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

Groene, S.G.

Chapter 8

Long-term effects of selective fetal growth restriction (LEMON): a cohort study of neurodevelopmental outcome in growth discordant identical twins in the Netherlands.

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Sophie G. Groene

Koen J.J. Stegmeijer

Ratna N.G.B. Tan

Sylke J. Steggerda

Monique C. Haak

Femke Slaghekke

Arno A.W. Roest

Bastiaan T. Heijmans

Enrico Lopriore

Jeanine M.M. van Klink

Abstract

Background. Singletons born after fetal growth restriction (FGR) are at increased risk of poor neurodevelopmental outcomes. Studies of singletons with FGR usually compare outcomes with those without FGR, a comparison that is inherently biased by obstetrical, parental, and genetic factors. We aim to compare neurodevelopmental outcomes between the smaller and larger twin in a population of discordant identical twins who shared a single placenta, naturally eliminating these confounders.

Methods. This study is part of the LEMON cohort study of monochorionic diamniotic twins with selective FGR. All monochorionic diamniotic twins with selective FGR who were born in Leiden University Medical Center (Leiden, Netherlands) between March 1, 2002, and Dec 31, 2017, were eligible for inclusion. Twin pregnancies that were complicated by twin–twin transfusion syndrome, twin anemia polycythemia sequence, or monoamnionicity were excluded. Cognitive performance was evaluated with two standardised psychometric age-appropriate tests, producing a full-scale intelligence quotient (FSIQ). Motor functioning was assessed with a standardized neurological examination. A composite outcome of neurodevelopmental impairment (NDI) was used, subdivided into mild NDI (defined as FSIQ <85, minor neurological dysfunction or cerebral palsy grade 1, or mild visual or hearing impairment) and severe NDI (defined as FSIQ < 70, severe neurological dysfunction, or severe visual or hearing impairment).

Findings. Between Jan 25, 2021, and March 15, 2022, 47 twin pairs were enrolled in the study and underwent neurodevelopmental assessment. The median gestational age at birth was 33.9 weeks (IQR 31.3–36.0) for the 47 included twin pairs, with median birthweights of 1400 g (1111–1875) in the smaller twin and 2003 g (1600–2680) in the larger twin. The median age at neurodevelopmental assessment was 11 years (8–13). Median FSIQ was 94 (86–101) for the smaller twin and 100 (92–108) for the larger twin ($p < 0.0001$). More smaller twins had mild NDI (36% (17/47)) than did the larger twins (11% (5/47); odds ratio 4.8 (95% CI 1.6–14.1); $p = 0.0049$). There was no difference in the proportion of children with severe NDI (4%(2/47) in both groups, $p = 1.0$).

Interpretation. As mild NDI can impede children in their daily functioning, we recommend standardized long-term follow-up, including neurodevelopmental testing, for monochorionic diamniotic twins with selective FGR to facilitate early identification of children at risk.

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Introduction

The intrauterine environment sets the foundation for lifelong health. Unfavorable intrauterine circumstances, such as fetal growth restriction (FGR), in which the fetus does not reach its growth potential, are associated with health disadvantages[1]. High rates of perinatal morbidity and substantial long-term neurodevelopmental impairment (NDI), with poor cognitive performance and neurological dysfunction, have been reported for singletons with FGR[2,3]. In these studies, however, singletons with FGR are primarily compared with singletons without FGR. This comparison is inherently biased by obstetrical, parental, and genetic factors, impeding a proper risk assessment. A study population of identical twins who are discordant for fetal growth naturally eliminates these confounders.

Monochorionic diamniotic (MCDA) twins are genetically identical and share a single placenta. In 15% of MCDA twins, this placenta is unequally shared: one twin has a much smaller placental share than their co-twin, causing FGR for the twin with the smaller share, which is termed selective FGR (sFGR)[4,5]. Similar to FGR in singletons, the severity of sFGR in twins is classified according to the umbilical artery Doppler flow pattern in the smaller twin, as proposed by Gratacós and colleagues, with poorer outcomes in children from pregnancies with persistent (type II) or intermittent (type III) absent or reversed end-diastolic flow (A/REDF) than in children from pregnancies with positive end-diastolic flow (type I)[6]. Assessment of MCDA twins with sFGR can be considered a unique natural experiment in which a twin with restricted growth can be compared with its genetically identical co-twin without growth restriction, allowing evaluation of the true effect of FGR on neurodevelopmental outcomes. Little is known about the long-term outcomes of these twins at present.

Neonatal neurological outcomes of MCDA twins with sFGR have been widely reported, with a high incidence of cerebral injury (i.e., up to 33%) and an overall restriction in brain growth for the smaller twin on cerebral ultrasound[7,8]. Yet, well designed studies of long-term neurodevelopmental outcomes are scarce. The existing studies are underpowered; differ extensively in methodology, timing, and type of neurodevelopmental evaluation; and do not give detailed perinatal information[9]. The aim of this study is to compare neurodevelopmental outcomes between the smaller and larger twin in MCDA twin pairs with sFGR.

Methods

Study design and participants

This study is part of the LEMON study (Long-Term Effects of selective fetal growth restriction in MONochorionic twins), which is a cohort study, including all MCDA twin pairs with sFGR born in the Leiden University Medical Center (LUMC), Leiden, Netherlands, the national referral center for complications specific to monochorionic twins, such as twin–twin transfusion syndrome, twin anemia polycythemia sequence, and sFGR. The LEMON study was reviewed and approved by the ethics committee of the LUMC (P20.089). For children younger than 12 years, only parents were asked for written informed consent. For children 12 years and older, both children and parents were asked for written informed consent. Patient recruitment began in January 2021, and inclusion was finalized in January 2022.

All MCDA twins with sFGR who were born in the LUMC between March 1, 2002, and Dec 31, 2017, were eligible for this study, with sFGR defined as a birth weight discordance (BWD) ≥ 20% (calculated as (birth weight larger twin – birth weight smaller twin)/birth weight larger twin x 100)[10]. Twin pregnancies complicated by twin-twin transfusion syndrome, twin anemia polycythemia sequence or monoamnionicity were excluded[11,12]. Cases in which one or both twins died were excluded as within-pair analyses impossible. Lastly, twins with twin reversed arterial perfusion or other congenital abnormalities were excluded.

Procedures

The following baseline characteristics were collected: Gratacós type, with type I defined as positive end-diastolic flow, type II defined as persistent A/REDF, and type III defined as intermittent A/REDF in the umbilical artery of the smaller twin[6]; gestational age at diagnosis of sFGR (i.e., the first moment that the combination of an estimated fetal weight in <10th centile and an estimated fetal weight discordance of ≥20% was observed, categorized into early onset (< 24 weeks) and late onset (≥ 24 weeks)[13]); gestational age at birth; sex; delivery mode; birth weight and birthweight discordance; whether the child was small for gestational age (i.e., birth weight in <10th centile[14]); severe neonatal morbidity; current weight and BMI; and maternal education (primary and secondary school; intermediate vocational education; or higher vocational education and university). The perinatal baseline characteristics were retrospectively collected from patient files by SGG and KJJS. Weight and BMI as well as maternal education were documented at the time of the neurodevelopmental assessment (which is described in the next paragraph). Over the span of this study,

the sole change in management of MCDA twin pregnancies in the Netherlands was the advice to induce delivery between 36 and 37 weeks, which was gradually introduced between 2007 and 2008 (before 2007, there was no advice on delivery of MDCA twins). Severe neonatal morbidity was defined as at least one of the following: respiratory distress syndrome (i.e., respiratory failure needing mechanical ventilation or surfactant); persistent pulmonary hypertension of the neonate (i.e., the failure of circulatory transition after birth requiring treatment with nitric oxide); patent ductus arteriosus requiring medical treatment or surgical closure; necrotizing enterocolitis of at least stage 2; neonatal sepsis (i.e., a clinically ill neonate with positive blood cultures); bronchopulmonary dysplasia (i.e., supplemental oxygen for ≥ 28 days) [15]; and severe cerebral injury (i.e., intraventricular hemorrhage ≥ grade 3, cystic periventricular leukomalacia ≥ grade 2, ventricular dilatation > 97th percentile, arterial or venous infarction, or porencephalic or parenchymal cysts).

When informed consent was obtained, a follow-up appointment was scheduled. At this follow-up appointment, cognitive performance was evaluated with two standardised psychometric tests: the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition, for children aged 4–6 years[16] and the Wechsler Intelligence Scale for Children, Fifth Edition, for children older than 6 years[17]. These tests generate a full-scale intelligence quotient (FSIQ) score representing a child's general intellectual ability and five primary index scores measuring intellectual functioning in five cognitive areas: the Verbal Comprehension Index, Visual Spatial Index, Fluid Reasoning Index, Working Memory Index, and Processing Speed Index. The index scores and the FSIQ are on a standard score metric with a mean of 100 and an SD of 15. Mild cognitive delay was defined as a test score of less than 1 SD and severe cognitive delay as a test score of less than 2 SD. Motor functioning was assessed using a standardised neurological examination developed by Touwen and colleagues[18], modified by Hadders-Algra [19], to establish the presence of dysfunction in the following domains: posture, reflexes, involuntary movements, coordination, fine manipulation, associated movements, sensory function, and cranial nerve function. Simple minor neurological dysfunction was defined as the presence of one or two dysfunctional domains before the onset of puberty or an isolated presence of dysfunctional posture and tone regulation, choreiform dyskinesia, excessive associated movements, mild sensory dysfunction, or mild cranial nerve dysfunction after onset of puberty. Complex minor neurological dysfunction was defined as the presence of three or more dysfunctional domains before onset of puberty or the presence of mild coordination problems or fine manipulative disability after onset of

puberty[19]. Cerebral palsy was classified according to the Gross Motor Function Classification System[20]. Severe neurological dysfunction was defined as any severe motor impairment, including cerebral palsy of at least grade 2. The presence of any visual or hearing impairment was recorded, graded as mild visual impairment (i.e., requiring treatment by an ophthalmologist, strabismus, a correction of a maximum of plus or minus 3.0 with glasses or contact lenses, or a correction of more than plus or minus 3.0 adequately corrected with glasses or lenses), severe visual impairment (i.e., blindness or partially sighted), mild hearing impairment (i.e., hearing loss up to 30 decibels with or without amplification), or severe hearing impairment (i.e., bilateral deafness). Data on neurodevelopmental outcomes and visual or hearing impairments were collected by SGG and KJJS at follow-up examination.

NDI was used as primary composite outcome and subdivided into two categories of severity: mild NDI, defined as FSIQ less than 85, the presence of simple or complex minor neurological dysfunction (or a cerebral palsy grade 1), or mild visual or hearing impairment; and severe NDI, defined as FSIQ less than 70, the presence of severe neurological dysfunction, or severe visual or hearing.

Statistical analysis

Statistical analyses were performed with IBM Statistics version 25.0. Data are presented as median (IQR), n (%) of N, or n (%). To test for an association between sFGR and the intelligence quotient scores (numerical values), motor and sensory functioning (categorical values), and NDI (categorical values), a generalized estimating equation was used. This analysis considers that observations between co-twins are not independent. An unstructured covariance matrix was used. As the generalized estimating equation cannot be used when an outcome event does not occur in one of the groups (i.e., smaller or larger twin), an adjustment to the data was applied, in which an unaffected twin (i.e., outcome not present) was changed into an affected twin (i.e., outcome present) for both the smaller and larger twin. This adjustment generates more conservative p values than other available analyses for paired data. To test for association between Gratacós type and gestational age at birth and within-pair difference in FSIQ, a generalized estimating equation was also used. A univariate linear regression model was applied for identification of pair-related risk factors for a lower FSIQ. The Gratacós type and amount of birth weight discordance were included as well as gestational age at birth and maternal education level. When a significant association was found in the univariate analysis, the variable was included in a multivariate linear regression model. A *p*-value of less than 0.05 was

considered significant. The differences in within-pair intelligence quotient scores between the larger and smaller twin for the primary indexes and FSIQ scores and within-pair difference in FSIQ were depicted in a sinaplot using RStudio version 2021.9.2.382.

This study is registered with the Netherlands Trial Register, ID NL9833.

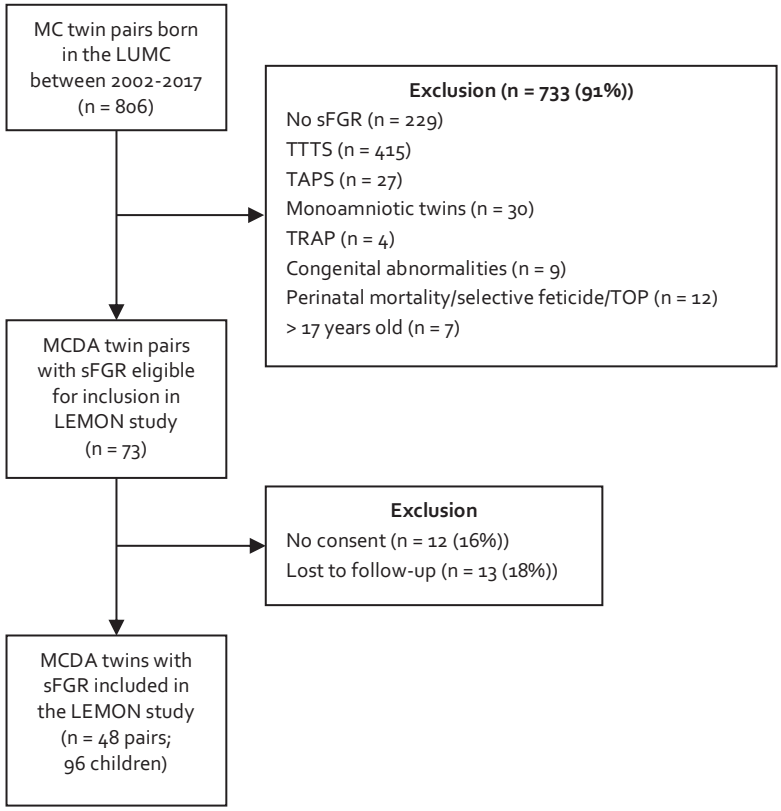

Figure 1. Flowchart of LEMON study inclusion**.** LUMC: Leiden University Medical Center. MCDA: monochorionic diamniotic. sFGR: selective fetal growth restriction. TOP: termination of pregnancy.
*Twin pairs aged 18 years or older at the start of this study (January 2021) were excluded.
†One of 48 twin pairs completed only questionnaires and did not complete the follow-up (and is therefore not included in the analysis).

Results

Between March 1, 2002, and Dec 31, 2017, 806 MCDA twin pairs were born in the LUMC, of which 73 were eligible for inclusion in the LEMON study. Of these twin pairs, 12 (16%) did not want to participate in the study, 13 (18%) were lost to follow-up (five twin pairs moved abroad and eight pairs could not be reached for inclusion), and one (1%) twin pair participated only in the questionnaire assessment of the LEMON study, leaving 47 twin pairs to be included in the neurodevelopmental follow-up (an inclusion rate of 64% for the present study; the inclusion rate for the LEMON study overall, including the twin pair who participated only in the questionnaire assessment, was 66% (48/73); Figure 1). Recruitment, data collection, and neurodevelopmental assessment took place between Jan 25, 2021, and March 15, 2022. Baseline characteristics were compared between the group of children who were included and the group of children who were lost to follow-up, and no significant differences were identified (Table A1).

Table A1. Comparison of perinatal baseline characteristics for the included twin pairs and the twin pairs that were lost to follow-up or who did not give consent for follow-up.

Characteristic	Included twins (n=47 pairs, 94 children)	Lost to follow-up/no consent (n=25 pairs, 50 children)	*p*-value
Gratacós type*			0.294
Type I	24/47 (51)	9/23 (39)	
Type II	10/47 (21)	5/23 (22)	
Type III	13/47 (28)	9/23 (39)	
Gestational age at birth – *weeks*	33.9 (31.3-36.0)	34.0 (31.4-36.0)	0.867
Sex			0.224
Female	48 (51)	18 (36)	
Male	46 (49)	32 (64)	
Caesarean	54 (94)	34 (68)	0.383
Birth weight discordance – *%*	30.1 (26.1-33.4)	36.0 (26.4-40.2)	0.085
Birth weight – *grams*			
Smaller twin	1400 (1111-1875)	1345 (925-1660)	0.475
Larger twin	2003 (1600-2680)	2140 (1455-2620)	0.973
Small for gestational age			
Smaller twin	46 (98)	24 (96)	0.651
Larger twin	11 (23)	6 (24)	0.955

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

*Gratacós type was unknown in two pregnancies of the lost to follow-up/no consent group.

Baseline characteristics

Baseline maternal, obstetrical, and neonatal characteristics are presented in table 1. Maternal education level was comparable to the general Dutch population[21]. In one twin pair, cognitive testing could not be performed due to a language barrier; a neurological examination was performed and, combined with their above-average school performance, no NDI was found.

Table 1. Maternal, obstetrical and neonatal characteristics for the included sFGR twins.

Characteristics	MCDA twins (n=94; 47 pregnancies)	Smaller twin (n=47)	Larger twin (n=47)
Gratacós type*			
Type I	24/47 (51)		
Type II	10/47 (21)		
Type III	13/47 (28)		
Gestational age at diagnosis of sFGR[†] – *weeks*	20.9 (16.9-24.6)		
Early onset (< 24 weeks)	29/39 (74)		
Late onset (≥ 24 weeks)	10/39 (26)		
Gestational age at birth – *weeks*	33.9 (31.3-36.0)		
Female	48/94 (51)		
Caesarean	54/94 (57)		
Birth weight discordance – *%*	30.1 (26.1-33.4)		
Birth weight – *grams*		1400 (1111-1875)	2003 (1600-2680)
Small for gestational age		46/47 (98)	11/47 (23)
Severe neonatal morbidity		10/47 (21)	10/47 (21)
RDS		3 (6)	10 (21)
PPHN		1 (2)	0 (0)
PDA		2 (4)	3 (6)
NEC		0 (0)	1 (2)
Sepsis		6 (13)	4 (9)
BPD		7 (15)	3 (6)
Severe cerebral injury		0 (0)	0 (0)
Maternal education			
Primary and secondary school	5/47 (11)		
Intermediate vocational education	20/47 (43)		
High vocational education or university	22/47 (47)		
Weight at assessment[‡] – *kg*		34.2 (22.9-49.5)	37.5 (27.8-52.3)
BMI at assessment[‡] – *kg/m²*		16.0 (14.9-19.2)	17.1 (16.0-20.2)

MCDA: monochorionic diamniotic. sFGR: selective fetal growth restriction, BMI: body mass index.
Outcomes are presented as median (interquartile range (IQR)), n/N (%) or n (%).
[†]Gestational age at diagnosis was unknown in eight twin pairs.
[‡]Weight not measured in two twin pairs for logistic reasons.

Table 2. Neurodevelopmental outcomes compared between the smaller and larger twin in sFGR twins.

Outcomes	Smaller twin (n=47)	Larger twin (n=47)	*p*-value
Age at participation	11 (8-13)	11 (8-13)	
Cognitive test score*			
FSIQ	94 (86-101)	100 (92-108)	**<0.0001**
Verbal Comprehension	96 (86-103)	103 (92-113)	**<0.0001**
Visual Spatial	92 (85-104)	97 (89-110)	**0.0012**
Fluid Reasoning	97 (90-105)	100 (93-109)	**0.016**
Working Memory	91 (85-100)	99 (88-110)	**<0.0001**
Processing Speed	95 (86-106)	100 (94-108)	**<0.0001**
Higher FSIQ‡	9/46 (20)	34/46 (74)	**<0.0001**
Cognitive delay			
Mild (score < 1 SD)	8/46 (17)	2/46 (4)	0.073
Severe (score < 2 SD)	1/46 (2)	0/46 (0)	0.322
Neurological examination			
Simple MND	7/47 (14)	2/47 (4)	0.069
Complex MND	1/47 (2)	2/47 (4)	0.571
Cerebral palsy	1/47 (2)	0/47 (0)	0.322
Severe neurological dysfunction	1/47 (2)	0/47 (0)	0.322
Visual impairment			
Mild	1/47 (2)	1/47 (2)	1.000
Severe	2/47 (4)	0/47 (0)	0.178
Hearing impairment			
Mild	4/47 (9)	1/47 (2)	0.101
Severe	0/47	0/47	1.000
Neurodevelopmental impairment			
Mild	17/47 (36)	5/47 (11)	**0.0049**
Severe	2/47 (4)	2/47 (4)	1.000

FSIQ: full scale intelligence quotient, SD: standard deviation, MND: minor neurological dysfunction. Outcomes are presented as median (interquartile range (IQR)), n/N (%) or n (%).

*Cognitive test scores were not available in one twin pair. ‡The FSIQ was the same in three twin pairs.

The median age at neurodevelopmental assessment was 11 (IQR 8–13 years). Median FSIQ was significantly lower for the smaller twin (Table 2). All index scores were affected similarly with a disadvantage for the smaller twin (Figure 2): verbal comprehension was 7 points lower, visual spatial was 5 points lower, fluid reasoning was 3 points lower, working memory was 8 points lower, and processing speed was 5 points lower (Table 2). Median within-pair differences for FSIQ and the indexes are presented in Table A2. Age (p = 0.85), weight (p = 0.50), and BMI (p = 0.165) at follow-up did not affect the size of the within-pair FSIQ difference. The smaller twin had a higher FSIQ than the larger twin in nine (20%) of 46 twin pairs for whom an FSIQ could be generated, whereas the larger twin had a higher FSIQ than the smaller twin in 34

(74%) twin pairs (p < 0.0001). The FSIQ was the same in three twin pairs. Mild cognitive delay was present in eight (17%) of 46 smaller twins as opposed to two (4%) of 46 larger twins (p = 0.073).

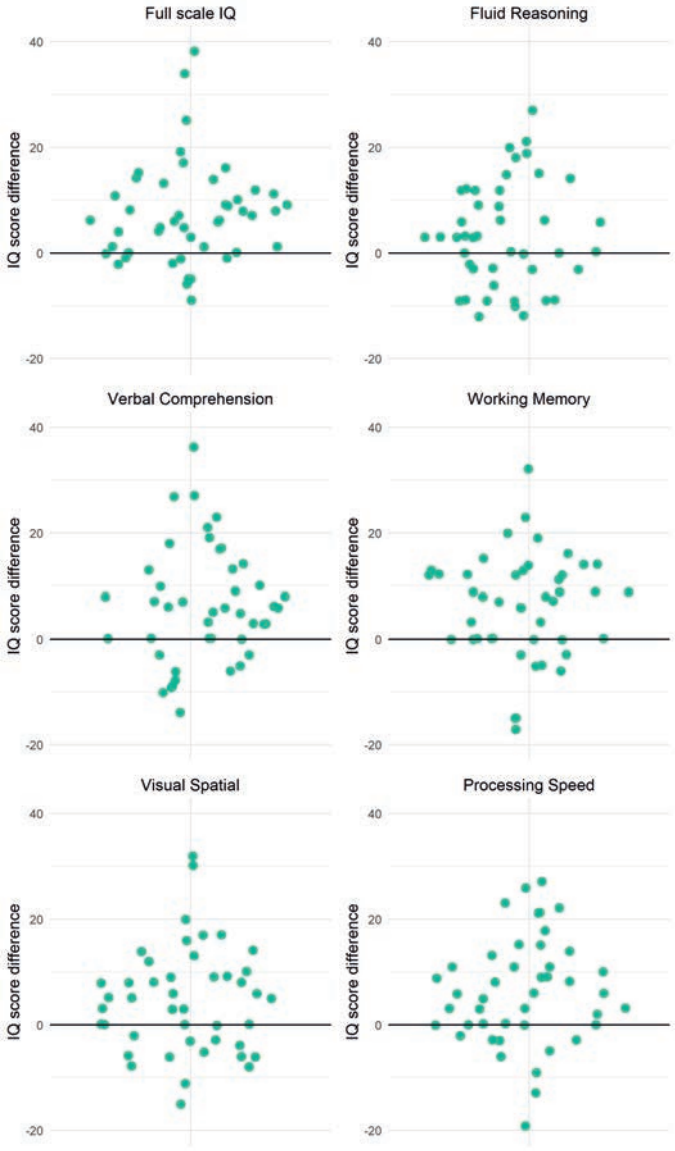

Figure 2. Sinaplot of the within-pair IQ score differences between the larger and the smaller twin per index. The calculation for the within-pair difference was: IQ score of larger twin minus IQ score of smaller twin. A positive score difference indicates that the smaller twin had a lower IQ score than the larger twin. A negative score difference indicates that the larger twin had a lower IQ score than the smaller twin.

Two factors were univariately associated with FSIQ: Gratacós type (β coefficient –12.2 (95% CI –20.8 to –3.5) for type II and β coefficient –9.5 (–17.3 to –1.8) for type III)—i.e., an FSIQ that was 12.2 points lower for type II and 9.5 points lower for type III than with type I (p = 0.0062)—and gestational age at birth (β coefficient 2.1 (0.8–3.5); i.e., for each additional week in gestational age at birth, FSIQ increases by 2.1 points (p = 0.0019); Table 3). Multivariate analysis did not identify these two factors as independent.

Table 3. Uni- and multivariate risk factor analysis for lower FSIQ in MC twins with sFGR.

	Univariate analysis			**Multivariate analysis**		
Characteristic	**β coefficient (95% CI)**	**SE**	***p*-value**	**β coefficient (95% CI)**	**SE**	***p*-value**
Gratacós type			**0.0062**			0.289
Type I	-	-		-	-	
Type II	-12.2 (-20.8--3.5)	4.416		-6.7 (-15.1-1.8)	3.985	
Type III	-9.5 (-17.3--1.8)	3.933		-3.8 (-15.3-6.7)	5.528	
Gestational age at birth – *weeks*	2.1 (0.8-3.5)	0.690	**0.0019**	1.5 (-0.3-3.3)	0.919	0.109
Birth weight discordance – %	-0.3 (-0.8-0.2)	0.233	0.191			
Maternal education			0.234			
Primary and secondary school	-5.3 (-14.7-3.5)	4.623				
Intermediate vocational education	3.0 (-4.7-10.7)	3.925				
High vocational education or university	-	-				

CI: confidence interval, SE: standard error.
Outcomes are presented as median (interquartile range (IQR)).

Regarding the different Gratacós types, gestational age at birth and FSIQ were significantly lower in children from pregnancies classified as type II and type III than children from pregnancies classified as type I. Children from pregnancies classified as type I were born at a median gestational age of 35.7 weeks (IQR 34.0–36.7) with a median FSIQ of 102 (94–109), those from pregnancies classified as type II were born at a median gestational age of 31.3 weeks (30.4–32.6) with a median FSIQ of 94 (85–99), and those from pregnancies classified as type III were born at a median gestational age of 31.7 weeks (29.7–34.1; p < 0.0001) with a median FSIQ of 93 (86–100; p = 0.0062; Table A3; Figure 3). The within-pair difference in FSIQ was numerically larger,

although not significantly so (p = 0.086), for type II pregnancies than for type I and III pregnancies (6 points (IQR 4–9) for type I, 14 points (4–27) for type II, and 6 points (1–10) for type III).

Simple minor neurological dysfunction was more often present in the smaller twin than in the larger twin (Table 2). One smaller twin presented with cerebral palsy grade I and another smaller twin presented with severe neurological dysfunction (epilepsy and severe developmental delay substantially impeding the neurological examination). The two observed severe visual impairments in the smaller twins in our population consisted of a correction of –10.0 following extensive retinopathy of prematurity and a unilateral coloboma (i.e., a congenital defect in the iris of the eye). Of the five children with a mild hearing impairment (four were smaller twins, one was a larger twin), four presented with a unilateral hearing aid (three were smaller twins, one was the larger twin). The hearing loss was congenital in origin (in two of five children), caused by chronic inner ear infections (in two children), or a cholesteatoma (in one child).

Table A2. Overview of within-pair differences in IQ scores and rate of NDI per twin pair.

Characteristic	MCDA twins (n=47 pregnancies)
Within-pair difference in cognitive test scores	
FSIQ	6 (0-11)
Verbal Comprehension	6 (0-14)
Visual Spatial	5 (-3-10)
Fluid Reasoning	3 (-3-12)
Working Memory	8 (0-13)
Processing Speed	6 (0-13)
Mild NDI per twin pair	
No mild NDI	27/47 (57)
Only smaller twin	15/47 (32)
Only larger twin	3/47 (6)
Both twins	2/47 (4)
Severe NDI per twin pair	
No severe NDI	44/47 (94)
Only smaller twin	1/47 (2)
Only larger twin	1/47 (2)
Both twins	1/47 (2)

MCDA: monochorionic diamniotic, FSIQ: full scale intelligence quotient. NDI: neurodevelopmental impairment.
Outcomes are presented as median (interquartile range (IQR)) or n/N (%).

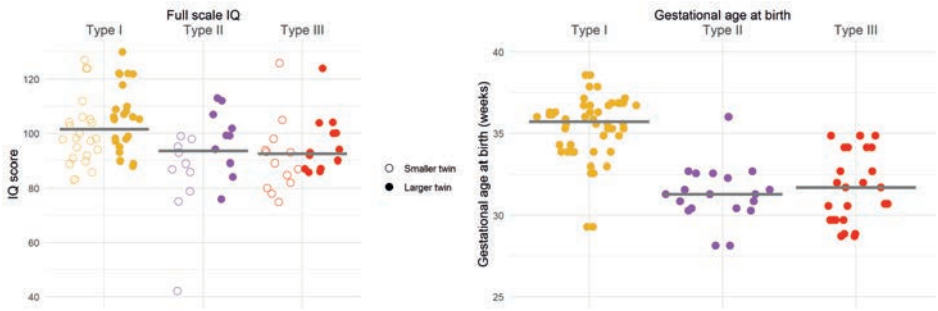

Figure 3. Sinaplot of the FSIQ and gestational age at birth per Gratacós type, with the grey line representing the median.

Smaller twins presented with significantly more frequent mild NDI than the larger twins (Table 2), and a higher odds of developing mild NDI than larger twins (odds ratio 4.8, 95% CI 1.6–14.1) based on the generalized estimating equation model. Of the children with mild NDI, 14% (3/22) children presented with multiple impairments on different domains (all smaller twins). Age (p = 0.28), weight (p = 0.45), and BMI (p = 0.22) at follow-up did not affect the presence of mild NDI. There was no difference in the presence of severe NDI (4% (2/47) children in both groups; p = 1.0). Of the children with severe NDI, 75% (3/4) children presented with multiple impairments (two were smaller twins). The proportions of mild and severe NDI per twin pair are presented in Table A2.

Table A3. Gestational age at birth and FSIQ scores in sFGR twins per Gratacós type.

Characteristic	Type I (n = 24)	Type II (n = 10)	Type III (n =13)	*p*-value
Gestational age at birth – *weeks*	35.7 (34.0-36.7)	31.3 (30.4-32.6)	31.7 (29.7-34.1)	**<0.0001**
FSIQ	102 (94-109)	94 (85-99)	93 (86-100)	**0.006**
Difference in FSIQ	6 (4-9)	14 (4-27)	6 (1-10)	0.086

FSIQ: full scale intelligence quotient.
Outcomes are presented as median (interquartile range (IQR).

Discussion

In MCDA twins with sFGR, the smaller twin presents with a lower intelligence quotient across all indexes and an increased rate of mild NDI compared with the larger co-twin. To our knowledge, we are the first to show that FGR poses a substantial risk for long-term neurodevelopment in this unique identical twin model controlling for maternal, obstetrical, and genetic factors.

We report that the prevalence of mild NDI in smaller twins with sFGR (36%) was more than double that of the general population (14%; intelligence follows a normal distribution), stressing the clinical importance of our results. This increased prevalence of mild NDI could be considered a consequence of prematurity, as research has shown an exponential increase in prevalence of developmental delay as gestational age at birth decreases[22]. However, in a large population (n = 1461) with a similar gestational age at birth (i.e., 30–34 weeks) to the twins in our study, the prevalence of mild NDI was estimated at 16%[23]. The prevalence of mild NDI for the smaller twins in our study was more than double this estimate, supporting our hypothesis that FGR also affects neurodevelopmental outcomes for a given gestational age. The larger twins in our study had a lower rate of mild NDI than did the participants in this same population (11% vs 16%), which suggests that the larger twin might be spared from adverse neurodevelopmental outcomes to a greater extent than are singletons without FGR. Being a twin is often thought to be a risk factor for NDI, but studies report no differences for twins and singletons when matched for gestational age and birthweight[24]. As we have not included a group of singletons in our study, no well-founded statements can be made.

Our findings agree with the scientific literature on neurodevelopmental outcome after FGR in singletons. A systematic review by Murray and colleagues described a 0.5 SD difference in cognitive test score for children with FGR when compared with children without FGR, exacerbated to 0.7 SD in children born at less than 35 weeks gestational age[25]. This finding is consistent with the difference of 6 points in FSIQ between the smaller and larger twin in our study. Another systematic review by Sacchi and colleagues concluded that preterm children with FGR were 1.6 times more likely to have mild cognitive delay and 2.8 times more likely to have severe cognitive delay than were children without FGR[26]. This association did not reach statistical significance in our study population due to the small sample size, but eight (17%) smaller twins had mild cognitive delay compared with two (4%) larger twins. On the

basis of the available scientific literature, we present the most complete overview of long-term neurodevelopmental outcome in a cohort of MCDA twins with sFGR.

The observed deficits for the smaller twin are hypothesised to be the consequence of prenatal adversity. The development of the brain during pregnancy is an intricate process requiring a stable and favourable environment. When this environment is suboptimal, as is the case in FGR, it can induce major changes in brain development[27]. White matter injury, a persistent reduction in grey matter volume, and altered brain connectivity on MRI have been reported in singletons with FGR[27]. In a previous study about structural changes on cerebral ultrasound, we showed that the smaller twin presents with an overall reduction in brain growth.8 All of these structural adaptations have been linked to increased rates of NDI in children with FGR.

Regarding the different Gratacós types specific for MCDA twins, our analysis shows that twins born after a pregnancy classified as type II (persistent A/REDF) or type III (intermittent A/REDF) have significantly lower FSIQ scores than those born after a pregnancy classified as type I, supporting previous research[28]. The changing umbilical artery doppler flow pattern as observed in type III pregnancy is thought to be the consequence of large arterio-arterial anastomoses on the shared placenta[5,6]. These large anastomoses can cause episodes of acute feto-fetal transfusion, which can affect brain development through either vascular overload or hypovolemic events[6]. These results should be interpreted cautiously. Children from type II and type III pregnancies were also born significantly earlier than children from type I pregnancies. It is well known that prematurity is one of the most important determinants of long-term neurodevelopmental outcomes[29]. The lower FSIQ score for children with abnormal umbilical artery Doppler flow patterns could therefore be a direct consequence of the increased rate of iatrogenic prematurity, as also reflected by our univariate and multivariate linear regression analyses for FSIQ. Both Gratacós type and gestational age at birth were univariately associated with FSIQ in our population. On multivariate analysis, these associations ceased to exist, suggesting a relationship between Gratacós type and gestational age at birth.

Our study has limitations that should be considered when interpreting the results. First, because we included live twin pairs (i.e., both twins had to be alive to be eligible) and have a low number of children from type II and type III pregnancies, we might have an under-representation of severe cases (i.e., children with more adverse perinatal outcomes). Additionally, our inclusion rate of 66% (64% in the present study)

might introduce bias into the results. Baseline characteristics were compared between the group of children who were included and the group of children who were lost to follow-up, and no significant differences were identified. Lastly, our twin design might not serve as an infallible proxy for FGR in singletons due to different pathophysiological mechanisms. FGR in singletons is primarily caused by placental insufficiency (i.e., multifactorial in origin), whereas the mechanism in MCDA twins is associated with unequal placental sharing[5]. Similarly, the neurodevelopmental outcomes of MCDA twins can differ from those of both dichorionic twins and singletons because MCDA twins share a placenta with vascular anastomoses connecting the circulatory systems of the twins[30]. Nevertheless, we present an extensive long-term follow-up in a cohort of MCDA twins with sFGR, including a broad spectrum of neurodevelopmental outcomes throughout childhood. Whereas previous studies primarily reported on neurodevelopment at the age of 2 years assessed with a surrogate questionnaire, we performed actual neurodevelopmental testing at an older age (median age 11 years), thereby increasing the reliability of our results. Moreover, in using this identical twin model, we were able to uncover the true effect of FGR on neurodevelopmental outcomes by eliminating fundamental confounders, such as gestational age at birth and genetic predisposition.

The information provided by our study allows clinicians to more accurately counsel parents about the future development of their child than before. Even though the impairments in our study population are mainly classified as mild, children are still impeded in their daily functioning. Children at risk can now be identified at an early stage after birth and in childhood, and targeted interventions can be administered to optimise development. The next step in research on neurodevelopmental outcomes in MCDA twins with sFGR involves linking the functional consequences of FGR to probable alterations in brain growth, maturation, and connectivity on MRI. Finally, the insights presented in this study are also crucial in forming a specific management protocol for MCDA twins with sFGR and emphasise that survival should not be the sole indicator of successful perinatal management.

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