Early Human Development 151 (2020) 105224

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Growth trajectories of the human fetal brain in healthy and complicated pregnancies and associations with neurodevelopmental outcome in the early life course

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ARTICLE INFO

Keywords:
Fetal brain trajectories
Cortical folding
Fetal programming
Neurodevelopment
Children

ABSTRACT

Background: There is a need for non-invasive prenatal markers of the brain to assess fetuses at risk for poor postnatal neurodevelopmental outcome. Periconceptional maternal conditions and pregnancy complications impact prenatal brain development.
Aims: To investigate associations between growth trajectories of fetal brain structures and neurodevelopmental outcome in children in the early life course.
Study design: Periconceptional prospective observational cohort.
Subjects: Singleton pregnancies were included in the Rotterdam periconception cohort. Two- and three-dimensional ultrasound scans at 22, 26 and 32 weeks gestational age were analysed.
Outcome measures: Head circumference (HC), cerebellum, corpus callosum (CC), Sylvian fissure, insula and parieto-occipital fissure (POF) were measured. Neurodevelopment was evaluated using the Age-and-Stages-questionnaire-3 (ASQ-3) and the Child-Behaviour-Checklist (CBCL) at 2 years of age. Linear mixed models, used to estimate the prenatal brain growth trajectories, and linear regression models, used to evaluate the associations between prenatal brain structures and neurodevelopmental outcomes, were applied in the total study population, and in subgroups: fetal growth restriction (FGR), preterm birth (PTB), fetal congenital heart disease (CHD), and uncomplicated controls.
Results: Consent for participation was received from parents on behalf of their child 138/203 (68%). ASQ-3 was completed in 128/203 children (63%) and CBCL in 93/203 children (46%). Significant smaller subject-specific growth trajectories (growth rate of CC, HC, left insula, left POF and right POF and the baseline size of CC, HC, left POF and right POF) were found in the FGR subgroup, compared to the other subgroups (all p-values < 0.05). In the total group ($n = 138$), the growth rate of the left insula was associated with poorer ASQ-3 score ($\beta = -869.51$; $p < 0.05$). Healthy controls ($n = 106$) showed a comparable association ($\beta = -1209.87$; $p < 0.01$). FGR ($n = 10$) showed a larger baseline size of the right Sylvian fissure in association with poorer CBCL-score ($\beta = 4.13$; $p < 0.01$). In CHD ($n = 12$) the baseline size of the left Sylvian fissure and its growth rate were associated with respectively poorer and better CBCL-scores ($\beta = 3.11$; $p < 0.01$); ($\beta = -171.99$; $p < 0.01$). In PTB ($n = 10$) no associations were found.
Conclusions: This explorative study suggests associations between ultrasound measurements of fetal brain growth and neurodevelopmental outcome at 2 years of age. In future, this non-invasive technique may improve early identification of fetuses at risk for neurodevelopmental outcome and follow-up postnatal clinical care.

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https://doi.org/10.1016/j.earlhumdev.2020.105224
Received 26 March 2020; Received in revised form 3 September 2020; Accepted 3 October 2020
Available online 12 October 2020

1. Introduction

Accumulating evidence from non-invasive cerebral ultrasound measurements applied in pregnancy show a fetal and even embryonic origin of abnormal brain development [1–9] Periconceptional and prenatal factors are involved in the growth and development of organs, including the brain in second and third trimester of pregnancy [10–12]. These factors do not only affect fetal development and brain growth, but also neurodevelopment in later life [13–15]. This is in line with the paradigm 'Developmental Origins of Health and Disease' (DOHaD) postulating that an adverse fetal environment leads to developmental adaptations that permanently program organ structures, physiology and metabolism [16].

Cortical folding is an important process in prenatal brain development, starting at around 18 weeks of gestation age (GA). During this complex process the cerebral surface transforms from a smooth surface to the irregular system of sulci and gyri [17]. Deviations in cortical folding may be related to pathological cortical functioning. For example, studies have shown that brain growth and cortical folding are affected by medical conditions influencing the fetal environment, like fetal growth restriction (FGR), congenital heart defects (CHD) and prematurity [4,6,8].

In fetuses with CHD, prenatal brain abnormalities on a tissue level are often observed, like white matter injuries, reduced brain volume, delay in brain maturation, and altered brain circulation [3,5,7]. In addition, structural brain abnormalities in CHD that have been reported are ventriculomegaly, vermian hypoplasia, corpus callosum agenesis, and cerebellar hypoplasia [5]. Moreover, small deviations in trajectories of cortical folding, e.g. left insula and right POF, have been reported [6]. Also in FGR, it has been postulated that placental insufficiency, leading to chronic hypoxia and undernutrition, may lead to abnormal brain development. For example, MRI studies have shown a reduction in cortical grey matter and alterations in the gyrification and sulcation [1,2,9]. In preterm born children (PTB), disturbances in axonal and neuronal development and injury to the developing white matter can lead to multiple brain abnormalities, e.g. interruptions of thalamocortical, corticothalamic and cortico-cortical connections and decrease in cortical and deep nuclear grey matter volumes [8]. These abnormalities can result from an adverse fetal environment, like hypoxia-ischemia, infection, or chronic inflammation [18].

Both FGR and CHD are developmental abnormalities, that have a life-long health impact and may lead to impaired neurodevelopment [19–23]. Neurodevelopment outcomes can be assessed using the Ages-and-Stages questionnaire (ASQ), in which psychological and locomotive neurodevelopment are evaluated, and the Childhood Behaviour Checklist (CBCL), in which behavioural and emotional characteristics are evaluated. These validated parental report questionnaires are easy in use, little time consuming, have low costs and are easy to interpret [24,25].

Studies reporting on neurodevelopmental outcome in FGR reveal adverse motor, cognitive and behaviour outcome [19–21]. In CHD, the reported prevalence of internalizing problems (anxiety, depression, withdrawal, somatization) and externalizing problems (attention, aggression) ranges for both between 15 and 25% [23]. However, the psychomotor development seems more affected than the mental development [22]. Multiple studies report on neurodevelopmental outcome, using the ASQ, in PTB children. They show a large proportion of children (36.2–50.2%, depending on the GA at birth) below the ASQ threshold, especially for the communication and personal-social domains, and are therefore considered at risk of developmental delay [26,27].

We hypothesize that specific measurements of structures of prenatal fetal brain and its trajectories are associated with neurodevelopmental outcome in the early life course up until 2 years of age. In search for a non-invasive marker for postnatal neurodevelopmental outcome, and to be able to identify fetuses at risk for poorer neurodevelopmental outcome, this explorative study aims to evaluate associations between growth trajectories of several structures of the human fetal brain and neurodevelopment during the early life course, which we define as a timespan from preconception up until the age of 2 years, using the ASQ -3 and CBCL. Having available a biological marker of altered clinical neurodevelopment already during the intra-uterine period, will greatly increase the understanding of the impact of prenatal factors on neurodevelopment. This increased knowledge can guide clinical management and preconception and pregnancy counseling of the individual parents. The secondary aim of this study is to elucidate whether fetuses prenatally exposed to maternal pregnancy complications, such as uteroplacental insufficiency or CHD, are at risk of impaired postnatal neurodevelopmental functioning. This would warrant more attention in clinical practice regarding brain development in these children.

2. Methods

2.1. Subjects

The DREAM-study is embedded in the Rotterdam Periconceptional Cohort (Predict Study), an ongoing hospital-based open birth cohort study at the Erasmus MC, University Medical Centre, Rotterdam, The Netherlands [28], investigating periconceptional influences on placental, embryonic and fetal growth, and maternal pregnancy outcomes.

From June 2013, pregnant women participating in the Predict Study were asked to also participate in the DREAM-study, which entailed three additional three-dimensional ultrasound (3D-US) examinations of the fetal brain during pregnancy at 22, 26 and 32 weeks gestational age (GA). The total cohort consists of children (n = 227), born with complications (e.g. FGR, n = 22; PTB, n = 16; CHD, n = 20) and without these complications (healthy controls, n = 155). FGR was defined as an abdominal circumference (AC) < p5 or an estimated fetal weight (EFW) < p5. PTB was defined as a delivery before 37 weeks of GA. When fetuses were both growth restricted and PTB, they were assigned to the FGR group. The prematurity of children in the FGR group was considered as the iatrogenic consequence of the growth restriction and thus secondary to the growth restriction. All parents of the living children, whose mother had participated in the DREAM-study, were approached and asked to participate with their child in this follow-up study at the age of 24 months ± 3 months (corrected for GA at birth). Exclusion criteria of the child were confirmed brain abnormalities and Down syndrome. All participants received advanced structural ultrasound scanning and were only included if there were no structural brain abnormalities visible on the fetal ultrasound. Furthermore, children were excluded when parents reported a structural brain abnormality or when parents reported major events concerning brain development or brain damage. Finally, to validate the selection of the study group, hospital records of the child were checked by the researcher. All parents gave written informed consent before participation of their child. The Central Committee of Human Research in the Hague and the regional Medical Ethical and Institutional Review Board of the Erasmus MC University Medical Centre approved the study (MEC-2016-177, 4 April 2016).

2.2. Ultrasound measurements

The 2D- and 3D-US were performed on the Voluson E8 system (GE Medical Systems, Zipf, Austria) using a 1–7 MHz transabdominal transducer or a 6–12 MHz transvaginal transducer. Biometric measurements of the head and brain structures were obtained including total cerebellar diameter (TCD) and head circumference (HC) using 2D-US. These fetal brain structures were measured according to the ISUOG guidelines [29,30]. The corpus callosum (CC), left and right Sylvian, insula and parieto-occipital fissure (POF) depth measurements were performed offline using specialized 3D software (4D View, version 5.0, GE Medical Systems) [6]. This software enables to upload the

performed 3D-ultrasound volumes offline and manually adjust planes in three-dimensions (sectional planes). The volumes were edited manually by the operator, ensuring a perfectly corrected plane for the measurements. All brain fissure depth measurements were performed perpendicular to the midline of the brain. First, a mid-baseline was drawn as a reference line to optimize precision. Second, the insula and Sylvian fissure depth measurements were performed perpendicular to the midline of the brain, in the standard axial transventricular plane just above the trans-thalamic plane used for biparietal diameter (BPD) and HC measurements, according to the ISUOG guidelines [30]. Thirdly, in an axial plane slightly above this transventricular plane, slightly rotated along the z-axis, the POF measurement was performed perpendicular to the midline of the brain, with the cavum septum pellucidum as a reference point. Reorientation of the 3D-US image according to a standard approach ensured left/right differentiation and optimizes precision of the measurements. To enhance precision of the measurements a certified ultrasonographer carried out all ultrasounds and a researcher was trained according to protocol and performed all offline measurements.

2.3. Follow up study procedures and outcomes

Psychological and locomotive neurodevelopment was measured using the Ages and Stages Questionnaire-3 (ASQ-3). This questionnaire is a validated parental questionnaire evaluating milestones in development [24]. The ASQ-3 includes five domains (communication, gross motor, fine motor, problem solving ability and personal-social skills), each measured by six questions. Parents were asked to evaluate whether their child has achieved a milestone (yes, 10 points), has partly achieved a milestone (partly, 5 points) or has not yet achieved a milestone (no, 0 points). If a question was not answered the mean score of that domain was imputed. If more than two items in a section were left blank, the questionnaire was excluded from analysis. All points in one domain were added to calculate area scores, which could range from 0 to 60 points. The total ASQ-3 score was calculated by summing all the area scores (0–300 points), only total score was used as proxy for overall development in further analysis. A high ASQ-3 score indicates decent developmental progress.

Behavioural development was evaluated using the preschool version of the Child Behaviour Check-list (CBCL), which is a validated parent-completed questionnaire assessing the child's abilities and behavioural and emotional characteristics [25]. The questionnaire consists of 99 statements; for each statement the parent evaluates if for their child the statement is true (2 points), somewhat or sometimes true (1 point) or not true (0 points). These points were added to a Total Problems score (CBCL sum score), ranging between 0 and 198 points, which can be used to compare behavioural problems in different groups. The CBCL sum score was used as proxy for behavioural development in further analyses. A high CBCL sum score indicates behavioural and/or emotional problems which suggests poor development.

Due to logistics, parents were first asked to complete the Ages and Stages questionnaire during a hospital visit. Afterwards the Childhood Behaviour Check-list was given to them to fill in at home and sent back when completed.

2.4. Statistical analysis

All statistical analyses were performed using SPSS 21.0 (SPSS for Windows, SPSS Inc., Chicago, Illinois, USA) and RStudio 3.4.0 (RStudio: Integrated Development for R. RStudio, Inc., Boston, MA). All statistical tests were 2-tailed with the significance level set at 0.05. No adjustments were made for multiple testing because the aim of this study was explorative and hypotheses-generating [31]. General characteristics were calculated for all children. Normal continuous data was compared using oneway-ANOVA. Non-normal, continuous data was compared using Kruskal-Wallis tests. Categorical data were compared using Pearson's Chi-squared tests. All continuous data are expressed as medians with interquartile ranges, all categorical data are expressed as numbers and percentages.

First, linear mixed models were used to analyse the longitudinal brain growth data to estimate the growth trajectories of the fetal brain structures, taking into account the correlation between the repeated measurements. The advantage of linear mixed model is that this technique allows for use of measurements at other scanning periods to approximate the brain structure size for missing ultrasound measurements. In this model, GA and the quadratic term of GA were used as predictors. In the analyses the differences between the subjects are estimated, leading to a variance for the intercept and slope. For every subject, a subject-specific intercepts, called random intercept (RI), and a subject-specific coefficients of GA, called random slope (RS), were calculated. Because we placed the start of the GA scale at around 22 weeks, RI can be interpreted as the baseline and relative size of the brain structure at 22 weeks GA. For the brain fissures, an increased baseline size refers to an increased fissure depth. RS should be interpreted as the growth rate of the specific brain structure. RI and RS for the brain structures were compared between the groups using one-way ANOVA or Kruskal-Wallis tests, followed by respectively Tukey and Dunn-Bonferroni Post Hoc tests. Afterwards, the association between prenatal brain structures and neurodevelopmental outcomes in linear regression models were assessed with the random effects as a predictor and neurodevelopmental outcomes as the response. In order to obtain the differences in outcome in the ASQ-3 and CBCL large coefficients may be expected in the linear regression calculation. The CBCL sum score and total ASQ-3 score were studied as continuous outcomes. To approximate a normal distribution, the CBCL sum score was square root transformed.

The analyses were done for the total group and all the subgroups separately (FGR, PTB, CHD and controls). Adjustment for confounders could only be done in the total and control group, because of the limited sample sizes of the case groups. The confounders were selected beforehand, based on literature and expert knowledge; these comprise maternal level of education, parity, mode of conception, periconceptional smoking, preconceptional folic acid supplement use, and gender of the child [10].

3. Results

Of 227 children enrolled, 213 survived up to 2 years of age. 10 children were excluded, because of brain abnormalities diagnosed and confirmed using neuroimaging [8] and Down syndrome [2]. This resulted in 203 children eligible for neurodevelopmental evaluation (Fig. 1). Consent for participation was received from parents on behalf of their child 138/203 (68%). ASQ-3 was completed in 128/203 children (63%) and CBCL in 93/203 children (46%). The main baseline characteristics of children and their mothers during follow-up compared with those lost to follow-up are presented in supplemental Table A. Maternal geographic background, maternal education, and mode of conception were significantly different between the mothers of participating children and those lost to follow-up. The mothers of the recruited children had more often a Dutch background, were higher educated and the children were more often conceived after IVF or ICSI treatment. Table 1 shows the baseline characteristics of the children and their mothers for all groups. Neurodevelopment was evaluated at a median corrected age of 24.4 months (interquartile range, 24.2–24.7 months). The Kruskal-Wallis H test showed a significantly lower GA and birthweight at birth in the FGR and PTB group, compared to the CHD and control group, which is inherent to these outcomes. There were no other significant differences between the different subgroups and controls.

Supplemental Table C reports the number of ultrasound measurements made per scanning period in total group and subgroups. Table 2 shows subject-specific growth profiles of the fetal brain structures for

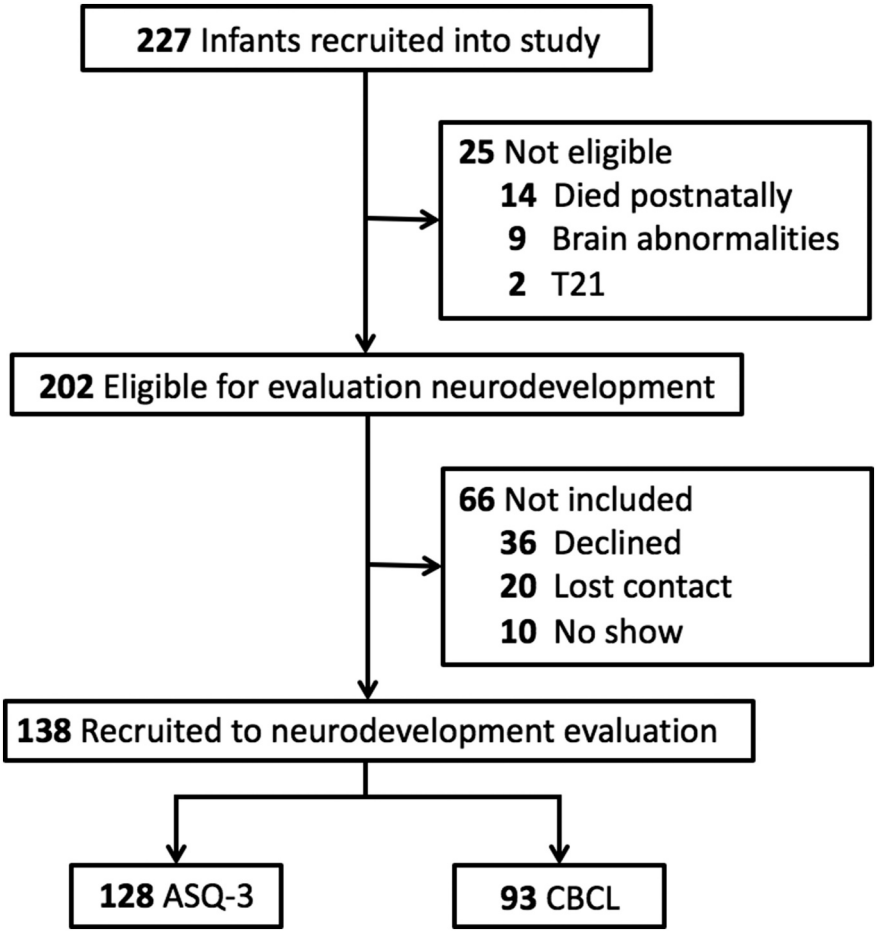

Fig. 1. Flowchart of follow-up Cohort.

on forehand selected brain structures for all subgroups. Significant differences were found between the subgroups in growth rate of CC, HC, left insula, left POF and right POF (*p*-values respectively 0.0001, 0.0001, 0.023, 0.005 and 0.002), and baseline size of CC, HC, left POF and right POF (*p*-values respectively 0.001, 0.0001, 0.009 and 0.007). The post hoc tests showed that this all was due to smaller brain growth trajectories in FGR subgroup compared to the other subgroups (FGR vs CHD, FGR vs PTB and FGR vs Controls, supplemental Table D and E).

Table 3 shows the total ASQ-3 score and CBCL scores for all subgroups. Total ASQ-3 scores were not significantly different between the groups (Table 3). In the total group a significant association was observed between the growth rate of the left insula and the ASQ-3 ($\beta = -869.51$, $p = 0.027$). A similar significant association was seen in the healthy controls group ($\beta = -1209.87$, $p = 0.005$) (Table 4).

There were no significant differences in total CBCL score between all groups (Table 3). In the FGR subgroup a significant association was observed between the baseline size of the right Sylvian fissure at around 22 weeks GA and the CBCL ($\beta = 4.13$, $p = 0.009$). In the CHD subgroup a significant association was established between the baseline size of the left Sylvian fissure at around 22 weeks GA and the CBCL ($\beta = 3.11$, $p = 0.003$) and growth rate of the left Sylvian fissure and the CBCL ($\beta = -171.99$, $p = 0.003$) (Table 5).

4. Discussion

In this prospective cohort study, serial measurements of several structures of fetal brain development in the second half of pregnancy were studied in association with subsequent neurodevelopment at 2 years of age in children with FGR, PTB, or CHD and uncomplicated controls. Prior to investigating associations, comparisons between groups in brain measurements and outcomes measures were performed. Comparisons in brain measurements showed significantly smaller and/or slower brain growth trajectories in the FGR subgroup compared with the other groups. Overall neurodevelopmental outcomes were not significantly different between the groups. Investigation of the associations showed the following results: in the total group an association was seen between the growth rate of the left insula and poorer outcome of the ASQ-3 score. In the control group a similar association was established between the growth rate of the left insula and poorer outcome of the ASQ-3 score. In the FGR subgroup an association was observed between the baseline size of the right Sylvian fissure at around 22 weeks GA and poorer outcome of the CBCL score. No significant associations were observed between fetal brain trajectories and neurodevelopmental outcomes in the PTB group. However, in the CHD subgroup an association was observed between the baseline size of the left Sylvian fissure at around 22 weeks GA and a poorer outcome of the CBCL score and an association between the growth rate of the left Sylvian fissure and a better CBCL score.

In the second half of pregnancy, fetal brain growth trajectories were different across the groups. The FGR subgroup showed already significantly smaller baseline brain structures at around 22 weeks GA and smaller growth rates of CC, HC, left insula and left and right POF, when compared with the other groups. These smaller growth rates could be explained by the general growth restriction and reported brain abnormalities in fetuses with FGR due to chronic hypoxia and undernutrition [1,2,9].

Some of these smaller and/or slower brain growth trajectories were also found in the PTB and CHD subgroups. In CHD, only the baseline

Table 1
General characteristics of the study population and the subgroups fetal growth restriction, preterm birth, congenital heart disease and controls.

	FGR n = 10	Missings	PTB n = 10	Missings	CHD n = 12	Missings	Controls n = 106	Missings	Total n = 138	Missings	*p*-value
Maternal characteristics											
Age, years[1]	29.7 (28.2–31.9)		32.7 (26.4–35.6)		32.0 (28.2–35.3)		32.4 (29.5–35.1)		32.4 (29.4–35.0)		0.738[c]
Geographic background[2]											0.603[a]
Dutch	9 (90.0)		9 (90.0)		11 (91.7)		81 (76.4)		110 (79.7)		
Western-other			1 (10.0)				8 (7.5)		9 (6.5)		
Non-Western	1 (10.0)				1 (8.3)		16 (15.1)		19 (13.8)		
Education[2]											0.091[a]
Low	1 (10.0)		1 (10.0)				8 (7.5)		10 (7.2)		
Intermediate	7 (70.0)		6 (60.0)		3 (25.0)		35 (33.0)		51 (37.0)		
High	2 (20.0)		3 (30.0)		9 (75.0)		63 (59.4)		77 (55.8)		
Pre-pregnancy BMI (kg/m^2)[1]	22.6 (19.7–24.5)	2	25.7 (19.5–31.0)	3	24.6 (22.8–29.4)		23.0 (20.7–27.0)	6	23.1 (20.8–27.0)	11	0.368[a]
Nulliparous[2]	6 (60.0)		2 (20.0)		7 (58.3)		46 (43.4)		61 (44.2)		0.223[a]
Mode of conception: IVF/ICSI[2]	2 (20.0)		4 (40.0)		2 (16.7)		34 (32.1)		42 (30.4)		0.541[a]
Periconceptional use of alcohol[2]	2 (20.0)	1	2 (20.0)	1	8 (66.7)		32 (30.2)	1	44 (31.9)	3	0.059[a]
Periconceptional smoking[2]	2 (20.0)		3 (30.0)		1 (8.3)		16 (15.1)		22 (15.9)		0.537[a]
Preconceptional initiation of folic acid[2]	5 (50.0)	1	8 (80.0)	1	11 (91.7)		70 (69.3)	7	94 (68.1)	9	0.780[a]
Neonatal characteristics											
Gestational age at birth, weeks[1]	34.7 (33.1–38.3)		35.6 (31.1–36.3)		40 (38.6–40.9)		39 (38.1–39.9)		38.9 (37.7–39.7)		**< 0.001**[b]
Birth weight, grams[1]	1443 (1311–2316)		2233 (1719–3039)		3475 (3400–3748)		3355 (3108–3673)	1	3295 (2933–3640)	1	**< 0.001**[b]
Male gender[2]	4 (40.0)		5 (50.0)		7 (58.3)		55 (51.9)		71 (51.4)		0.857[a]
Child characteristics											
Age at assessment, months[1]	24.1 (23.9–24.2)		24.0 (23.6–24.1)		24.0 (23.8–24.2)	1	24.1 (23.8–24.4)	1	24.1 (23.8–24.3)	2	0.799[b]

Data are presented as median and interquartile range[1] or number (n) and percentage (%)[2]. Significant differences are in bold font. FGR, fetal growth restriction; PTB, preterm birth; CHD, congenital heart disease; BMI, body mass index in kilograms/square meter; IVF/ICSI, in vitro fertilization/intra-cytoplasmic sperm injection.
[a] Calculated using chi-squared.
[b] Calculated using oneway anova.
[c] Calculated using Kruskal wallis H.

size of CC was evidently smaller. No literature to date, report on the prenatal size of CC in fetuses with CHD. Multiple studies show decreased prenatal head circumference in CHD [3]; also in this study a slower growth rate of HC was seen, however baseline size was bigger in this subgroup. In the PTB group a smaller baseline size of the right Sylvian fissure was seen. Several studies, report on chronic inflammation being involved in PTB, also affecting prenatal brain growth causing brain injury and developmental abnormalities [18,32].

Previous studies have reported on neurodevelopmental delays in children with FGR, PTB, and CHD [19–23,27]. Pierrat et al. studied a large cohort of 2506 PTB children and found developmental delays, also measured with ASQ, in children who are born before 35 weeks' gestation [27]. Children with a history of FGR are reported to be at high risk of developing neurobehavioral and neurocognitive deficits [19–21]. In children with CHD abnormal neurologic examinations and gross and fine motor abnormalities have been described [22,23]. In our study, however, no differences in various domains of neurodevelopment were found between cases and controls.

The results of this explorative study suggest that differences in gyrification of the insula and Sylvian fissure in both control group and subgroups is associated with neurodevelopmental outcome. Firstly, a significant association between a higher growth rate of the left insula and lower outcome of the ASQ-3 in the total and controls group was seen. Though before cortical folding was thought to be driven mechanically by expansion of the brain, literature to date shows that abnormal cortical folding reflects underlying microstructural changes in the formation, migration and differentiation of neuronal cells. Matsuda et al. states that underlying intracortical axonal connections can influence cortical gyrification. This mechanical tension hypothesis states that cortical regions with greater neural connectivity are associated with greater tension, resulting in the formation of cortical gyri [33]. This suggests that patterns of cortical folding reflect cellular morphogenesis, which might be impacted by factors from the intra-uterine environment. Indeed, abnormal cortical folding patterns have been observed in individuals with abnormal neurodevelopmental outcome [33–36].

Furthermore, in the CHD group of children, we showed an association between a larger baseline size of the left Sylvian fissure and a poorer outcome of the CBCL. Multiple studies have shown that prenatal brain growth, like TCD, BPD, and HC, can be impaired in children with CHD [3,37]. Also fetal brain development, by means of fetal cortical folding, is influenced by CHD [6]. Brain and heart development occur simultaneously in the human fetus and often share the same morphogenetic programs [38]. These related developmental processes have many genes, signalling pathways and cell lineages, like the neural crest, in common [39]. Therefore, discrepancies in one of these pathways could lead to abnormal development of both organs and may consequently cause neurodevelopmental impairment. Moreover, other pathways may play a role in the origin of CHD-related brain abnormalities, like derangements in haemodynamic mechanisms. These derangement of circulatory flow affects many vital organs, whereas the brain is especially vulnerable because of the high need of oxygenated blood and

Table 2
Fetal brain growth trajectories of the study groups.

	FGR	PTB	CHD	Controls	Total	*p*-value
	n = 10	n = 10	n = 12	n = 106	n = 138	
TCD						
RI	−0.062 (−0.703–0.165)	−0.010 (−0.117–0.218)	0.058 (−0.427–0.326)	−0.022 (−0.316–0.387)	−0.016 (−0.329–0.316)	0.486[a]
RS	−0.003 (−0.019–0.003)	−0.002 (−0.011–0.002)	−0.001 (−0.008–0.014)	0.001 (−0.006–0.008)	−0.001 (−0.007–0.007)	0.077[a]
CC						
RI	−0.785 (−1.829; −0.337)	0.388 (0.148–1.205)	−0.281 (−0.473–0.295)	0.113 (−0.271–0.466)	0.095 (−0.374–0.006)	**0.001**[b]
RS	−0.011 (−0.027; −0.005)	0.005 (0.002–0.017)	−0.004 (−0.007–0.004)	0.002 (−0.004–0.007)	0.001 (−0.005–0.006)	< **0.001**[a]
HC						
RI	−5.599 (−13.279; −3.072)	0.976 (−0.786–4.489)	0.330 (−3.476–4.496)	1.453 (−1.858–4.339)	0.989 (−2.384–4.231)	< **0.001**[b]
RS	−0.061 (−0.120; −0.029)	0.006 (−0.011–0.031)	−0.011 (−0.041–0.019)	0.015 (−0.022–0.050)	0.006 (−0.027–0.047)	< **0.001**[a]
Sylvian fissure left						
RI	−0.347 (−0.528–0.024)	0.019 (−0.621–0.330)	0.000 (−0.422–0.431)	0.206 (−0.215–0.561)	0.160 (−0.283–0.496)	0.057[b]
RS	−0.009 (−0.016–0.004)	0.000 (−0.009–0.005)	−0.003 (−0.009–0.004)	0.001 (−0.005–0.009)	0.001 (−0.006–0.007)	0.160[b]
Sylvian fissure right						
RI	0.005 (−0.595–0.255)	−0.112 (−0.433–0.377)	0.069 (−0.355–0.654)	0.206 (−0.073–0.488)	0.163 (−0.224–0.469)	0.166[a]
RS	0.001 (−0.009–0.009)	−0.001 (0.004–0.003)	0.001 (−0.006–0.005)	0.003 (−0.003–0.006)	0.001 (−0.006–0.006)	0.262[a]
Insula left						
RI	−0.146 (−0.275; −0.028)	0.010 (−0.098–0.324)	0.005 (−0.156–0.131)	0.046 (−0.114–0.187)	0.024 (−0.122–0.169)	0.176[a]
RS	−0.009 (−0.016; −0.001)	0.003 (−0.006–0.009)	0.001 (−0.006–0.005)	0.001 (−0.005–0.006)	0.001 (−0.006–0.006)	**0.023**[a]
Insula right						
RI	−0.036 (−0.152–0.045)	−0.019 (−0.117–0.052)	0.019 (−0.068–0.055)	0.007 (−0.102–0.133)	−0.003 (−0.102–00114)	0.655[a]
RS	−0.004 (−0.016–0.003)	−0.004 (−0.018–0.004)	0.002 (−0.013–0.010)	0.002 (−0.005–0.011)	0.001 (−0.007–0.010)	0.151[b]
POF left						
RI	−0.693 (−0.874; −0.187)	−0.026 (−0.194–0.248)	0.206 (−0.187–0.434)	0.111 (−0.311–0.469)	0.078 (−0.281–0.409)	**0.009**[a]
RS	−0.015 (−0.0177; −0.004)	0.000 (−0.005–0.004)	0.003 (−0.003–0.009)	0.002 (−0.006–0.009)	0.001 (−0.006–0.007)	**0.005**[a]
POF right						
RI	−0.523 (−1.022; −0.259)	0.142 (−0.023–0.252)	0.293 (−0.275–0.443)	0.041 (−0.359–0.454)	0.057 (−0.355–0.395)	**0.007**[a]
RS	−0.019 (−0.037; −0.005)	0.002 (−0.002–0.007)	0.008 (−0.013–0.213)	0.001 (−0.009–0.012)	0.001 (−0.009–0.011)	**0.002**[a]

Data are presented as median and interquartile range. Significant differences are in bold font. FGR, fetal growth restriction; PTB, preterm birth; CHD, congenital heart disease; TCD, transcerebellar diameter; CC, corpus callosum; HC, head circumference; POF, parieto-occipital fissure; RI, random intercept (baseline size); RS, random slope (growth rate); n, number.

[a] Calculated using oneway-ANOVA.

[b] Calculated using Kruskall-Wallis H.

nutrients [7]. Also in FGR a derangement or adaptation in circulatory flow can be involved, this is called the 'brain sparing effect' due to placental insufficiency. This effect refers to the cerebro-placental blood flow redistribution causing the same derangements of circulatory flow [1,19]. In the FGR subgroup, a larger baseline size of the Sylvian fissure corresponds to a poorer outcome of the CBCL. Possibly, a larger baseline size of the Sylvian fissure in FGR reflects cortical thinning that also results in poorer neurodevelopmental outcome. Though this might seem contradictory, these results could be explained by FGR impacting fetal brain growth in several ways. Firstly, FGR is associated with reduced grey matter in specific areas of the brain, including the insular region [40]. Secondly, FGR is associated with reduced white matter throughout the whole brain [40]. Both the reduced overall white matter and the local reduced grey matter in specific areas of the brain might result in altered cortical folding and a larger depth of the Sylvian fissure. Finally, most importantly for this study, FGR impacts cortical folding with accelerated cortical development reaching maturation of the Sylvian fissure [1]. So, even though FGR newborns show reduced cortical folding compared to newborns born appropriately grown for GA, they show a higher sulcation index in comparison with those born with similar cortical surface measurements [41]. Hence, in FGR newborns the netto result of the impact of general cortical white matter thinning, local grey matter thinning and altered gyrification, results in deeper fissure measurements of the insula, which is in line with the results of this study [2].

These brain abnormalities are likely associated with neurological deficits and neurodevelopmental delays [19,20]. Moreover, fetuses with FGR may experience more stress resulting in higher cortisol levels, which may affect gyrification and possibly subsequently neurodevelopmental outcome [42].

Table 3
Total development questionnaire outcome scores of the study groups.

	FGR	PTB	CHD	Controls	Total	Missings	*p*-value
	n = 10	n = 10	n = 12	n = 106	n = 138		
ASQ-3 total	255 (203–270)	260 (210–280)	255 (245–280)	255 (235–279)	255 (234–275)	10	0.571[a]
CBCL total	13 (8–33)	26 (9–38)	16 (10−23)	26 (13–38)	22 (13–37)	45	0.281[b]

Data are presented as median and interquartile range. FGR, fetal growth restriction; PTB, preterm birth; CHD, congenital heart disease; ASQ-3, Ages and Stages Questionnaire-3; CBCL, Child Behaviour Check-list; n, number.

[a] Calculated using oneway-ANOVA.

[b] Calculated using Kruskall-Wallis H.

Table 4
Associations between fetal growth trajectories and ASQ-3-score.

	FGR ß (SE)	*p*-Value	PTB ß(SE)	*p*-Value	CHD ß (SE)	*p*-Value	Controls (+ confounders) ß (SE)	*p*-value	Total (+ confounders) ß (SE)	*p*-Value
ASQ-3 (points)										
TCD	**n = 9**		**n = 9**		**n = 12**		**n = 96**		**n = 124**	
RI	129.19 (111.71)	0.300	44.77 (81.02)	0.600	−11.27 (31.54)	0.729	5.68 (8.86)	0.523	7.691 (7.832)	0.328
RS	−3333.43 (4523.53)	0.494	−462.94 (1909.04)	0.816	0.90 (1041.31)	0.999	−157.95 (488.64)	0.747	−51.896 (371.09)	0.889
CC	**n = 8**		**n = 8**		**n = 9**		**n = 80**		**n = 104**	
RI	−1404.72 (983.75)	0.213	2117.89 (1319.57)	0.169	1580.00 (936.70)	0.143	−250.09 (275.30)	0.367	−112.077 (239.909)	0.642
RS	98,517.91 (68,332.12)	0.209	−148,770.02 (92,687.96)	0.169	−109,900 (64930)	0.142	16,860 (19155)	0.382	7585.945 (16,715.377)	0.651
HC	**n = 9**		**n = 9**		**n = 12**		**n = 96**		**n = 125**	
RI	−8.478 (9.559)	0.409	−1.726 (5.810)	0.776	−0.920 (2.00)	0.657	−0.634 (0.759)	0.406	0.354 (0.835)	0.672
RS	1369.275 (925.550)	0.190	36.068 (366.789)	0.925	−116.071 (215.936)	0.604	−11.434 (64.601)	0.860	−15.200 (65.949)	0.818
Sylvian fissure left	**n = 8**		**n = 9**		**n = 12**		**n = 96**		**n = 123**	
RI	−17.73 (101.95)	0.869	42.98 (63.46)	0.524	−1.57 (16.75)	0.927	1.08 (7.98)	0.893	2.198 (7.206)	0.761
RS	−533.29 (4034.37)	0.900	−1778.20 (4445.77)	0.703	−1502.84 (884.88)	0.124	27.18 (428.24)	0.950	−105.229 (397.122)	0.792
Sylvian fissure right	**n = 8**		**n = 9**		**n = 12**		**n = 96**		**n = 123**	
RI	−3.66 (62.33)	0.955	−39.83 (59.85)	0.531	−15.92 (19.76)	0.441	3.75 (6.87)	0.587	0.0738 (5.774)	0.990
RS	1656.56 (3540.88)	0.660	2912.92 (6151.33)	0.653	247.38 (1689.31)	0.887	219.63 (428.27)	0.610	122.966 (388.530)	0.752
Insula left	**n = 8**		**n = 9**		**n = 12**		**n = 96**		**n = 123**	
RI	−695.76 (467.13)	0.197	10.15 (80.09)	0.903	−60.82 (45.80)	0.217	12.74 (14.55)	0.384	5.2 (13.773)	0.706
RS	13,651.95 (8381.30)	0.164	−1311.70 (2341.71)	0.596	−409.12 (1167.74)	0.734	**−1209.87 (416.72)**	**0.005**	**−869.513 (387.903)**	**0.027**
Insula right	**n = 8**		**n = 9**		**n = 12**		**n = 96**		**n = 123**	
RI	252.95 (12.49)	0.914	402.35 (199.17)	0.090	51.79 (97.19)	0.607	−48.66 (31.20)	0.123	−17.920 (27.788)	0.520
RS	1075.17 (3204.58)	0.751	−2400.53 (1845.72)	0.241	−430.46 (1018.86)	0.683	271.83 (338.63)	0.424	259.156 (289.437)	0.373
POF left	**n = 8**		**n = 9**		**n = 12**		**n = 96**		**n = 121**	
RI	−282.90 (418.10)	0.536	−124.19 (252.98)	0.641	111.94 (79.09)	0.191	6.14 (26.46)	0.817	6.908 (25.734)	0.789
RS	14,424.00 (21,067.00)	0.531	6296.84 (13,167.40)	0.649	−4732.47 (3864.26)	0.252	−292.09 (1368.45)	0.831	−138.983 (1321.785)	0.917
POF right	**n = 8**		**n = 9**		**n = 12**		**n = 96**		**n = 123**	
RI	332.61 (750.52)	0.681	−23.08 (88.56)	0.803	6.30 (43.19)	0.887	−11.33 (16.74)	0.501	−8.090 (15.368)	0.600
RS	−8312.31 (20,517.76)	0.706	250.77 (2610.86)	0.927	168.11 (1294.19)	0.900	636.59 (547.14)	0.248	524.547 (489.018)	0.286

Data are presented as coefficient (SE) calculated using linear regression models. Data of the control group has been adjusted for on forehand chosen confounders (maternal level of education, parity, mode of conception, periconceptional smoking, preconceptional folic acid use, and gender of the infant). Significant differences are in bold font. ASQ-3, Ages and Stages Questionnaire-3; FGR, fetal growth restriction; PTB, preterm birth; CHD, congenital heart disease; TCD, transcerebellar diameter; CC, corpus callosum; HC, head circumference; POF, parieto-occipital fissure; RI, random intercept (baseline size); RS, random slope (growth rate); ß, beta value; SE, standard error; n, number.

In contrast an association between steeper growth rate of the left Sylvian fissure and a better outcome of the CBCL was found in the CHD group. This suggests that faster growth of this fissure in a fetus with CHD is associated with better neurodevelopmental outcomes.

In this study, associations were found between neurodevelopment and specifically left or right brain trajectories. Studies have shown that left-right asymmetry in cortical folding is a normal developmental phenomena prenatally [43]. This phenomena makes it difficult to hypothesize why specifically left or right brain trajectories are associated. Further research is needed to evaluate and clarify these left-right differences.

For imaging of the insula and the Sylvian fissure, 2D imaging seems to be sufficient. However, for reliable measurement of the depth of the sulci, it is necessary to verify whether this is measured in the correct unskewed plane, to avoid overestimating lengths. The verification can only be done by checking in a different plane. Though experienced operators might be able to make accurate measurements by using only 2D, for optimal reliability of measurements, we recommend, in line with other authors, 3D evaluation to check whether the measurement is placed in a perfectly straight plane (A-plane) by checking the B- and C-plane of the 3D-US sectional planes.

A powerful strength of this study is its prospective periconceptional cohort design with a follow-up until two years of age, the serial precise and reliable fetal brain measurements, and the fact that multiple domains of neurodevelopment were evaluated. Two validated questionnaires (ASQ-3 and CBCL) were used to assess the psychological and locomotive development as well as the behavioural development.

This study has also some limitations. Firstly, reporting bias of parents in questionnaires is always an issue of concern as responses can be influenced by social desirable answers. Furthermore, development was assessed once at two years of age rather than longitudinally. Data from this study should be interpreted with caution because of small sample sizes in the subgroups, which made adjustment for confounding impossible, therefore the presence of residual confounding cannot be excluded. Some parents of children with disabilities due to the PTB, FGR or CHD and/or abnormal neurodevelopment, declined to participate in this study. Therefore, selection bias due to loss of follow-up cannot be excluded.

To our knowledge, this explorative study is the first in associating longitudinal measured fetal brain growth and neurodevelopmental outcome at two years of age. This study shows an association between prenatal brain growth and postnatal developmental outcome. Further optimising future research by incorporating objective evaluation of child development and long-term follow-up, for example until 12 years

Table 5
Associations between fetal growth trajectories and CBCL-score.

	FGR ß (SE)	*p*-Value	PTB ß(SE)	*p*-Value	CHD ß (SE)	*p*-Value	Controls (+ confounders) ß (SE)	*p*-Value	Total (+ confounders) ß (SE)	*p*-Value
CBCL (√points)										
TCD	**n = 5**		**n = 6**		**n = 12**		**n = 69**		**n = 91**	
RI	5.43 (3.89)	0.298	7.05 (8.03)	0.447	1.09 (1.64)	0.523	−0.87 (0.75)	0.249	−0.779 (0.614)	0.208
RS	−69.35 (143.08)	0.676	−59.27 (174.42)	0.756	−43.24 (54.08)	0.445	−1.77 (39.33)	0.964	5.902 (26.676)	0.825
CC	**n = 6**		**n = 5**		**n = 9**		**n = 56**		**n = 75**	
RI	−3.99 (29.55)	0.901	−142.39 (44.96)	0.087	−22.72 (80.49)	0.787	14.55 (25.95)	0.578	−2.960(4.734)	0.534
RS	−341.73 (2036.01)	0.877	10,033.08 (3189.02)	0.088	1596.17 (5579.91)	0.784	−1038 (1814)	0.570	230.443 (364.737)	0.530
HC	**n = 6**		**n = 6**		**n = 12**		**n = 69**		**n = 92**	
RI	0.119 (0.315)	0.731	0.375 (0.260)	0.245	−0.027 (0.105)	0.805	0.002 (0.084)	0.981	0.037 (0.060)	0.539
RS	3.420 (32.826)	0.924	−9.499 (22.459)	0.701	12.316 (11.378)	0.307	−10.003 (5.762)	0.088	−8.419 (4.413)	0.060
Sylvian fissure left	**n = 6**		**n = 6**		**n = 12**		**n = 69**		**n = 91**	
RI	−0.39 (0.71)	0.889	−1.84 (3.54)	0.639	**3.11 (0.79)**	**0.003**	0.40 (−0.61)	0.516	0.563 (0.490)	0.254
RS	155.14 (126.58)	0.308	252.03 (181.06)	0.258	**−171.99 (41.86)**	**0.003**	−51.83 (32.3)	0.114	−42.349 (25.960)	0.107
Sylvian fissure right	**n = 6**		**n = 6**		**n = 12**		**n = 69**		**n = 92**	
RI	**4.13 (0.68)**	**0.009**	0.49 (3.85)	0.907	−1.42 (1.06)	0.213	−0.72 (0.51)	0.163	−0.518 (0.391)	0.189
RS	−104.69 (37.90)	0.070	−5.85 (345.15)	0.988	143.56 (90.37)	0.147	4.79 (31.85)	0.881	21.819 (26.240)	0.408
Insula left	**n = 6**		**n = 6**		**n = 12**		**n = 69**		**n = 91**	
RI	5.47 (28.04)	0.858	−7.52 (2.92)	0.082	1.42 (2.68)	0.608	−1.15 (1.15)	0.319	−1.142 (0.859)	0.188
RS	−16.58 (385.90)	0.968	172.66 (82.55)	0.128	2.35 (68.31)	0.973	57.77 (32.94)	0.085	46.411 (23.319)	0.051
Insula right	**n = 6**		**n = 6**		**n = 12**		**n = 69**		**n = 92**	
RI	−0.38 (19.27)	0.986	−0.02 (11.07)	0.999	−4.33 (5.23)	0.429	3.41 (2.65)	0.204	2.592 (1.973)	0.193
RS	65.99 (174.02)	0.730	102.78 (118.80)	0.451	50.71 (54.20)	0.374	−24.54 (26.17)	0.352	−10.114 (20.910)	0.630
POF left	**n = 6**		**n = 6**		**n = 12**		**n = 69**		**n = 92**	
RI	−22.08 (11.01)	0.139	−20.33 (24.59)	0.469	−4.15 (5.30)	0.454	0.25 (2.44)	0.918	0.467 (1.624)	0.775
RS	1214.84 (561.51)	0.119	1449.42 (1408.86)	0.379	209.30 (259.31)	0.440	−13.45 (126.09)	0.915	−20.834 (83.880)	0.804
POF right	**n = 6**		**n = 6**		**n = 12**		**n = 69**		**n = 92**	
RI	−24.32 (20.12)	0.313	−4.89 (12.67)	0.725	0.12 (2.55)	0.964	0.85 (1.46)	0.563	0.890 (1.069)	0.408
RS	689.99 (548.17)	0.297	141.17 (490.94)	0.792	7.33 (76.23)	0.926	−32.22 (48.87)	0.512	−30.592 (34.669)	0.380

Data are presented as coefficient (SE), calculated using linear regression models. Data of the control group has been adjusted for on forehand chosen confounders (maternal level of education, parity, mode of conception, periconceptional smoking, preconceptional folic acid use, and gender of the infant). Significant differences are in bold font. CBCL, Child Behaviour Check-list; FGR, fetal growth restriction; PTB, preterm birth; CHD, congenital heart disease; TCD, transcerebellar diameter; CC, corpus callosum; HC, head circumference; POF, parieto-occipital fissure; RI, random intercept (baseline size); RS, random slope (growth rate); ß, beta value; SE, standard error; n, number.

of age, will yield more in depth understanding of both the pathophysiology and clinical implications of this association. To replicate our findings at the age of 2 years and to evaluate the impact on longer term development, further research is needed with larger sample sizes and standardized long-term neurodevelopmental follow-up, including objective evaluation such as Bayley Scales of Infant and Toddler Development III [24]. Also, the addition of prenatal gyrification scoring systems and postnatal MRI and resting state functional MRI at 6 months, 2 years and 10 years would provide valuable information [1].

In this study, associations between fetal brain growth and neurodevelopment at 2 years of age are investigated. It would also be interesting to study these associations even earlier during pregnancy in the embryonic brain.

In conclusion, this explorative study shows that growth of several prenatal brain structures in the second half of pregnancy is associated with neurodevelopment at two years of age, as evaluated by ASQ-3 and CBCL, in the FGR and CHD subgroups and the control and total groups. Further research is needed to confirm these findings and to elucidate the underlying pathophysiological mechanisms and clinical implications.

Funding

Department of Obstetrics and Gynaecology, Erasmus MC, and Sophia Research Foundation for Medical Research, Rotterdam, The Netherlands (SSWO grant number 644).

CRediT authorship contribution statement

Mila S. Welling: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Sofie C. Husen:** Writing - review & editing, Visualization. **Attie T.J.I. Go:** Writing - review & editing. **Irene A.L. Groenenberg:** Writing - review & editing. **Sten P. Willemsen:** Methodology, Software. **Hilmar H. Bijma:** Conceptualization, Writing - review & editing. **Régine P.M. Steegers-Theunissen:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors report no conflict of interest.

Acknowledgments

We would like to thank all participating children and their parents, the Rotterdam periconception cohort team and the outpatient clinic of Obstetrics and Prenatal Medicine at the Erasmus MC, University Medical Centre, Rotterdam, The Netherlands, for their contribution to the study. We would like to thank dr. Irene V. Koning, who was responsible for performing and collecting of all ultrasounds measurements. This study was funded by the Department of Obstetrics and Gynaecology of the Erasmus MC, University Medical Centre, Rotterdam, The Netherlands, and Sophia research foundation for Medical Research, Rotterdam, The Netherlands.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2020.105224.

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