)), lighter (93% (41/44) and had a smaller head circumference (88% (38/43)) at the follow-up examination, with $p < 0.0001$).

Table 3. Childhood growth measurements in the smaller vs. the larger twin in sFGR twin pairs.

Outcomes	Smaller twin (n=45)	Larger twin (n=45)	*p*-value
Age at participation	11 (8-13)	11 (8-13)	
Height – *SDS*	-0.6 (-1.7--0.1)	-0.3 (-1.3-0.3)	**<0.0001**
Weight – *SDS*	-0.5 (-1.4-0.3)	-0.1 (-0.6-1.0)	**<0.0001**
Head circumference – *SDS*	-0.5 (-1.4-0.3)	0.2 (-0.4-0.8)	**<0.0001**
BMI – *kg/m²*	16.0 (14.9-19.4)	17.2 (16.0-20.3)	**<0.0001**
Pubertal status‡			0.915
Pre-pubertal	10 (22)	10 (22)	
Early pubertal	19 (42)	17 (38)	
Mid-pubertal	6 (13)	9 (20)	
Late pubertal	8 (18)	7 (16)	
Post-pubertal	2 (4)	2 (4)	
Within-pair size differences at follow-up			
Smaller height	41 (91)	4 (9)	**<0.0001**
Lower weight	41 (93)	3 (7)	**<0.0001**
Smaller head circumference*	38 (88)	5 (12)	**<0.0001**

SDS: standard deviation score, BMI: body mass index, kg: kilograms, m: meters, TH: target height.
Outcomes are presented as median (interquartile range (IQR)) or n (%).
‡Pubertal status was unknown in one twin pair.
*Two twin pairs had the same head circumference at follow-up.

Next, we investigated all 1072 growth measurements available for both twins on the same date, starting at birth followed by all standardized measurements by the primary care system and any other follow-up appointments by physicians, up until the final follow-up study visit. Within-twin pair difference in height SDS decreased steadily from 0- 17 years, with the most rapid decrease in the first two years after birth (Figure 1). At the age of 17, a within-pair difference in height of 0.3 SDS remained. Similarly, the within-twin pair difference in BMI decreased predominantly in the first

year to subsequently stabilize around 1 kg/m^2. The within-pair difference in head circumference SDS also decreased most in the first year and stabilized at approximately 0.7 SDS.

Finally, we compared the individual height SDS minus TH SDS between the smaller and larger twin according to age (Figure 2). The larger twin was found to rapidly catch-up to its TH range at six months. This rapid catch-up growth continued until the age of two. The smaller twin showed a similar rapid catch-up growth in the first two years of life, albeit still incomplete in the majority of cases at this age. Further catch-up growth slowed down from two years onwards and was completed between ages 8-11 years. Both the smaller and larger twin displayed an additional gradual increase in height SDS between ages 10-18 years.

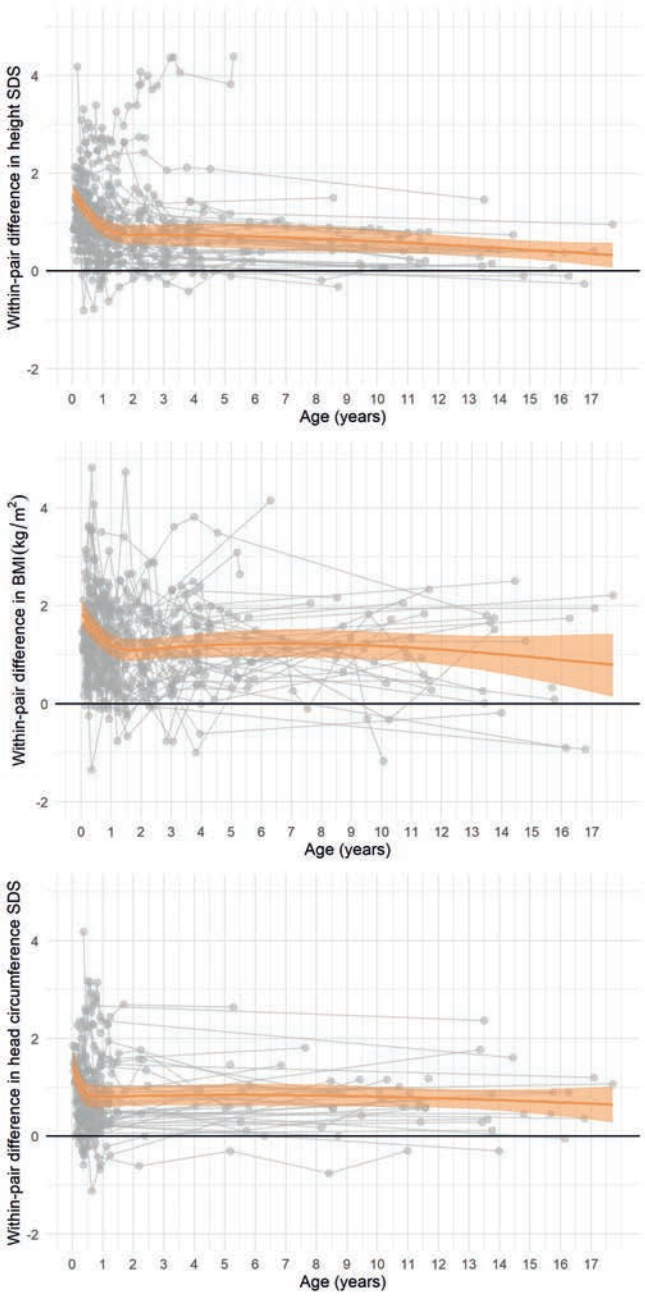

Figure 1. Mixed effects-model depicting the within-pair difference in height SDS, BMI and head circumference SDS according to age.

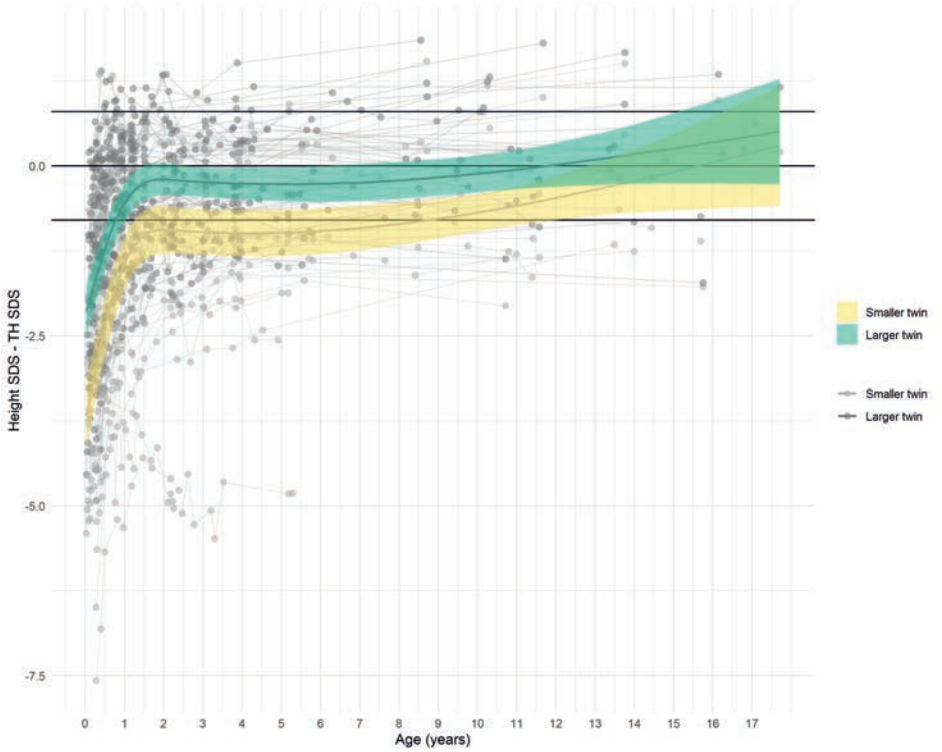

Figure 2. Mixed-effects model depiciting the difference in height SDS and TH SDS according to age for the smaller and larger twin. The horizontal lines represent the TH range of -/+ 0.8 SDS.

Discussion

Our analysis of genetically identical twins with sFGR shows that FGR results in modest but persistent differences in height, weight and head circumference throughout childhood, despite rapid catch-up growth in the first two years after birth. This is indicative of lasting growth-inhibitory effects of an adverse intrauterine environment. The median persistent height difference in our study between the smaller and the larger twin is 0.3 SDS at seventeen years, which corresponds to approximately 2-3 cm at adult height.

Our results are in line with previous studies on singleton SGA children: rapid catch-up growth generally occurs in the first two years after birth but near-adult height tends to still be below TH[3]. Similarly, we found that both twins rapidly catch-up within two years after birth following premature birth. While the larger twin already reaches its TH range during this period, the smaller twin continues to catch-up, albeit much slower, until completion between 8-11 years. The within-pair difference in height, weight and head circumference persists well into adolescence. Importantly, two previous dizygotic twin studies report an increasingly discordant growth with advancing age[11,13]. This further substantiates the use of our monozygotic twin model.

At present, research on growth patterns of discordant monozygotic twins is limited (Table 1). Available studies are largely in line with our results and describe a normal growth pattern for monozygotic twins with a birth weight discordance in which the smaller twin remains only marginally (between 0-8 cm) shorter, albeit using different definitions of catch-up growth[9-14]. However, we did not replicate being born SGA or low birth weight (< 1.95 kg) as risk factors for absence of catch-up growth as previously described[11]. We now provide strong evidence on catch-up growth and childhood growth patterns in a cohort of identical twins with known chorionicity and extensive longitudinal growth measurements from birth until late adolescence, including individual height relative to genetically determined TH range.

It is reassuring for physicians and parents alike to know that the vast majority of the smaller twins end up with a near-adult height in their genetic target range without the need for additional growth-promoting therapies such as recombinant growth hormone. Our data suggests that catch-up growth may take longer than previously expected (at least in MC twins with sFGR) and may not be completed until 8-11 years. Interestingly, both the smaller and larger twin seem to further grow into their TH range between ages 10-18 years. It should be noted, however, that relatively few

growth measurements in our study were available during adolescence, resulting in a wider confidence interval for this particular period. Growth hormone therapy is often considered when catch-up growth in SGA children is still insufficient between ages two and four. The 'late' catch-up growth in our cohort may support a more expectant approach, because part of these children will eventually catch-up with time. This is especially relevant for borderline cases in which parents or other caregivers are hesitant to start growth hormone therapy and burden their 2–4-year-old child with daily subcutaneous injections[22]. Our data suggests that in some cases a prolonged watchful waiting approach beyond four year may be perfectly feasible, thereby substantially reducing the time pressure that some parents may face while having to make this complicated decision together with their child's health care provider.

Several limitations of our study design should be taken into account when interpreting our results. Firstly, growth measurements were retrospectively retrieved from our national, standardized primary care system, potentially introducing information bias. Secondly, height measurements before the age of two (which are the predominant data in our study) tend to be less accurate due to interobserver measurement variation[23]. Lastly, it is important to consider that the etiological mechanisms of FGR in singletons and sFGR in MC twins may differ, thereby possibly affecting the direct extrapolation of our results to singletons. Where sFGR is presumed to primarily be caused by unequal sharing of a healthy placenta, with a smaller placental share and volume for the smaller twin, FGR in singletons is the result of impaired trophoblast invasion with subsequent placental insufficiency[7,24]. In addition, MC twin placentas have vascular connections allowing for intertwin blood flow during pregnancy. Even though we have excluded cases with evident imbalanced transfusion (TTTS and twin anemia polycythemia sequence), there is always a certain level of blood exchange that may affect the outcomes. Furthermore, it is unknown whether the growth trajectory of the larger twin accurately reflects the growth of an appropriately-grown singleton. Future research is necessary to determine whether these factors actually influence comparability between singletons and twins, as this is currently unknown. We now report similar outcomes in our twin population as were found for singletons with FGR, corroborating the use of our monozygotic twin model as well as the impact of FGR in itself. We were able to identify the more subtle but persistent differences in postnatal growth by conducting a within-pair comparison instead of solely focusing on growth within normal range on population growth curves.

It is currently unknown which mechanisms underlie the long-term effects of an adverse prenatal environment on growth, although epigenetic programming is considered a plausible candidate[25,26]. Likewise, questions remain about the impact of FGR on overall health in adulthood. Several studies have reported increased rates of obesity and metabolic disease due to a permanently altered insulin sensitivity[27]. This can in turn render individuals more susceptible to cardiovascular disease at later in life[28]. In addition, a smaller head circumference has been shown to be an important, independent predictor of adverse neurodevelopmental outcome[29,30]. This is substantiated by our study as well, as we have shown that the smaller twin (with the smaller head circumference) presents with significantly lower cognitive test scores as opposed to the larger twin in a previous analysis of the neurodevelopmental outcomes of the LEMON study[15]. The size of the within-pair difference in head circumference SDS and the within-pair difference in full scale IQ did not correlate significantly (p = 0.374).

Conclusion

This study provides a detailed description of childhood catch-up growth from birth until late puberty in a large cohort of genetically identical twins with discordant prenatal growth. We show that the majority of smaller twins born after sFGR will remain shorter and lighter than their larger co-twin throughout childhood, suggestive of a persistent inhibitory effect of FGR on growth which may affect neurodevelopmental outcome and adult health. The smaller twin will reach a height within their target range between ages 8-11 years. This information may reassure parents of newborn MC twins who are concerned about the future growth potential of their children. Moreover, these results provide guidance to treating physicians, favoring a more expectant approach in the early years after birth.

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