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Cortical development in fetuses with congenital heart defects using an automated brain-age prediction algorithm

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Abstract

Introduction: Congenital heart defects are associated with neurodevelopmental delay. It is hypothesized that fetuses affected by congenital heart defect have altered cerebral oxygen perfusion and are therefore prone to delay in cortical maturation. The aim of this study was to determine the difference in fetal brain age between consecutive congenital heart defect cases and controls in the second and third trimester using ultrasound.

Material and methods: Since 2014, we have included 90 isolated severe congenital heart defect cases in the Heart And Neurodevelopment (HAND)-study. Every 4 weeks, detailed neurosonography was performed in these fetuses, including the recording of a 3D volume of the fetal brain, from 20 weeks onwards. In all, 75 healthy fetuses underwent the same protocol to serve as a control group. The volumes were analyzed by automated age prediction software which determines gestational age by the assessment of cortical maturation.

Results: In total, 477 volumes were analyzed using the age prediction software (199 volumes of 90 congenital heart defect cases; 278 volumes of 75 controls). Of these, 16 (3.2%) volume recordings were excluded because of imaging quality. The age distribution was 19-33 weeks. Mixed model analysis showed that the age predicted by brain maturation was 3 days delayed compared with the control group ($P = 0.002$).

Conclusions: This study shows that fetuses with isolated cases of congenital heart defects show some delay in cortical maturation as compared with healthy control cases. The clinical relevance of this small difference is debatable. This finding was consistent throughout pregnancy and did not progress during the third trimester.

KEYWORDS

congenital heart defects, fetus, malformations of cortical development, neurodevelopmental outcome, ultrasonography

Abbreviations: CHD, congenital heart defect; GA, gestational age; MRI, magnetic resonance imaging; POF, parieto-occipital fissure; SF, sylvian fissure.

1 | INTRODUCTION

Improvements over time in the quality of neonatal care and cardiothoracic surgery in children with congenital heart defects (CHD) have resulted in an increased survival of children with severe CHD. This has stimulated longer term follow up and a recognition that there is an association between CHD and impaired neurodevelopmental outcome.[1,2] Developmental delay, decreased IQ and behavioral disorders have been reported, even in non-syndromic CHD children.[1]

Previously, these sequelae were attributed to perioperative hypoxia or thrombo-embolic events during surgery. Recent studies suggest, however, that signs of abnormal neurological development may be present prior to surgery.[3-5] Imaging studies in pregnancy using magnetic resonance imaging (MRI)[6,7] and ultrasound,[8,9] have shown signs of delayed fetal brain development. It has been suggested that it is these abnormal findings that result in the altered neurological outcome later in life.[5,6] The hypothesized mechanism is that the abnormal development of the brain is the result of altered brain oxygenation in fetal life.[10,11]

However, there is no robust evidence for delayed fetal brain maturatio, because the current studies are subject to potential bias due to the small number of included affected women and the selection of participants with regard to the type of cardiac defect.[4]

Therefore, the aim of this study is to assess fetal brain development and maturational changes over time in a prospective, consecutive cohort of fetuses with isolated CHD, to avoid selection bias. In this study, ultrasound (US) imaging was used, which not only enables the inclusion of a larger number of fetuses (and thus reduces selection bias) but also facilitates multiple examinations in the same fetus, to evaluate brain development and changes over time. Furthermore, the used technique assesses brain maturation automatically and is therefore blinded, which, in combination with repeated measurements, are important differences with previous studies.

We hypothesize that the patterns of brain maturation of fetuses with CHD are delayed compared with control fetuses.

Key message

Fetuses with congenital heart defects are shown to have a slight delay in cortical maturation when compared with controls, using a novel brain-age prediction algorithm.

2 | MATERIAL AND METHODS

2.1 | Data acquisition

All consecutive pregnant women, diagnosed with a fetal CHD before 32 weeks' gestation at the Leiden University Medical Center between March 2014 and December 2016, were approached to participate in the Heart And Neurodevelopment (HAND)-study. To account for natural variation of cortical development in the healthy population, we constructed a control group by the recruitment of unselected pregnant women after a normal structural anomaly scan. Control cases were not offered additional genetic testing but had a postnatal visit in which dysmorphic featured were assessed. Gestational age (GA) in both the CHD cases and the control cases was based on first-trimester ultrasound at approximately 10 weeks' gestation, according to Dutch national guidelines. For both cases and controls, we excluded: maternal age <18 years, multiple gestation, genetic or syndromic defects (prenatally diagnosed or postnatally apparent up to the age of 6 months), cases with placental pathology (preeclampsia, severe growth restriction) and cases that showed normal cardiac anatomy after birth. In the CHD group, non-isolated cases were excluded. The reasons for only including isolated CHD were that altered neurodevelopment could otherwise be attributed to genetic or syndromic defects. Furthermore, cases with aortic valve stenosis that underwent fetal balloon valvuloplasty were excluded, since fetal brain oxygenation may have changed due to the intervention during pregnancy.[12] Also, strictly minor cases (persistent left caval vein, mild pulmonary stenosis and restrictive foramen ovale) were also excluded, since in these cases, blood flow towards the brain is expected to be uncompromised. The sample size calculation for the normal reference population was based on the available evidence from two MRI studies[7,13] that compared hypoplastic left heart syndrome (HLHS) fetuses with controls, to detect a difference in mean brain age of 2 weeks. The normal reference population was calculated to consist of 60 fetuses. The CHD group contains all the women who met the inclusion criteria and were referred between March 2014 and December 2016.

A CHD in combination with minor associations—namely a single umbilical artery; enlarged first-trimester nuchal translucency with normal chromosomal analysis and small for GA with normal Doppler recordings—were considered as isolated CHD. These cases were not excluded unless genetic syndromes became apparent postnatally.

A detailed neurosonographic examination was performed in cases and controls every 4 weeks after the diagnosis or, in the case of controls, after a normal standard anomaly scan. Examinations were undertaken by experienced sonographers (F.J., A.T., S.E.) using a RAB 6D three-dimensional transducer on a Voluson E8 or E10 (GE Health Care, Chicago, IL, USA). The examination was conducted transabdominally in four scanning planes: axial, coronal, sagittal and parasagittal. At these visits, we assessed the presence of structural brain anomalies and fetal biometry. Multiple 3D volume recordings were obtained in the axial plane, starting at head circumference level of the transthalamic plane. The 3D acquisition was performed in the maximum quality setting (6-12 seconds) or on high quality setting (2-8 seconds) to limit the amount of movement artifacts.

2.2 | Brain-age prediction algorithm

The evaluation of brain maturation by 2D ultrasound imaging is known to have an acceptable rate of interobserver variation. Data from recent MRI studies show a strong correlation between the degree of gyrification and GA,[14,15] and neuropathologists consider the

appearance and stage of the sulci to be so precise[14] that cortical complexity can be used as an accurate proxy for intrauterine neurodevelopment. Therefore, we used a semi-automated age prediction algorithm as a proxy for cortical maturation. At each visit, a mean of 2.7 (0.9) 3D volumes for cases and 3.5 (1.2) for controls were recorded. These volume recordings were examined to identify cases with poor acquisition quality due to fetal motion artifacts. The recording with the highest quality was selected to enter into the algorithm. All 3D volumes were processed with a study-code, which did not reveal the presence or absence of a heart defect. Plane localization was annotated manually in each 3D volume using the ITK-SNAP tool.[16] The algorithmic details on the process of predicting brain maturation from a 3D ultrasound volume were previously described.[17] Briefly, a 3D surface-based coordinate system is spatially aligned to the cranial pixels in the image. This coordinate system allows for the sampling of brain regions based on surface locations. The US image and its corresponding surface are passed into a regression forest model, where they traverse the nodes of a set of pretrained binary decision trees within the forest. At each node, a binary test is applied to a sampled brain region to evaluate whether it is indicative of a more or less advanced stage of maturation. In this way, each brain region (eg, callosal sulcus, thalamic region, cingulate sulcus, parieto-occipital fissure [POF], sylvian fissure [SF], central sulcus and ventricular regions) stands for a particular brain age (Figure 1). The final prediction of brain maturation is achieved by averaging the votes from the brain regions, across the full set of decision trees in the forest. Thus, the algorithm is able to estimate the brain age according the pattern of gyrification of the fetal cortex, which varies during gestation (Figure 2). Furthermore, since the true GA was known for each case, we were able to compare the brain age with the true age to determine any delay in cortical maturation. A more extensive description of the algorithm is available as Appendix S1.

2.3 | Data handling

The prenatal diagnosis was compared with the postnatal echocardiographic findings. In case of discrepancy, the postnatal diagnosis or the results of postmortem examination in the case of pregnancy termination, were considered the definitive cardiac diagnosis. In cases in which the parents did not give consent for

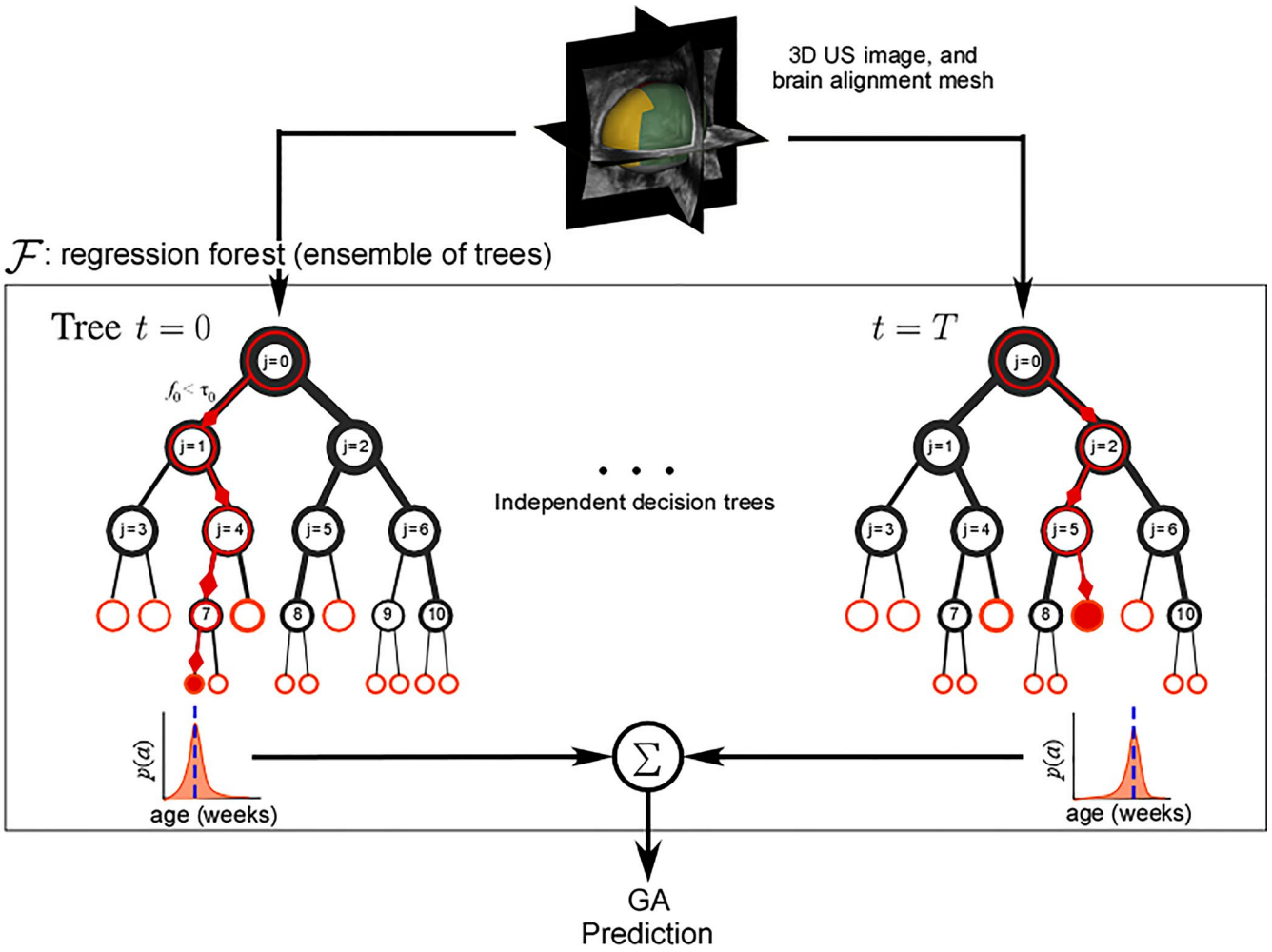

FIGURE 1 Schematic representation of a regression forest. Different brain regions are sampled to calculate the brain age in a 3D US volume [Color figure can be viewed at wileyonlinelibrary.com]

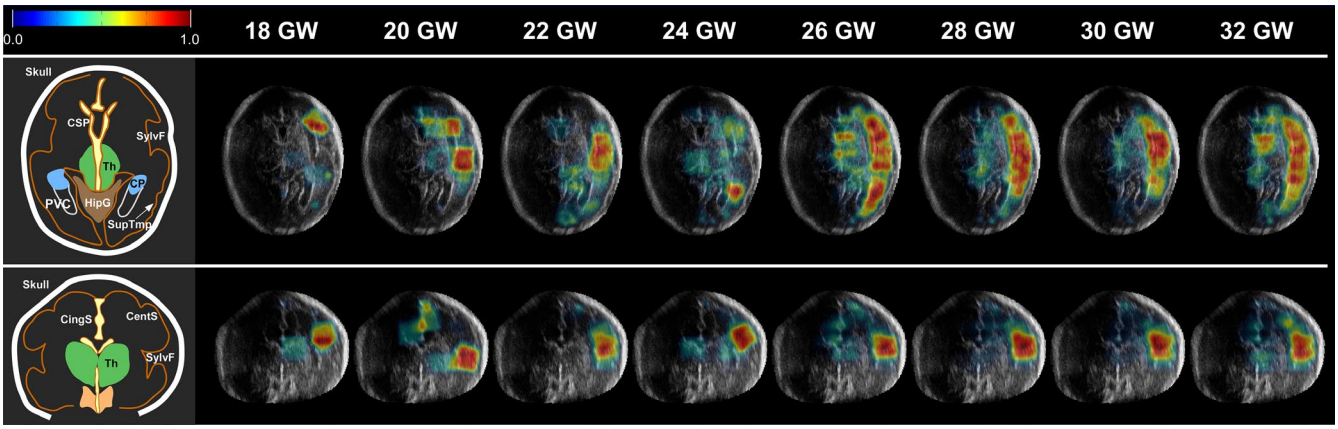

FIGURE 2 A visual representation of gestational age-discriminating brain regions between 18 and 32 wk gestation. Color scale is shown in the top left, top row: axial plane and bottom row: coronal plane. The colors closest to 1.0 represent brain regions that are selected most frequently by the algorithm [Color figure can be viewed at wileyonlinelibrary.com]

postmortem examination, the prenatal diagnosis was used for this study. We have previously shown that the rate of discrepancies is low in our unit.[18]

2.4 | Statistical analyses

We investigated evidence of the presence of systematic between-group differences in brain age, as calculated by the age prediction algorithm, between the CHD group and the control group. We have selected the data from measurements at 19-33 weeks, since the age prediction algorithm had been validated in this GA.[17]

As multiple volume measurements were acquired from the same patient during pregnancy (longitudinal repeated-measures data) linear mixed modeling must be applied to account for systematic within-patient correlation. The mixed-effect regression model corrected for GA (assumed to relate linearly to the age prediction), group (CHD cases vs controls) and the interaction between GA and group as fixed effects. Within-patient correlation was modeled by inclusion of a random-effect intercept per individual. The presence of a between-group difference was then assessed by removing both the interaction term and the main group effect from the full model and assessing the associated likelihood ratio test with two degrees of freedom. As the likelihood ratio test confirmed the presence of group effect, two follow-up hypothesis tests were investigated. First, the main group difference was assessed at the median GA by comparing the (marginal) mean brain age in that set. Secondly, regression slopes were compared between CHD cases and controls to assess whether groups differed in their maturation speed. In a sensitivity analysis, we repeated the tests, allowing for a quadratic effect of GA. All statistical analysis was performed using IBM SPSS statistics version 24.0.0.0 (IBM). Statistical significance was determined when $P \leq 0.05$.

2.5 | Ethical approval

This study was approved by the local ethics committee on 17 March 2014 under ref. number P13.107.

3 | RESULTS

In the study period, 90 consecutive CHD cases and 75 controls were included (see Table 1 for study characteristics). The groups were not prospectively matched for baseline characteristics; however, the groups did not differ significantly in maternal age, parity, body mass index or maternal diabetes. We excluded 14 cases according the defined exclusion criteria, of which eight were postnatal diagnoses of genetic syndromes (three CHARGE syndrome, two Kabuki syndrome, three with postnatal multiple dysmorphic features, final genetic diagnosis pending). The genetic diagnosis of the CHD cases was followed up until 1 year postnatally. In all, 30% of control cases opted for first-trimester screening. No genetic or structural abnormalities were found in the control group up to 6 months postnatally. Thus, 152 CHD cases and controls were eligible for analysis. From these 152 women, volume recordings were made in 493 scanning sessions. Sixteen of these volumes (3.2%) were excluded due to ultrasonographic factors (oblique insonation, fetal movement artifacts or very poor image quality), resulting in 477 volumes suitable for analysis by the age prediction algorithm. In total, 199 volumes in 77 cases (mean of 2.4 recorded volumes per woman) and 278 volumes in 75 controls (mean of 3.7 recorded volumes per woman) were analyzed using the automated age prediction algorithm. The CHD cases were scanned at 1-5 different time points during pregnancy, with 63% of the women scanned more than once. For the control group, all cases were measured more than once.

The fetal brain age of the healthy control cases was calculated by the age prediction algorithm. This cohort of normal fetuses showed a calculated brain age by the algorithm which did not differ statistically from the true GA[17] based on first-trimester ultrasound, suggesting the model is applicable to our cohort. The predicted brain age increased in a perfectly linear way in the second trimester and the algorithm tends slightly to underestimate the brain age during the third trimester (Figure 3).

The overall test indicated that the time trend significantly differed between CHD cases and controls ($P = 0.005$), indicating that indeed there was a group effect. When comparing CHD

TABLE 1 Baseline characteristics of included cases

Characteristics	Value		
	CHD cases	**Controls**	**Total**
No. of women	90	75	
No. of analyzed volumes	199 (42%)	278 (58%)	477 (100%)
			***P*-Value**
Maternal age in years, mean (SD)	29.76 (4.2)	32.08 (4.39)	0.30
BMI (kg/m^2), mean (SD)	23.79 (4.2)	23.24 (3.8)	0.11
Primigravidae (%)	44 (42)	25 (33)	0.28
Diabetes, n (%)	3 (2.9)	0 (0)	0.14
Total no. of CHD cases	**90**		n.a.
Major CHD			
HLHS	7		
Transposition of the great arteries	13		
Aortic arch hypoplasia and/or aortic stenosis	21		
Tricuspid or pulmonary atresia	11		
Tetralogy of Fallot or Fallot-like defect	15		
(un)balanced atrioventricular septal defect	7		
Other major CHD[a]	14		
Minor CHD			
Ventricular septal defect	2		
Excluded cases	**14**		**n.a.**
Fetal intervention	3		
Postnatal non-isolated/syndromic	8		
Postnatal normal heart	3		
Pregnancy outcome			
Live birth	75 (83%)	75 (100%)	n.a.
Termination of pregnancy	15 (17%)	0 (0%)	

BMI, body mass index; CHD, congenital heart defect; HLHS, hypoplastic left heart syndrome; SD, standard deviation; TGA, transposition of the great arteries.
Bold values indicate the combined CHD cases.
[a]Other major CHD includes: truncus arteriosus, multiple level left obstruction syndrome (Shone's complex), double outlet right ventricle-TGA, congenitally corrected TGA.

cases with controls, the brain age determined by the algorithm was lower compared with controls at the median true GA (26.20 weeks vs 26.61 weeks; difference 3 days, 95% CI 1.07-4.63, P = 0.001; Figure 4) The speed of the development of the brain maturation (ie, slopes of the curves) between both groups did not differ statistically significant. Cortical maturation was estimated to increase with 4.45 d/wk vs 4.52 d/wk (P = 0.78) for CHD cases and controls, indicating similar speed of maturation between CHD cases and controls. This was also analyzed with a quadratic age trend analysis, which confirmed the similar increase in cortical maturation between cases and controls.

4 | DISCUSSION

In this study of a consecutive cohort of fetuses with isolated CHD fetuses, we found a delay in fetal brain age of 3 days, compared with normal fetuses. The delay was continuous throughout our study period, which opposes the earlier findings that suggest further delay in cortical maturation with advancing gestation.[7,19] This study is the first to implement a validated automated algorithm to assess fetal cortical development using ultrasound in a clinically relevant group.

Neurodevelopmental delay in CHD children has been recognized for decades, even with optimized preoperative and neonatal care.[20] Prenatal brain damage is hypothesized to result from the altered hemodynamics caused by the cardiac defect, which may result in decreased flow or oxygenation of the blood directed towards the brain,[21,22] resulting in delayed brain development. An increased N-acetylaspartate to choline (NAA:Cho)-ratio and increased lactate levels in MRI and spectroscopy studies support a decrease in brain oxygenation in the developing fetal brain of fetuses with CHD.[19,23]

Cortical maturation by measuring fissure depth has been described before using both MRI[14] and US[24,25] in non-CHD fetuses.

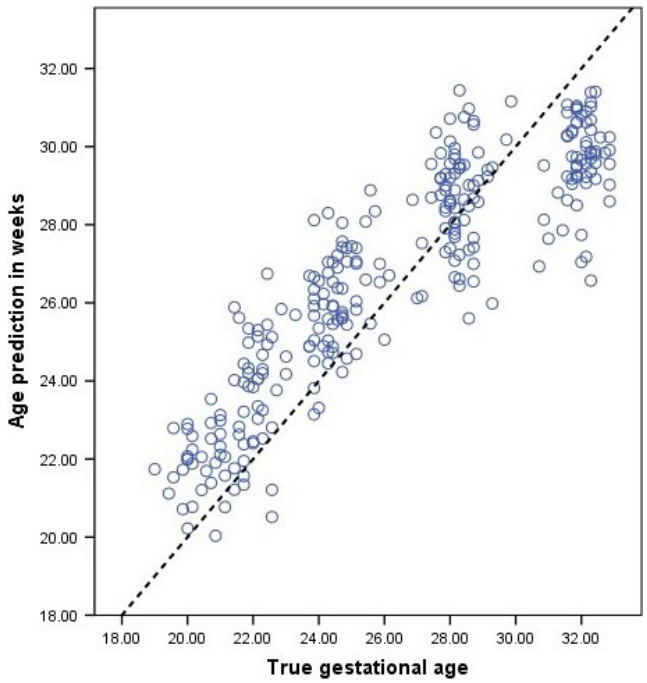

FIGURE 3 Regression plot for 75 control cases: gestational age ("true age") on the *x*-axis and age prediction on the *y*-axis [Color figure can be viewed at wileyonlinelibrary.com]

Application of these techniques shows significant differences in the depth of the POF and calcarine fissure in CHD cases as compared with controls.[6-9] These fissures were also reported to be shallower in CHD neonates than in controls with a comparable GA,[3] which was explained as delayed maturation. The findings in these studies are, however, not in full agreement with each other. A significant decrease in depth of the SF, POF and calcarine fissure was found by some authors,[8] whereas others did not find a significant difference in the SF depth[6] but did find an overall decrease in brain maturation.[9] The differences in the results of these studies can be explained by the small sample sizes, different methodologies, and the differences in statistical analysis of the data.[9]

Our study is the first to convey the development of cortical maturation with ultrasound by using maturational age as an outcome measure. Thus, the used methodology in this study is capable of determining the extent of the delay, which was demonstrated to be small (3 days). Moreover, we do not see a difference in the slopes of the development between CHD and control cases, indicating no further delay in the cortical growth trajectory in the third trimester, as described by other authors.[7,9] A possible explanation for this absence of third trimester difference might be that the role of fetal brain oxygenation is being magnified in the literature due to case selection. However, decreased head growth as a proxy for brain development and developmental delay has also been demonstrated in other types of CHDs, which suggests a role for placental, genetic or epigenetic factors.

A common method of assessing fetal cortical development in the previously mentioned studies is a manual, sometimes unblinded, measurement of the depth of two to three fissures.[6-9] The applied algorithm in our study automatically selects the most age-discriminating regions of the entire fetal brain. As cortical maturation is an excellent proxy for brain age, this does not imply that the sulcation in itself is a linear phenomenon.[14,26] The sampled locations (eg, callosal, cingulate and central sulcus, thalamic region, POF and SF) are proven as the most distinct points to assess maturation speed, as the algorithm used automated deep learning in a large cohort of normal fetuses.[17] It is therefore arguable whether the maturation patterns of the commonly chosen fissures in previous studies (SF, POF and calcarine fissure) are sensitive enough to detect brain maturation and are representative of the global cortical development, as our algorithm selected more sulci to be able to assess brain age with a precision of 6 days.[17]

Another important difference from previous studies is that we included cases with isolated CHD and excluded neonates that were diagnosed with genetic syndromes (routinely tested with microarray or whole exome sequencing) after birth. Although previous studies report the exclusion of aneuploid fetuses,[6-8] only de Koning et al[9] report the postnatal exclusion of syndromic cases. Since a significant amount of genetic syndromes present with mental retardation, abnormal brain development could be caused not solely by the CHD in itself.

Whether a delay of 3 days is clinically relevant, is debatable. On the other hand, one could argue that even though differences are small, they could still have an impact on long-term outcome, since the detected delay is visible in early life.[27] Two of the studies mentioned above[6,8] found significant differences when correlating cortical maturation and neurodevelopmental outcome by performing Bayley Scales of Infant and Toddler Development (BSID). However, authors performed BSID in a minority of infants and, paradoxically, only in milder CHD cases. With this sparse evidence, it is indisputable that there is an urgent need to explore the relation between altered fetal brain maturation and neurodevelopmental outcome further. As this is a limitation of the current study, we are planning to correlate the findings in this cohort to postnatal neurodevelopment.

It is a matter of controversy which imaging modality is superior to detect abnormalities in fetal brain development. While we acknowledge that MRI is regarded as the gold standard for detecting structural brain abnormalities,[28] both previously mentioned MRI studies only comprise a single MRI acquisition during pregnancy, with slice thicknesses of 1.5-3 mm, which will influence the accuracy of the measurements as well. We believe that repeated measurements by US in the hands of experienced sonographers are sensitive enough to study brain maturation trajectories.

A limitation of this study is the assessment of all CHD cases combined. We acknowledge that fetuses with lower oxygen delivery to the brain might be prone to delayed cortical development, reduced head circumference and brain lesions.[10,19,22,29] However, reduced head circumference, as a proxy for brain development, has been reported in fetuses with only a single ventricular septal defect.[30] We have chosen not to stratify according to CHD, as the current group is

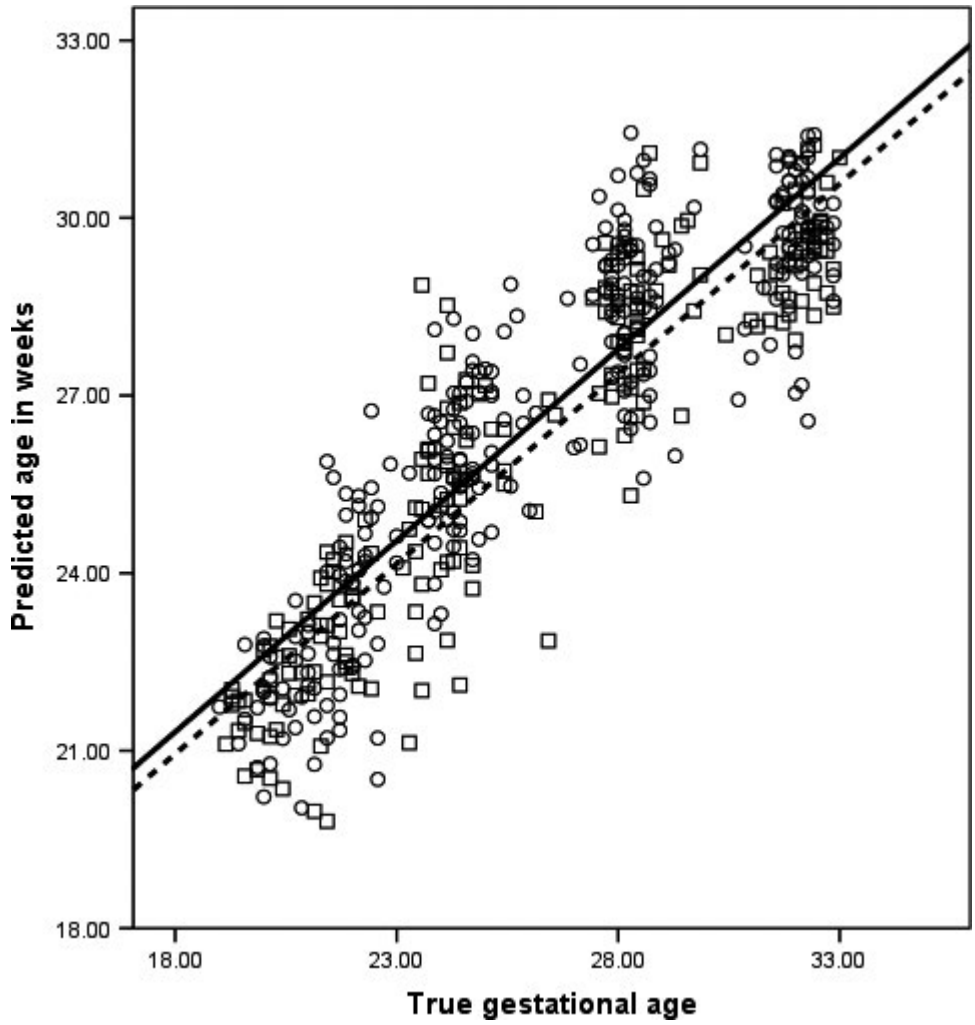

FIGURE 4 The *x*-axis shows the gestational age at ultrasound ("true age"), the *y*-axis shows age as predicted by the algorithm. □, CHD cases; - -, interrupted line; ○, control cases; ——, continuous line

too small to make statements on cortical development. Stratification according lesion physiology will be possible in the future as we continue monitoring these cases.

A second limitation is the upper GA limit of included cases, because brain visibility is obscured due to acoustic shadowing and fetal position in the late third trimester.

5 | CONCLUSION

This study shows that fetuses with isolated cases of CHDs show some delay in cortical maturation as compared with healthy control cases. The clinical relevance of this small difference is debatable. This finding was consistent throughout pregnancy and did not progress during the third trimester.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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