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Original Research

Fetal growth restriction inhibits childhood growth despite catch-up in discordant identical twins: an observational cohort study

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Abstract

Objective: Research suggests that postnatal catch-up growth after fetal growth restriction (FGR) occurs frequently. 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.

Design: Observational cohort study.

Methods: Monochorionic twins with sFGR born between 2002 and 2017 (aged 3-17 years) were eligible. Growth measurements (height, weight, head circumference, and body mass index) were performed at follow-up. Detailed growth curves documented by a systematic primary care system in the Netherlands were collected. Measurements were converted to standard deviation scores (SDSs). A mixed-effects model was used to assess within-pair 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 (interquartile range 8-13) years. At the last measurement, smaller twins at birth had a lower height SDS [−0.6 vs −0.3, $P < .001$, median difference 0.5 (95%CI 0.4-0.7)], lower weight SDS [−0.5 vs −0.1, $P < .001$, median difference 0.8 (95%CI 0.5-1.0)], and lower head circumference SDS [−0.5 vs 0.2, $P < .001$, median difference 0.8 (95%CI 0.6-0.9)] compared to larger twins. These differences persisted until the age of 17. Smaller twins showed rapid catch-up growth in the first 2 years and reached their target height range between 8 and 11 years.

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

Keywords: fetal growth restriction, identical twins, catch-up growth, monochorionic twins, selective fetal growth restriction

Significance

Children born after fetal growth restriction are reported to complete postnatal catch-up growth within 2 years. However, growth-restricted children are generally compared to unrelated controls with normal intrauterine growth or population growth curves.

We describe longitudinal growth patterns in identical twins discordant for fetal growth and aged between 3 and 17 years, controlling for factors that influence catch-up growth, showing that smaller twins partially catch up to their larger co-twin, but fail to do so completely.

Our results are suggestive of a persistent inhibitory effect of fetal growth restriction on childhood growth. This information may reassure parents of monochorionic twins who are concerned about their future growth potential. Moreover, these results provide guidance to physicians, favoring an expectant approach in early years.

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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. Children born small for gestational age (SGA) generally complete catch-up growth within 2 years after birth, and approximately 90% has reached a normal height, ie, above −2 SDS, at 8 years.[2,3] At 12 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 target height (TH) range.[4] Yet, comparisons of childhood growth measurements of appropriately-grown singletons cannot control for 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.

Monochorionic twins are monozygotic twins, who share a single placenta. 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 is more than 20%, this is defined as selective FGR (sFGR).[5–7] 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 of FGR on growth.

At present, research on catch-up growth in birth weight discordant monozygotic twins is scarce (Table 1).[8–13] In the available studies, sample sizes are often limited, chorionicity is largely unknown, and neither body mass index (BMI) nor pubertal status was recorded. Additionally, timing and number of growth measurement varied substantially, and 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 (ie, height within TH range) occurs in smaller twins, using comprehensive growth measurements from birth up to 17 years of age.

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) between 2002 and 2017 and in the age range of 3-17 years.[14] The LUMC is the national referral center for complicated MC twins in the Netherlands, so data of a large cohort of MC twins are available. The LEMON study was reviewed and approved by the ethics committee of the LUMC (P20.089) and was conducted according to the principles of the Declaration of Helsinki. All parents and/or children ≥ 12 years have provided written informed consent. A timeline of the study design is given in Supplement S1. The neurodevelopmental outcomes, including cognitive test scores, of twins included in the LEMON study have previously been described.[14]

All MC twins with sFGR born in the LUMC between 2002 and 2017 were eligible, with sFGR defined as a birth weight discordance ≥ 20% [calculated as (birth weight larger twin − birth weight smaller twin) / birth weight larger twin × 100].[7] 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.[15,16] Cases with twin reversed arterial perfusion or other congenital abnormalities were excluded as well.

The following baseline characteristics were collected from digital patient files as follows: Maternal age, gravidity, parity, Gratacós type based on umbilical artery Doppler flow patterns in smaller twins,[17] gestational age at birth, sex, delivery mode and birth weight from which birth weight discordance, SGA (birth weight < 10th centile), and birth weight < 3rd centile were derived.

After informed consent was obtained, a follow-up examination was scheduled in which standardized growth measurements [height, weight, BMI, and head circumference] were obtained. 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

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 and 11.5 years, 12 and 16 years, 18 and 22 years	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 and 9 years	Smaller twin 0.5 SD shorter and 0.8 SD lighter than larger twin.
Henrichsen et al. (1986)	14 discordant MZ twin pairs	One measurement between 9 and 17 years	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 between 0 and 6 years	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	Four measurements at a mean age of 2, 4,10, and 14.6 years	Smaller twin 0.53 SD shorter than larger twin at age 14.6 years.
Wilson (1978)	10 discordant MZ twin pairs	One measurement at 6 years	Smaller twin was 1.85 cm shorter and 2.19 kg lighter than larger twin at 6 years of age.

Outcomes are presented as median [interquartile range (IQR)] or *n* (%).
Abbreviations: MZ, monozygotic; MC, monochorionic; SD, standard deviation; TTTS, twin-twin transfusion syndrome.

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standard time points (3 months, 5-6 months, 10-12 months, 12-15 months, 22-26 months, 22-29 months, and 42-48 months). All height measurements from 22 months onwards are made homogenously in a standing position using a wall-mounted stadiometer. If twins were simultaneously followed up in a local hospital in case of prematurity/dysmaturity, these measurements were retrieved as well. Only measurements of both twins on the same day were used for analysis. We investigated all growth measurements in childhood, starting at birth followed by all standardized measurements by the primary care system and any other follow-up appointments by physicians, until the final follow-up study visit. Prior to the follow-up examination, parents were asked to report their own height and weight in a questionnaire. Children ≥8 years 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[18] to assess within-pair differences in pubertal status between smaller and larger twins that may explain any observed within-pair differences in childhood growth patterns.

All growth measurements were plotted in Dutch growth curves, generating appropriate standard deviation scores (SDSs).[19] 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. BMI was chosen rather than weight SDS, as the latter is strongly influenced by height. Within-pair differences in height SDS, BMI, and head circumference SDS were calculated as follows: SDS larger twin − SDS smaller twin. Within-pair differences in BMI were calculated in a similar manner: BMI larger twin − BMI smaller twin. TH was calculated according to the Dutch guidelines taking ethnicity into account and plotted in the growth curves as well.[20] TH for Dutch boys is calculated as follows: 44,5 + 0,376 × height father (cm) + 0,411 × height mother (cm), and TH for Dutch girls is calculated as follows: 47,1 + 0,334 × height father (cm) + 0,364 × height mother (cm). This calculation is slightly adapted for different ethnicities. As it concerns twin pairs, TH SDS was the same for the larger and smaller twins. TH range was defined as −0.8 to + 0.8 SDS. Subsequently, catch-up growth was defined as growth into TH range.[21]

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 for paired data (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 as can be seen in Supplement S2 containing the R script with the results. 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 larger twins and (2) individual height SDS minus TH SDS in relation to age (a negative value indicates a 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 and 2017, 73 twin pairs were eligible for inclusion. Of these twin pairs, 12 (16%) did not want to participate in the study (time investment was considered too large in 6 pairs, teenage twins did not wish to participate in 6 pairs, and no reasons was provided in 3 pairs) 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 (Figure 1). There were no significant differences in baseline characteristics between the included twin pairs and the group that was lost to follow-up.[14]

Baseline characteristics are presented in Table 2. The median age at participation was 11 (IQR 8-13) years. Two smaller twins had an indication to start with recombinant growth hormone therapy. One (age 5 years) was scheduled to start therapy after follow-up examination, so all growth measurements could still be included. The other (age 11 years) had started therapy at age 4, so only growth measurements up to this point of both smaller and larger twins were included. Moreover, in 1 twin pair growth measurements at follow-up examination could not be performed due to severe cognitive impairment and subsequent resistance to anthropometric measurements.

All growth SDS scores at the follow-up examination differed significantly between smaller and larger twins, with persistently lower SDS for smaller twins for all three main outcome measurements (height, weight, and head circumference) (Table 3). Smaller twins at birth had a lower height SDS [−0.6 vs −0.3, $P < .001$, median difference 0.5 (95%CI 0.4-0.7)], lower weight SDS [−0.5 vs −0.1, $P < .001$, median difference 0.8 (95%CI 0.5-1.0)], and lower head circumference SDS [−0.5 vs 0.2, $P < .001$, median difference 0.8 (95% CI 0.6-0.9)] compared to larger twins. BMI was significantly higher for the larger twin [17.2 (16.0-20.3) kg/m^2] as opposed to the smaller twin [16.0 (14.9-19.4) kg/m^2].

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—g	1744 (1219;2184)
Smaller twin	1400 (1111;1875)
Larger twin	2003 (1600;2680)
Small for gestational age	57 (61)
Smaller twin	46 (98)
<3rd centile	40 (85)
Larger twin	11 (23)
<3rd centile	2 (4)

Outcomes are presented as median [interquartile range (IQR)] or *n* (%).
Abbreviation: MC, monochorionic.

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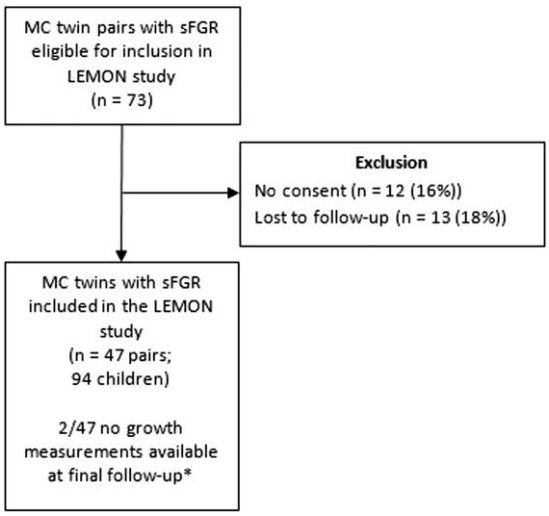

Figure 1. Flowchart of study inclusion. *Two twin pairs did not have growth measurements available at final follow-up, due to (1) recombinant growth hormone therapy from an earlier age and (2) severe cognitive impairment and subsequent resistance to anthropometric measurements. Their childhood growth measurements from the primary care system were included, up until the start of recombinant growth hormone therapy for the first pair.

Table 3. Childhood growth measurements in the smaller twin 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)	**<.0001**
Weight—SDS	−0.5 (−1.4;0.3)	−0.1 (−0.6;1.0)	**<.0001**
Head circumference—SDS	−0.5 (−1.4;0.3)	0.2 (−0.4;0.8)	**<.0001**
BMI—kg/m^2	16.0 (14.9;19.4)	17.2 (16.0;20.3)	**<.0001**
Pubertal status[a]			1.000
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)	**<.0001**
Lower weight	41 (93)	3 (7)	**<.0001**
Smaller head circumference[b]	38 (88)	5 (12)	**<.0001**

Outcomes are presented as median [interquartile range (IQR)] or *n* (%). Two twin pairs were excluded from the follow-up growth measurements. Significant associations ($P < .05$) are presented in bold.
Abbreviations: SDS, standard deviation score; BMI, body mass index; kg, kilograms; m, meters; TH, target height.
[a]Pubertal status was unknown in 1 twin pair.
[b]Two twin pairs had the same head circumference at follow-up.

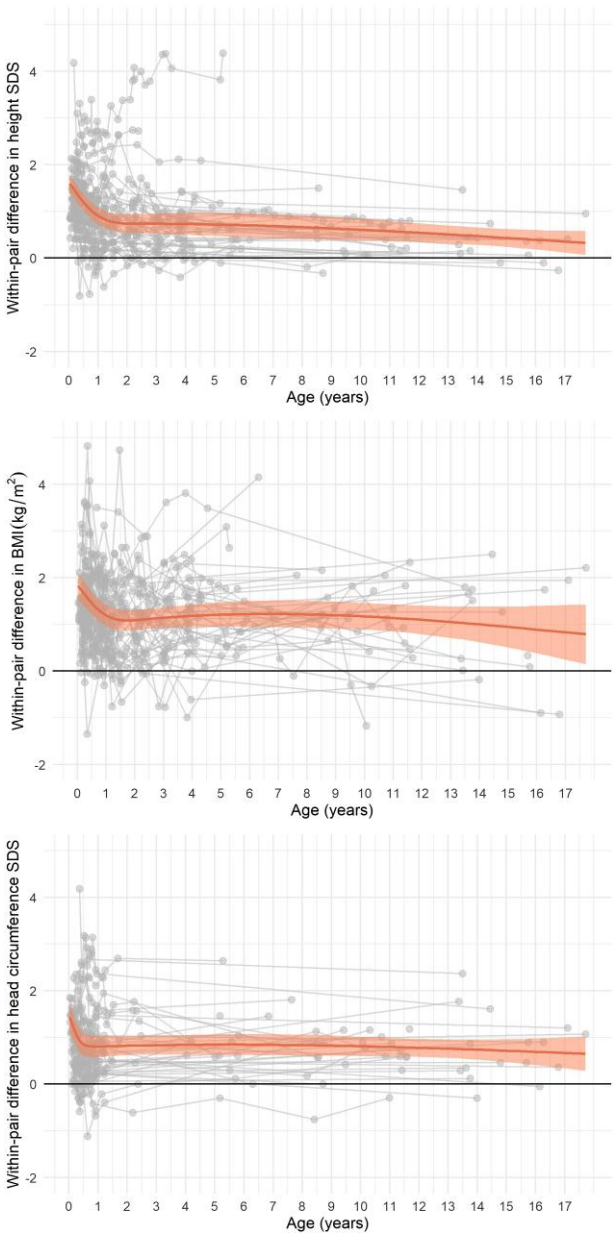

Figure 2. Mixed-effects model depicting the within-pair difference in height SDS, BMI, and head circumference SDS according to age. The line indicates the mean within-pair difference and the shading its 95% confidence interval.

In the majority of twin pairs, smaller twins were smaller [91% (41/45)], lighter [93% (41/44)], and had a smaller head circumference [88% (38/43)] at the follow-up examination ($P < .0001$).

Next, we investigated all 1072 growth measurements in childhood. Within-twin pair difference in height SDS decreased steadily from 0-17 years, with the most rapid decrease in the first 2 years after birth (Figure 2). At age 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 target height SDS between smaller and larger twins according to age (Figure 3). Larger twins were found to rapidly catch-up to their TH range at 6 months. This rapid catch-up growth continued until the age of 2. Smaller twins showed a similar rapid catch-up growth in the first 2 years of life, albeit still incomplete in the majority of cases at this age. Further catch-up growth slowed down from 2 years onwards and was completed between ages 8 and 11 years. Both smaller and larger

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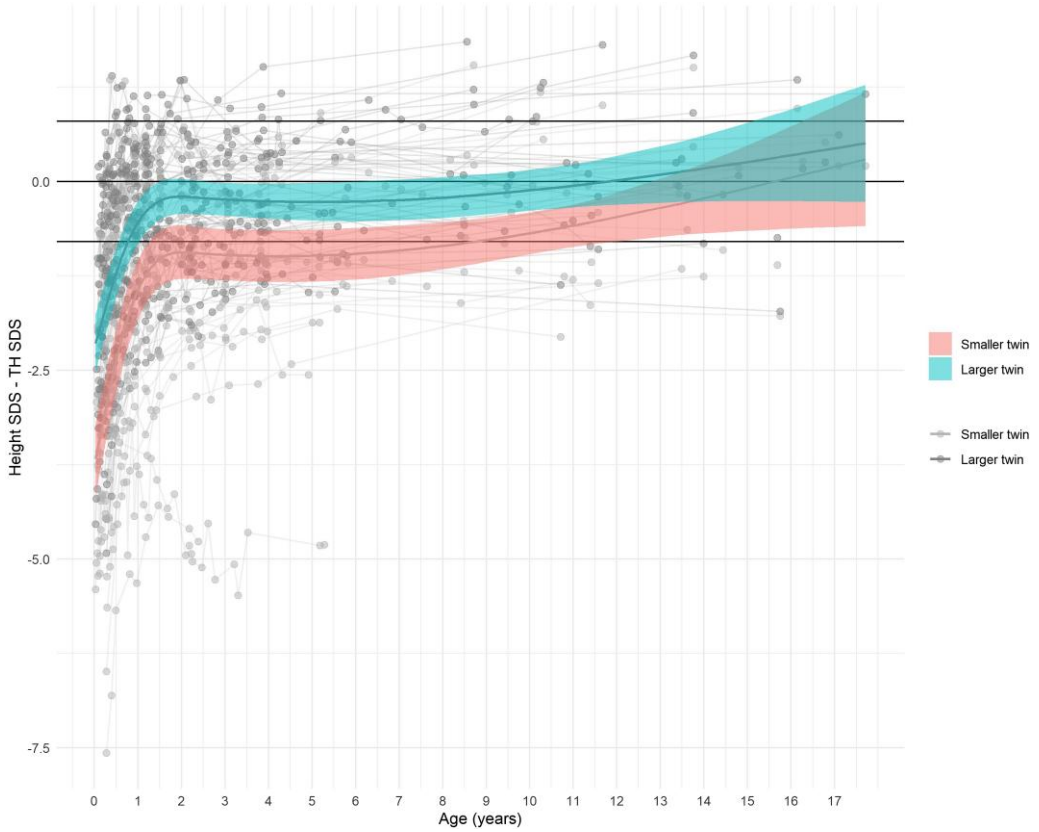

Figure 3. Mixed-effects model depicting the difference in height SDS and TH SDS according to age for the smaller and larger twins. The straight horizontal lines represent the TH range of ±0.8 SDS. The curved lines indicate the mean difference in height SDS and TH SDS and the shading their 95% confidence intervals for the smaller and larger twins. When the colored line and the lower limit of the 95% confidence interval passed into the TH range, this was considered completed catch-up growth.

twins grew further into their TH range between ages 10 and 17 years, with an additional gradual increase in height SDS of approximately 0.6 SDS. Of these 58 twins with available measurements ≥ 10 years of age, 34 were already mid-pubertal to post-pubertal at follow-up. There were no differences in gestational age at birth for those with ongoing catch-up growth between 10 and 17 years.

Discussion

Our analysis of genetically identical twins with sFGR shows that FGR results in modest but persistent differences in height (0.5 SDS), weight (0.8 SDS), and head circumference (0.8 SDS) throughout childhood, despite rapid catch-up growth in the first 2 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 smaller and larger twins is 0.3 SDS at 17 years, which corresponds to 2-3 cm at adult height. Additionally, BMI differed approximately 1 kg/m^2 and head circumference 0.7 SDS, corresponding to 1-1.5 cm.

Our results are in line with previous studies on singleton SGA children: Rapid catch-up growth in the first 2 years but a near-adult height below TH.[2] Similarly, we found that both twins rapidly catch-up within 2 years after birth following premature birth. While larger twins already reach their TH range during this period, smaller twins continue to catch-up, albeit much slower, until completion between 8 and 11 years. Within-pair differences in height, BMI, and head circumference persist well into adolescence. Importantly, dizygotic twin studies report an increasingly discordant growth with advancing age.[10,12] This substantiates our monozygotic twin model.

At present, research on growth patterns of discordant monozygotic twins is limited (Table 1). Available studies describe a normal growth pattern in which smaller twins remain only marginally (between 0 and 8 cm) shorter, albeit using different definitions of catch-up growth.[8–13] 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 98% of smaller twins in our population was born SGA and 80% had a birth weight < 1.95 kg and still exhibited catch-up growth.[10] 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 measurements, including individual height relative to genetically determined TH.

It is reassuring for physicians and parents alike to know that the vast majority of smaller twins end up in their genetic target height range without the need for additional growth-promoting therapies. Our data suggests that catch-up growth may take longer than previously expected and may not be completed until age 8-11 years. Interestingly, both smaller and larger twins seem to further grow into their TH range between ages 10 and 17 years. This may be the consequence of pubertal increase in growth velocity. It should also be noted that relatively few growth measurements in our study were available during adolescence, resulting in a wider confidence interval for this particular period.

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Growth hormone therapy is often considered when catch-up growth in SGA children is still insufficient between ages 2 and 4. The "late" catch-up growth in our cohort may support a more expectant approach, because part of these children will catch-up with time. This is relevant for borderline cases in which parents or other caregivers are hesitant to start 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 4 years may be feasible, reducing the time pressure that some parents may face while having to make this complicated decision together with their child's health care provider.[23] Yet, further research is necessary to determine the maximum duration of watchful waiting and to identify factors that allow for such an approach, as our current study design precludes these analyses.

Several limitations of our study design should be considered when interpreting our results. Firstly, growth measurements were retrospectively retrieved from our standardized primary care system. Secondly, height measurements before the age of 2 (which are the predominant data in our study) tend to be less accurate due to interobserver variation.[24] Thirdly, even though the Pubertal Development Scale is a standardized and validated questionnaire, it is still a self-assessment at a single time point and thereby inferior to performing formal Tanner staging. We were, therefore, unable to draw proper conclusions about the onset of puberty and its effect on the observed growth patterns. Additionally, the majority of the twins in this study have not reached their final height and any increases in height SDS during follow-up may be the result of premature adrenarche with advancing bone age. Lastly, 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 be caused by unequal sharing of a healthy placenta, FGR in singletons is the result of impaired trophoblast invasion with subsequent placental insufficiency.[6,25] 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 larger twins accurately reflects the growth of appropriately-grown singletons. 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.

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.[26,27] 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 permanently altered insulin sensitivity.[28] This can render individuals more susceptible to cardiovascular disease at later in life.[29] In addition, a smaller head circumference has been shown to be an important predictor of adverse neurodevelopmental outcome.[30,31] This is substantiated by our study, as we have shown that smaller twins presents with significantly lower cognitive test scores as opposed to the larger twin in a previous analysis of the neurodevelopmental outcomes.[14] The size of the within-pair difference in head circumference SDS and the within-pair difference in full scale IQ did not correlate significantly ($P = .374$). The difference in head circumference SDS was more pronounced at 17 years of age than the difference height SDS. This may be the consequence of its smaller range and relatively slower growth rate as opposed to height, thereby having less room for catch-up.

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. Smaller twins will reach a height within their target range between ages 8 and 11 years. This information may reassure parents of newborn MC twins who are concerned about 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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Supplementary material

Supplementary material is available at *European Journal of Endoicrinology* online.

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Conflict of interest: None declared.

Data availability

Individual participant data (including data dictionaries) that underlie the results reported in this article will, after de-identification, be available beginning 3 months and ending 10 years following article publication. The study protocol will also be made available. The data will be shared with researchers who provide a methodologically sound proposal and whose proposed use of the data has been approved by an independent review committee identified for this purpose and the medical ethical committee of the Leiden University Medical Center. Proposals should be directed to s.g.groene@lumc.nl. To gain access, data requestors will need to sign a data access agreement.

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