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

*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*

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**Neonatology** (S G Groene BSc, K J J Stegmeijer BSc, R N G B Tan MD, S J Steggerda MD PhD, Prof E Lopriore MD PhD, J M M van Klink PhD) **and Pediatric Cardiology** (A A W Roest MD PhD), **Willem-Alexander Children's Hospital, Department of Pediatrics, Leiden University Medical Center, Leiden, Netherlands; Molecular Epidemiology, Department of Biomedical Data Sciences** (S G Groene, Prof B T Heijmans PhD) **and Fetal Therapy, Department of Obstetrics** (M C Haak MD PhD, F Slaghekke MD PhD), **Leiden University Medical Center, Leiden, Netherlands**

Correspondence to: Ms Sophie G Groene, Neonatology, Willem-Alexander Children's Hospital, Department of Pediatrics, Leiden University Medical Center, 2333 ZA Leiden, Netherlands **s.g.groene@lumc.nl**

## Summary

**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 (monochorionic diamniotic), naturally eliminating these confounders.

**Methods** This study is part of the cohort study LEMON 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 anaemia polycythaemia 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 standardised 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 (17 [36%] of 47) than did the larger twins (five [11%] of 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 (two [4%] of 47 in both groups, $p=1·0$).

**Interpretation** As mild NDI can impede children in their daily functioning, we recommend standardised 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. Unfavourable 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

## Research in context

**Evidence before this study**

Fetal growth restriction (FGR) is associated with an increased risk of neurodevelopmental problems in childhood, with lower cognitive test scores and higher rates of impairment across different domains than for children without FGR. We searched PubMed on March 7, 2022, with the search terms "fetal growth restriction" and "neurodevelopment", with no date or language restrictions. We found that current evidence is primarily based on studies in which singletons with FGR are compared with singletons without FGR, a comparison that is inherently biased by obstetrical, parental, and genetic factors.

**Added value of this study**

Identical twins discordant for fetal growth are a unique population for studying the actual effect of FGR as they share their genetic make-up, sex, age, and family environment and, apart from the factors that led to discordant growth, had the same in utero conditions and the same gestational age at birth. Our study presents extensive long-term neurodevelopmental follow-up, including age-appropriate cognitive testing and standardised neurological examinations, in a cohort of discordant monochorionic diamniotic twins for whom comprehensive perinatal data are available.

**Implications of all the available evidence**

Consistent with previous studies, our identical twin study shows a strong association between FGR and neurodevelopmental impairment. Standardised long-term follow-up is essential for the early identification of children at risk of neurodevelopmental impairment. The next step in research on neurodevelopmental outcomes in monochorionic diamniotic twins with selective FGR is to perform MRI studies to identify any changes in structural brain development that underlie the observed functional consequences.

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 (ie, 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 centre for complications specific to monochorionic twins, such as twin–twin transfusion syndrome, twin anaemia polycythaemia 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 finalised 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 birthweight discordance of 20% or more, calculated as (birthweight of larger twin – birthweight smaller twin)/birthweight of larger twin × 100.[10] Twin pregnancies that were complicated by twin–twin transfusion syndrome, twin anaemia polycythaemia sequence, or monoamnionicity were excluded.[11,12] Cases in which one or both twins died were excluded because within-pair analyses were 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 (ie, the first moment that the combination of an estimated fetal weight in <10th centile and an estimated fetal weight discordance of ≥20% was observed, categorised into early onset [<24 weeks] and late onset [≥24 weeks][13]); gestational age at birth; sex; delivery mode; birthweight and birthweight discordance; whether the child was small for gestational age (ie, birthweight 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

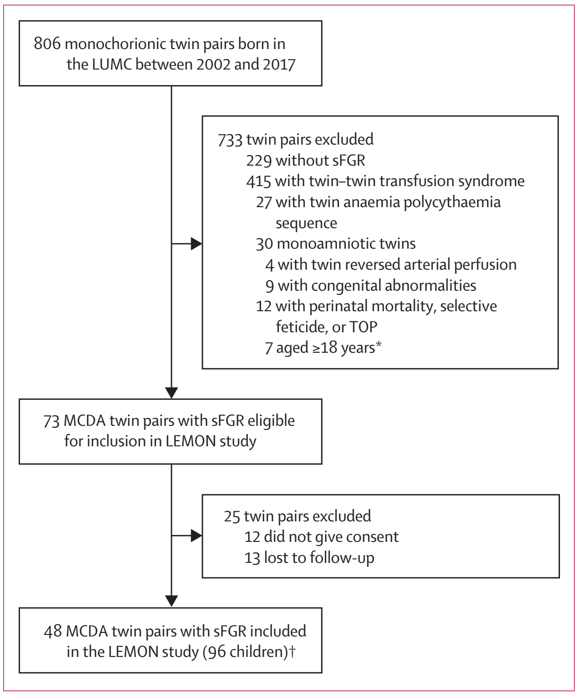


***Figure 1:*** **Flowchart of LEMON study inclusion**
LUMC=Leiden University Medical Center. MCDA=monochorionic diamniotic. sFGR=selective fetal growth restriction. TOP=termination of pregnancy. *Twin pairs aged 18 years or older at the start of this study (January, 2021) were excluded. †One of 48 twin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

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 (ie, respiratory failure needing mechanical ventilation or surfactant); persistent pulmonary hypertension of the neonate (ie, the failure of circulatory transition after birth requiring treatment with nitric oxide); patent ductus arteriosus requiring medical treatment or surgical closure; necrotising enterocolitis of at least stage 2; neonatal sepsis (ie, a clinically ill neonate with positive blood cultures); bronchopulmonary dysplasia (ie, supplemental oxygen for ≥28 days);[15] and severe cerebral injury (ie, intraventricular haemorrhage ≥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 (ie, 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 (ie, blindness or partially sighted), mild hearing impairment (ie, hearing loss up to 30 decibels with or without amplification), or severe hearing impairment (ie, 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 impairment.

Questionnaires regarding attachment, behaviour and psychosocial development, and school functioning were administered to the study population. Findings from the questionnaire assessment will be reported in a separate publication.

### 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 generalised estimating equation was used. This analysis considers that observations between co-twins are not independent. An unstructured covariance matrix was used. As the generalised estimating equation cannot be used when an outcome event does not occur in one of the groups (ie, smaller or larger twin), an adjustment to the data was applied, in which an unaffected twin (ie, outcome not present) was changed into an affected twin (ie, 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 generalised 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 birthweight 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.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

| | 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) | .. | .. |
| Sex | | | |
| Female | 48/94 (51%) | .. | .. |
| Male | 46/94 (49%) | .. | .. |
| Caesarean | 54/94 (57%) | .. | .. |
| Birthweight discordance, % | 30·1 (26·1–33·4) | .. | .. |
| Birthweight, g | .. | 1400 (1111–1875) | 2003 (1600–2680) |
| Small for gestational age | .. | 46 (98%) | 11 (23%) |
| Severe neonatal morbidity | .. | 10 (21%) | 10 (21%) |
| Respiratory distress syndrome | .. | 3 (6%) | 10 (21%) |
| Persistent pulmonary hypertension of the neonate | .. | 1 (2%) | 0 |
| Patent ductus arteriosus | .. | 2 (4%) | 3 (6%) |
| Necrotising enterocolitis | .. | 0 | 1 (2%) |
| Sepsis | .. | 6 (13%) | 4 (9%) |
| Bronchopulmonary dysplasia | .. | 7 (15%) | 3 (6%) |
| Severe cerebral injury | .. | 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 neurodevelopmental assessment‡, kg | .. | 34·2 (22·9–49·5) | 37·5 (27·8–52·3) |
| BMI at neurodevelopmental assessment‡, kg/m² | .. | 16·0 (14·9–19·2) | 17·1 (16·0–20·2) |

Outcomes are presented as median (IQR), n/N (%), or n (%). MCDA=monochorionic diamniotic. sFGR=selective fetal growth restriction. *Type I: positive end-diastolic flow; type II: persistent absent or reversed end-diastolic flow; type III: intermittent absent or reversed end-diastolic flow in the umbilical artery of the smaller twin. †Gestational age at diagnosis was unknown in eight twin pairs. ‡Weight not measured in two twin pairs for logistical reasons.

***Table 1:*** **Maternal, obstetrical, and neonatal characteristics for the included twins with sFGR**

## 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 of 73 twin pairs]; 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 (appendix p 1).

See Online for appendix

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.

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

| | Smaller twin (n=47) | Larger twin (n=47) | p value |
|---|---|---|---|
| Age at neurodevelopmental assessment, years | 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 | 0·32 |
| Neurological examination | | | |
| Simple minor neurological dysfunction | 7 (15%) | 2 (4%) | 0·069 |
| Complex minor neurological dysfunction | 1 (2%) | 2 (4%) | 0·57 |
| Cerebral palsy | 1 (2%) | 0 | 0·32 |
| Severe neurological dysfunction | 1 (2%) | 0 | 0·32 |
| Visual impairment | | | |
| Mild | 1 (2%) | 1 (2%) | 1·0 |
| Severe | 2 (4%) | 0 | 0·18 |
| Hearing impairment | | | |
| Mild | 4 (9%) | 1 (2%) | 0·10 |
| Severe | 0 | 0 | 1·0 |
| Neurodevelopmental impairment | | | |
| Mild | 17 (36%) | 5 (11%) | 0·0049 |
| Severe | 2 (4%) | 2 (4%) | 1·0 |

Outcomes are presented as median (IQR), n/N (%), or n (%). All analyses were performed with generalised estimating equations. FSIQ=full-scale intelligence quotient. sFGR=selective fetal growth restriction. *Cognitive test scores were not available in one twin pair. †FSIQ was the same between the smaller and larger twin in three twin pairs.

***Table 2:* Long-term neurodevelopmental outcomes compared between the smaller and larger twin in twins with sFGR**

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 the appendix (p 2). 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).

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)—ie, 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]; ie, 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.

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; appendix p 3; 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 (ie, 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).

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 generalised estimating equation model. Of the children with mild NDI, three (14%) of 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 (two [4%] of 47 children in both groups; p=1·0). Of the children with severe NDI, three (75%) of four children presented with multiple impairments (two were smaller twins). The proportions of mild and severe NDI per twin pair are presented in the appendix (p 2).

## 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 (ie, 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.

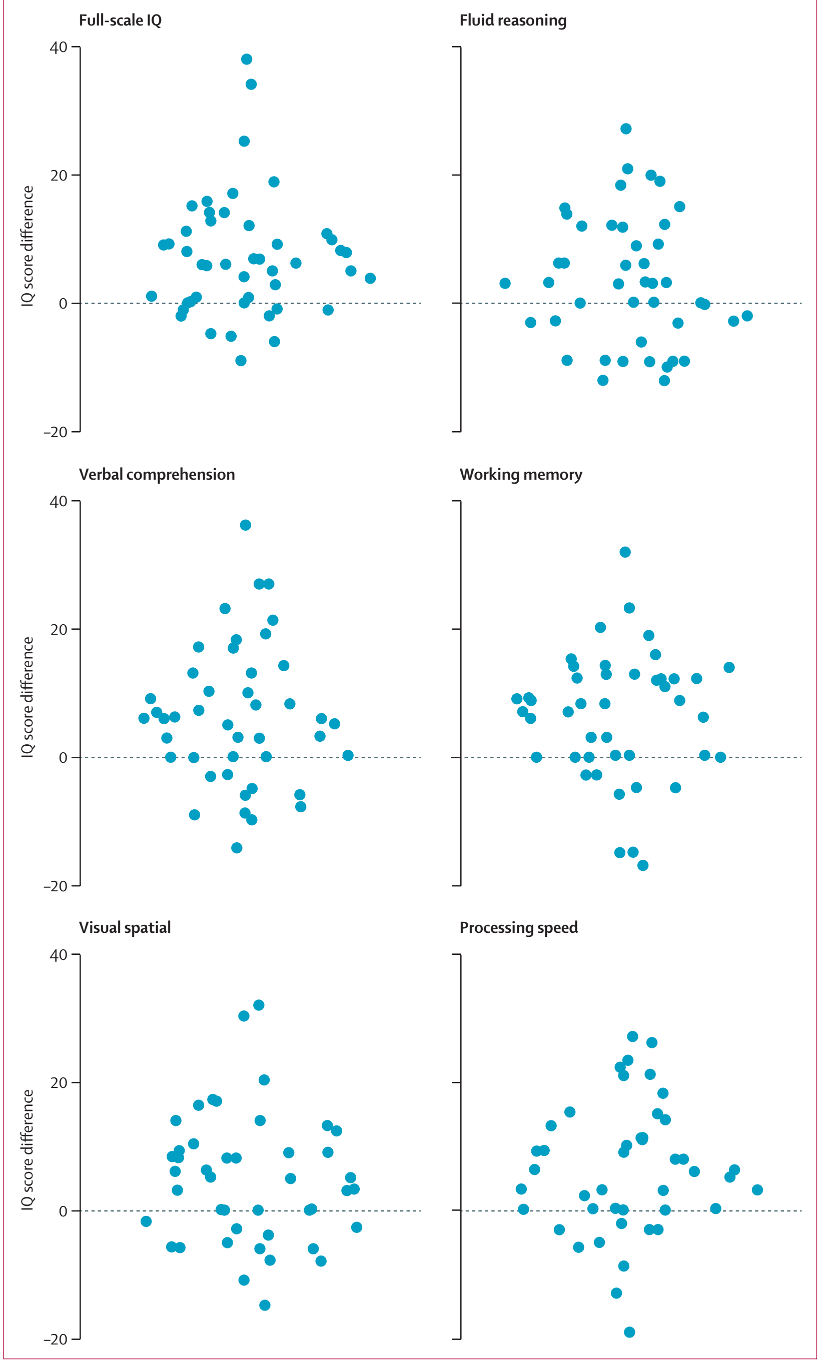


***Figure 2:* Sinaplot of the within-pair IQ score differences between the larger and the smaller twin per index**
The calculation for the within-pair difference was: IQ score of larger twin minus IQ score of smaller twin. A positive score difference indicates that the smaller twin had a lower IQ score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

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]

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | β coefficient (95% CI) | SE | p value | β coefficient (95% CI) | SE | p value |
| Gratacós type* | | | 0·0062 | | | 0·29 |
| Type I† | 0 | .. | .. | 0 | .. | .. |
| Type II | –12·2 (–20·8 to –3·5) | 4·416 | .. | –6·7 (–15·1 to 1·8) | 3·985 | .. |
| Type III | –9·5 (–17·3 to –1·8) | 3·933 | .. | –3·8 (–15·3 to 6·7) | 5·528 | .. |
| Gestational age at birth, weeks | 2·1 (0·8 to 3·5) | 0·690 | 0·0019 | 1·5 (–0·3 to 3·3) | 0·919 | 0·11 |
| Birthweight discordance, % | –0·3 (–0·8 to 0·2) | 0·233 | 0·19 | .. | .. | .. |
| Maternal education | | | 0·23 | | | .. |
| Primary and secondary school | –5·3 (–14·7 to 3·5) | 4·623 | .. | .. | .. | .. |
| Intermediate vocational education | 3·0 (–4·7 to 10·7) | 3·925 | .. | .. | .. | .. |
| High vocational education or university† | 0 | .. | .. | .. | .. | .. |

Outcomes are presented as median (IQR). All analyses were performed with generalised estimating equations. When a significant association was found in the univariate analysis, the variable was included in a multivariate linear regression model. *Type I: positive end-diastolic flow, type II: persistent absent or reversed end-diastolic flow, type III: intermittent absent or reversed end-diastolic flow in the umbilical artery of the smaller twin. †Reference category.

***Table 3:*** **Univariate and multivariate risk-factor analysis for lower full-scale intelligence quotient in monochorionic diamniotic twins with selective fetal growth restriction**

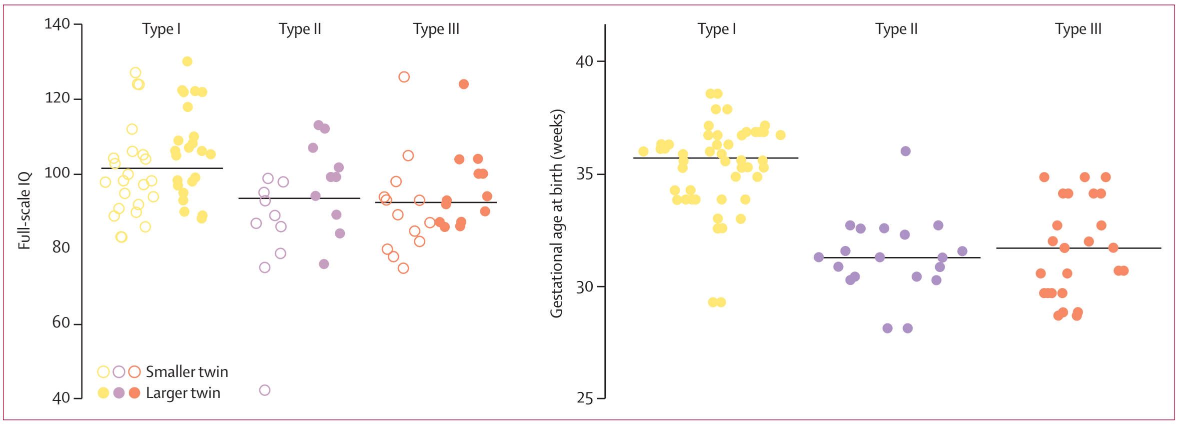


***Figure 3:*** **Sinaplot of the full-scale IQ and gestational age at birth per Gratacós type**
Grey line indicates the median. IQ=intelligence quotient.

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 hypovolaemic 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 (ie, 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 (ie, 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 (ie, 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.

#### Contributors

SGG, AAWR, BTH, EL, and JMMvK were responsible for the concept and design of the study. SGG, KJJS, and JMMvK collected, analysed, and interpreted the data, did the statistical analysis, and drafted the manuscript. All authors critically revised the manuscript. JMMvK supervised the study. SGG, KJJS, and JMMvK accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

We declare no competing interests.

#### Data sharing

Individual participant data (including data dictionaries) that underlie the results reported in this article (text, tables, figures, and appendices) and the study protocol will be available beginning 3 months and ending 10 years after publication. 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 (learned intermediary) identified for this purpose and the medical ethical committee of the Leiden University Medical Center, to achieve the aims in the approved proposal. 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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