Brain Injury and Neurodevelopmental Outcome in Congenital Heart Disease: A Systematic Review

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abstract

CONTEXT: Brain injury during prenatal and preoperative postnatal life might play a major role in neurodevelopmental impairment in infants with congenital heart disease (CHD) who require corrective or palliative surgery during infancy. A systematic review of cerebral findings during this period in relation to neurodevelopmental outcome (NDO), however, is lacking.

OBJECTIVE: To assess the association between prenatal and postnatal preoperative cerebral findings and NDO in infants with CHD who require corrective or palliative surgery during infancy.


STUDY SELECTION: We conducted 3 different searches for English literature between 2000 and 2016; 1 for prenatal cerebral findings, 1 for postnatal preoperative cerebral findings, and 1 for the association between brain injury and NDO.

DATA EXTRACTION: Two reviewers independently screened sources and extracted data on cerebral findings and neurodevelopmental outcome. Quality of studies was assessed using the Newcastle-Ottawa Quality Assessment Scale.

RESULTS: Abnormal cerebral findings are common during the prenatal and postnatal preoperative periods. Prenatally, a delay of cerebral development was most common; postnatally, white matter injury, periventricular leukomalacia, and stroke were frequently observed. Abnormal Doppler measurements, brain immaturity, cerebral oxygenation, and abnormal EEG or amplitude-integrated EEG were all associated with NDO.

LIMITATIONS: Observational studies, different types of CHD with different pathophysiological effects, and different reference values.

CONCLUSIONS: Prenatal and postnatal preoperative abnormal cerebral findings might play an important role in neurodevelopmental impairment in infants with CHD. Increased awareness of the vulnerability of the young developing brain of an infant with CHD among caregivers is essential.

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Ms Mebius conceptualized and designed the study, screened databases for eligible studies, drafted the initial manuscript, and revised the manuscript after feedback from coauthors; Dr Kooi conceptualized and designed the study, screened databases for eligible studies, and critically reviewed and revised the manuscript;

It has been well established that infants with congenital heart disease (CHD) are at risk for neurodevelopmental impairments. Reports have been published that indicate that in complex CHD, up to 50% of the infants have neurodevelopmental impairments. Impairments can manifest themselves variably, involving different aspects such as (mild) impairments in cognition, fine and gross motor skills, executive functioning, visual construction and perception, attention, social interaction, and core communication skills.

Threats for the young developing brain can arise at different stages during pre- and postnatal life. Research used to focus on the intraoperative and postoperative period, but we now know that brain injury in infants with CHD may already occur before cardiac surgery. Furthermore, there is increasing evidence that suggests that brain injury in infants with CHD already occurs during intrauterine life. The exact mechanism responsible for brain injury in CHD is not yet fully understood. There are 2 main theories. First, the brain could primarily develop differently in infants with CHD because of intrinsic (epi)genetic factors. A large part of heart and brain development occurs simultaneously in the human fetus and involves shared genetic pathways. A discrepancy in one of these pathways could lead to abnormal development of both organs and may thus cause neurodevelopmental impairments. Second, the heart defect may entail changes in oxygen saturation because of intracardiac or extracardiac mixing, which could in turn lead to circulatory alterations that affect oxygen and nutrient supply to the brain and could therefore disturb normal cerebral development.

Although several studies have reported on prenatal brain injury, preoperative brain injury, or neurodevelopmental outcome (NDO) in CHD, a systematic review of brain injury during both prenatal and postnatal preoperative life in relation to NDO is currently not available. The aim of this study was, therefore, to systematically review existing evidence for prenatal and postnatal preoperative brain injury in relation to NDO in infants with complex CHD.

**METHODS**

**Search Strategy**

This systematic review was performed according to the PRISMA guidelines for systematic reviews. There was no registered protocol available. A systematic search was conducted in PubMed and Embase independently by 2 researchers (M.J.M. and E.M.W.K.) on July 1, 2016. Publications from January 2000 to July 2016 that contained data on prenatal and/or postnatal preoperative cerebral findings and neurodevelopmental outcome in infants with congenital heart disease were selected for this review.

To assess all available literature on prenatal and postnatal preoperative brain injury in relation to NDO, we conducted 3 different searches. We started with a search on cerebral findings in fetuses with congenital heart disease. For this search, we selected all original research articles that were written in English and contained different combinations or synonyms of congenital heart disease, fetus, Doppler, MRI, sonography, and brain. Articles that exclusively focused on head biometry were excluded. For the second search, we used combinations or synonyms of congenital heart disease, neonate, infant, Doppler, MRI, near-infrared spectroscopy, EEG, and brain. Articles were selected if they were written in English, if participants were <3 months of age at the first examination, and if at least part of the study group was diagnosed prenatally with CHD. Articles that focused on infants with chromosomal or syndromal disorders were excluded because we were interested in the effect of the congenital heart defect on NDO in infants with complex CHD. For the purpose of the current review, we were not interested in developmental problems because of chromosomal disorders. In addition, we excluded articles with an interventional study design tailored to evaluate the direct impact of an experimental intervention on cerebral outcome variables. For the third search, we combined the first 2 searches and complemented it with neurodevelopmental outcome and word variants. Articles were selected only if they combined prenatal and/or postnatal preoperative cerebral findings with NDO in infants with CHD. Furthermore, NDO had to be assessed with validated tools such as the Bayley Scales of Infant Development II (BSID II) or the Bayley Scales of Infant and Toddler Development III (Bayley III). The complete search string is available online in Supplemental Information.

In addition to the database search, we screened the reference lists of all retrieved articles for additional relevant publications.

**Quality Assessment**

We assessed the quality of the selected articles using the Newcastle-Ottawa Quality Assessment Scale for case-control studies and cohort studies. This scale consists of 3 parts: selection, comparability, and exposure for case-control studies and selection,
comparability, and outcome for cohort studies. Each part consists of a different number of items and a different amount of points that can be acquired per item. Selection consists of 4 items with a maximum of 4 points, comparability consists of 1 item with a maximum of 2 points, and exposure or outcome consists of 3 items with a maximum of 3 points. Therefore, the total score ranges from 0 to 9, with 9 being an article of the highest quality. The quality scores of selected articles are presented online in Supplemental Tables 4 and 5.

RESULTS

Our initial search resulted in 503 articles. After removing duplicates, we assessed titles and abstracts of 260 articles, of which 40 were relevant. The main reasons for exclusion were chromosomal or syndromal disorders, not original research, and study being out of scope. From the reference lists, we found 7 additional articles. After reading the full text, 30 articles were included in the prenatal part of the review (Fig 1). Prenatal cerebral findings are presented in Table 1.

The second search resulted in 1347 articles. We assessed titles and abstract of 734 articles after removing duplicates. Reasons for exclusion at this stage were chromosomal or syndromal disorders, not original research, intraoperative or postoperative data, and study being out of scope. From the reference lists, we found another 3 articles. Eventually, we read 68 full-text articles, from which 51 were included in the postnatal part of the review (Fig 2). Postnatal cerebral findings are presented in Table 2.

The final search resulted in 882 articles. Many articles on neurodevelopmental outcome were not eligible because they did not combine prenatal or postnatal preoperative cerebral findings with neurodevelopmental outcome. Four additional relevant articles were found and added to either the prenatal or the postnatal preoperative part of the review. Results on the association between prenatal or postnatal preoperative cerebral findings and neurodevelopmental outcome are presented in Table 3.

Prenatally, 1 study included a small percentage of infants with nonisolated CHD, 13% of the studies did not report on whether they included infants with nonisolated CHD, and 84% focused exclusively on infants with isolated CHD. Postnatally, 32% of the studies did not report on including or excluding infants with nonisolated CHD and 1 study included a small percentage of infants with nonisolated CHD. When possible, only the results of infants with isolated CHD were presented.

Prenatal Cerebral Ultrasound

Twenty-two articles reported on Doppler parameters (Table 1). In general, these studies were case-control studies or cohort studies that compared Doppler parameters of fetuses with CHD with either healthy controls or reference values from the literature. Almost all studies used z scores to adjust for gestational age (the amount of SDs from the mean for a given gestational age).

The vast majority (86%) of the 22 studies that reported on Doppler parameters found the pulsatility index (PI) of the middle cerebral
Table 1: Prenatal Cerebral Findings in Infants with CHD

<table>
<thead>
<tr>
<th>Study (First Author, Journal, Year of Publication)</th>
<th>Study Design, No. Infants</th>
<th>CHD</th>
<th>Age</th>
<th>Methods</th>
<th>Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruiz et al, Ultrasound Obstet Gynecol, 2016</td>
<td>Retrospective study, N = 119</td>
<td>Mixed</td>
<td>Second and third trimester</td>
<td>Ultrasound (biometry, Doppler)</td>
<td>Normal MCA-PI and CPR during second trimester, 18% MCA-PI and CPR less than fifth percentile at first examination Lower MCA-PI in group with severe impairment of cerebral blood flow UA-PI increased with GA Smaller HC and BPD at diagnosis which remained during pregnancy Lower MCA-PI and decreased more as GA progressed Smaller HC at 24–29 wk GA and &gt;34 wk GA Fetal HC predictor of neonatal HC from 30 wk GA MCA-PI not associated with fetal and neonatal HC</td>
</tr>
<tr>
<td>Hahn et al, Ultrasound Obstet Gynecol, 2016</td>
<td>SVA, N = 133</td>
<td>Second and third trimester</td>
<td>Ultrasound (biometry, Doppler)</td>
<td>Lower MCA-PI</td>
<td></td>
</tr>
<tr>
<td>Zeng et al, Ultrasound Obstet Gynecol, 2015</td>
<td>Case-control study, N = 73/168</td>
<td>Mixed</td>
<td>Second and third trimester</td>
<td>Ultrasound (biometry, Doppler)</td>
<td>Lower MCA-PI</td>
</tr>
<tr>
<td>Zeng et al, Ultrasound Obstet Gynecol, 2015</td>
<td>Case-control study, N = 112/112</td>
<td>Mixed</td>
<td>20–30 wk</td>
<td>Ultrasound (Doppler)</td>
<td>No differences in MCA-PI and fractional moving blood volume between CHD diagnostic groups</td>
</tr>
<tr>
<td>Masoller et al, Ultrasound Obstet Gynecol, 2014</td>
<td>Case-control study, N = 95/95</td>
<td>Mixed</td>
<td>20–24 wk</td>
<td>Ultrasound (biometry, Doppler)</td>
<td>No differences in MCA-PI and fractional moving blood volume between CHD diagnostic groups</td>
</tr>
<tr>
<td>Williams et al, Am Heart J, 2013</td>
<td>Cohort study, N = 134</td>
<td>SVA</td>
<td>18–38 wk</td>
<td>Ultrasound (Doppler)</td>
<td>No differences in BPD and HC between CHD diagnostic groups</td>
</tr>
<tr>
<td>Yamamoto et al, Ultrasound Obstet Gynecol, 2013</td>
<td>Case-control study, N = 89/89</td>
<td>Mixed</td>
<td>32 wk</td>
<td>Ultrasound (biometry, Doppler)</td>
<td>No differences in MCA-PI and fractional moving blood volume between CHD diagnostic groups</td>
</tr>
<tr>
<td>Szwaust et al, Ultrasound Obstet Gynecol, 2012</td>
<td>Retrospective study, N = 131/92</td>
<td>SVA</td>
<td>18–40 wk</td>
<td>Ultrasound (Doppler)</td>
<td>No differences in MCA-PI and fractional moving blood volume between CHD diagnostic groups</td>
</tr>
<tr>
<td>Williams et al, J Matern Fetal Neonatal Med, 2011</td>
<td>Pilot study, N = 13</td>
<td>Mixed</td>
<td>20–24 wk</td>
<td>Ultrasound (Doppler)</td>
<td>No differences in MCA-PI and fractional moving blood volume between CHD diagnostic groups</td>
</tr>
<tr>
<td>Arduini et al, J Matern Fetal Neonatal Med, 2011</td>
<td>Case-control study, N = 60/65</td>
<td>SVA</td>
<td>30–38 wk</td>
<td>Ultrasound (biometry, Doppler)</td>
<td>No differences in MCA-PI and fractional moving blood volume between CHD diagnostic groups</td>
</tr>
<tr>
<td>Itsukicahi et al, Fetal Diagn Ther, 2011b</td>
<td>Retrospective study, N = 44/140</td>
<td>Mixed</td>
<td>28–34 wk</td>
<td>Ultrasound (biometry, Doppler)</td>
<td>No differences in MCA-PI and fractional moving blood volume between CHD diagnostic groups</td>
</tr>
<tr>
<td>McElhinney et al, Ultrasound Med Biol, 2010</td>
<td>Cohort study, N = 52</td>
<td>HLHS</td>
<td>20–31 wk</td>
<td>Ultrasound (Doppler)</td>
<td>MCA-PI measurements more often less than fifth percentile and UA-RI &gt;90th percentile</td>
</tr>
<tr>
<td>Beng et al, Ultrasound Obstet Gynecol, 2009</td>
<td>Case-control study, N = 113/1378</td>
<td>Mixed</td>
<td>19–41 wk</td>
<td>Ultrasound (biometry, Doppler)</td>
<td>Similar biometry measurements in fetuses &lt;10th and &gt;10th MCA-RI percentile</td>
</tr>
</tbody>
</table>

MCA-PI, mean cerebroplacental index; CPR, cardiac performance ratio; HC, head circumference; BPD, bi-parietal diameter; UA-PI, umbilical artery pulsatility index; TGA, tetralogy of Fallot; TOF, tetralogy of Fallot; LSOL, left-sided obstructive lesions; Rsol, right-sided obstructive lesions; CoA, coarctation of aorta; SVA, secon- d and third trimester; SAV, first and second trimester; MCA-PI, mean cerebral arteri- oplastic index; MCA-RI, mean cerebroplacental resistance index; CPR, cardiac perfor- mance ratio; HC, head circumference; BPD, bi-parietal diameter; UA-PI, umbilical artery pulsatility index; TGA, tetralogy of Fallot; TOF, tetralogy of Fallot; LSOL, left-sided obstructive lesions; Rsol, right-sided obstructive lesions; CoA, coarctation of aorta; SVA, secon- d and third trimester; SAV, first and second trimester; MCA-PI, mean cerebral arteri- oplastic index; MCA-RI, mean cerebroplacental resistance index; CPR, cardiac perfor- mance ratio; HC, head circumference; BPD, bi-parietal diameter; UA-PI, umbilical artery pulsatility index; TGA, tetralogy of Fallot; TOF, tetralogy of Fallot; LSOL, left-sided obstructive lesions; Rsol, right-sided obstructive lesions; CoA, coarctation of aorta; SVA, secon- d and third trimester; SAV, first and second trimester; MCA-PI, mean cerebral arteri- oplastic index; MCA-RI, mean cerebroplacental resistance index; CPR, cardiac perfor- mance ratio; HC, head circumference; BPD, bi-parietal diameter; UA-PI, umbilical artery pulsatility index; TGA, tetralogy of Fallot; TOF, tetralogy of Fallot; LSOL, left-sided obstructive lesions; Rsol, right-sided obstructive lesions; CoA, coarctation of aorta; SVA, secon- d and third trimester; SAV, first and second trimester; MCA-PI, mean cerebral arteri- oplastic index; MCA-RI, mean cerebroplacental resistance index; CPR, cardiac perfor- mance ratio; HC, head circumference; BPD, bi-parietal diameter; UA-PI, umbilical artery pulsatility index; TGA, tetralogy of Fallot; TOF, tetralogy of Fallot; LSOL, left-sided obstructive lesions; Rsol, right-sided obstructive lesions; CoA, coarctation of aorta; SVA, secon- d and third trimester; SAV, first and second trimester; MCA-PI, mean cerebral arteri- oplastic index; MCA-RI, mean cerebroplacental resistance index; CPR, cardiac perfor- mance ratio; HC, head circumference; BPD, bi-parietal diameter; UA-PI, umbilical artery pulsatility index; TGA, tetralogy of Fallot; TOF, tetralogy of Fallot; LSOL, left-sided obstructive lesions; Rsol, right-sided obstructive lesions; CoA, coarctation of aorta; SVA, secon- d and third trimester; SAV, first and second trimester; MCA-PI, mean cerebral arteri- oplastic index; MCA-RI, mean cerebroplacental resistance index; CPR, cardiac perfor- mance ratio; HC, head circumference; BPD, bi-parietal diameter; UA-PI, umbilical artery pulsatility index; TGA, tetralogy of Fallot; TOF, tetralogy of Fallot; LSOL, left-sided obstructive lesions; Rsol, right-sided obstructive lesions; CoA, coarctation of aorta; SVA, secon- d and third trimester; SAV, first and second trimester; MCA-PI, mean cerebral arteri- oplastic index; MCA-RI, mean cerebroplacental resistance index; CPR, cardiac perfor- mance ratio; HC, head circumference; BPD, bi-parietal diameter; UA-PI, umbilical artery pulsatility index; TGA, tetralogy of Fallot; TOF, tetra...
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<th>Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guong et al, Fetal Diagn Ther, 2009</td>
<td>Case-control study, N = 45/275</td>
<td>Mixed 20–40 wk Ultrasound (Doppler)</td>
<td>MCA-PI tended to be lower in LSOL and was lower in congestive heart failure</td>
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<tr>
<td></td>
<td>Chen et al, Am J Perinatol, 2009</td>
<td>Case-control study, N = 11/44</td>
<td>Ebstein anomaly 23–37 wk Ultrasound (Doppler)</td>
<td>Lower MCA-PI and CPR (no z scores)</td>
</tr>
<tr>
<td></td>
<td>Modena et al, Am J Obstet Gynecol, 2006</td>
<td>Case-control study, N = 71/71</td>
<td>Mixed 24–28 wk Ultrasound (Doppler)</td>
<td>MCA-PI more often less than fifth percentile (5/71 vs 0/71)</td>
</tr>
<tr>
<td></td>
<td>Kaltman et al, Ultrasound Obstet Gynecol, 2005</td>
<td>Case-control study, N = 58/114</td>
<td>Mixed 20–40 wk Ultrasound (Doppler)</td>
<td>No difference in UA-PI &gt;95th percentile (6/71 vs 3/71)</td>
</tr>
<tr>
<td></td>
<td>Donofrio et al, Pediatr Cardiol, 2003</td>
<td>Case-control study, N = 36/21</td>
<td>Mixed Second and third trimester Ultrasound (Doppler)</td>
<td>Most common: mild unilateral ventriculomegaly and increased extra-axial spaces, 2 white matter cysts, 2 inferior vermian hypoplasia, 1 white matter signal hyperintensity</td>
</tr>
<tr>
<td></td>
<td>Jouannic et al, Ultrasound Obstet Gynecol, 2002</td>
<td>Case-control study, N = 23/40</td>
<td>TGA 36–38 wk Ultrasound (Doppler)</td>
<td>No association between type of brain injury and CHD diagnosis</td>
</tr>
<tr>
<td></td>
<td>Meise et al, Ultrasound Obstet Gynecol, 2001</td>
<td>Case-control study, N = 115/100</td>
<td>Mixed 19–41 wk Ultrasound (Doppler)</td>
<td>Normal MCA-PI</td>
</tr>
<tr>
<td></td>
<td>Brossard-Racine et al, Am J Neuroradiol, 2016</td>
<td>Cohort study, N = 103</td>
<td>Mixed Second and third trimester MRI (structural)</td>
<td>16% fetal brain abnormalities (6 mild ventriculomegaly, 4 increased ventricular volumes/wider CSF spaces)</td>
</tr>
<tr>
<td></td>
<td>Brossard-Racine et al, Am J Neuroradiol, 2014</td>
<td>Case-control study, N = 144/194</td>
<td>Mixed 18–39 wk MRI (structural)</td>
<td>32% neonatal brain abnormalities, 27% acquired brain injury</td>
</tr>
<tr>
<td></td>
<td>Milczoch et al, Eur J Paediatr Neurol, 2013</td>
<td>Retrospective study, N = 53</td>
<td>Mixed 20–37 wk MRI (structural)</td>
<td>No association between type of brain injury and CHD diagnosis</td>
</tr>
<tr>
<td></td>
<td>Al Nafisi et al, J Cardiovasc Magn Reson, 2013</td>
<td>Case-control study, N = 22/12 controls</td>
<td>Mixed 30–38 wk MRI, volume</td>
<td>Fetuses with similar PA and Ao size had higher prevalence of brain injury compared with fetuses with PA &lt; Ao or Ao &lt; PA</td>
</tr>
<tr>
<td></td>
<td>Sun et al, Circulation, 2015</td>
<td>Case-control study, N = 30/30</td>
<td>Mixed 36 wk MRI (volume, O₂ saturation)</td>
<td>Lower total brain volume and cortical and subcortical volumes from 20 wk GA</td>
</tr>
</tbody>
</table>

a Unless Otherwise Stated
artery (MCA) to be lower in the entire study group (13 articles) or in selected CHD diagnoses (6 articles). In particular, fetuses with hypoplastic left heart syndrome (HLHS) or cardiac lesions that are associated with impaired cerebral oxygen supply had a lower pulsatility index of the middle cerebral artery (MCA-PI) compared with healthy controls.13–21 Fetuses with right-sided obstructive lesions14,15,19,20 often had a MCA-PI similar to healthy controls. Contradictory results were reported concerning MCA-PI in fetuses with transposition of the great arteries (TGA). On the one hand, TGA is one of the lesions associated with impaired cerebral oxygen supply because venous blood from the brain is redirected to the brain. This may lead to brain sparing, as suggested by the lower MCA-PI found by some studies.13,21,22 On the other hand, 3 studies specifically looking into the MCA-PI of fetuses with TGA found values similar to healthy controls.14,15,19

None of the studies on Doppler parameters in fetuses with CHD reported higher MCA-PI compared with healthy controls. Abnormally low MCA-PI was present from the second trimester onwards23 and tended to decrease more than would be expected for gestational age.24

Cerebroplacental ratio (CPR) was also reported to be lower in the majority of fetuses with CHD (75% of the selected articles). Again, fetuses with HLHS tended to have a lower CPR than fetuses with right-sided obstructive lesions and TGA.15,19

Two articles that did not use z scores found CPR values of <1.0 in 37% to 56% of the cases.16,18

Concerning PI of the umbilical artery (UA), which reflects intraplacental resistance to flow, 11 articles reported contradictory results. Five studies reported a higher pulsatility index of the umbilical artery (UA-PI),13,20,25–27 whereas another 5 studies reported similar UA-PI18,22,28–30 in fetuses with
CHD compared with healthy controls. One study reported both higher UA-PI (coarctation of the aorta and HLHS) as well as normal UA-PI (right-sided obstructive lesions and TGA) in different parts of the study group.\textsuperscript{15}

\textbf{MRI}

\textit{Prenatal MRI}

The main findings on MRI in fetuses with different types of CHD (majority TGA, HLHS, tetralogy of Fallot, single ventricle anomaly) were features of developmental delay of the cerebrum. In 16\% to 39\% of the cases, lesions such as (unilateral) mild ventriculomegaly and increased extra-axial cerebrospinal fluid spaces were present. These abnormalities are both thought to be markers of delay of cerebral development.\textsuperscript{31–33}

In addition to these lesions, other signs of developmental delay of the cerebrum such as a smaller head circumference (HC) and biparietal diameter, lower total brain weight, lower total brain volumes, higher ventricular volumes, and higher cerebrospinal fluid volumes were also common in fetuses with CHD.\textsuperscript{21,31–38} Another feature of developmental delay was an impaired sulcation with a delay of ∼3 to 4 weeks.\textsuperscript{21,36–38}

Furthermore, cerebral metabolism was altered in fetuses with CHD and included an increased myo-inositol/choline (Ino/Cho), decreased n-acetylaspartate/choline (NAA/Cho), and decreased choline/creatinine (Cho/Cr) ratio.\textsuperscript{21,33,37} These metabolic alterations are also in accordance with cerebral developmental delay.

Fetuses with CHD associated with impaired oxygen supply to the cerebrum (HLHS, critical aortic stenosis, interrupted aortic arch, and TGA) showed more pronounced developmental delay in comparison with fetuses with CHD associated with sufficient blood flow to the cerebrum.\textsuperscript{21,34,37} Infants with HLHS showed a progressive decline in volumetric growth of the cortical and subcortical gray matter in comparison with healthy controls. These differences in brain volumes became significant from a gestational age of 30 weeks.\textsuperscript{38} Because of the study design of most studies, a further differentiation according to the type of CHD was impossible.

\textit{Postnatal Preoperative MRI}

Forty studies used MRI to examine preoperative cerebral findings in infants with different types of CHD (Table 2). Signs of delayed development of the cerebrum were also common during this period. Infants with CHD had an overall reduction of 21\% in total brain volume,\textsuperscript{39} with all brain regions being affected.\textsuperscript{39–42} The largest regional difference between neonates with CHD and healthy controls seemed to be in the corpus callosum (31\% smaller), cortical gray matter (29.5\% smaller), and the occipital lobes (28.5\% smaller).\textsuperscript{39–41,43} These differences in brain volumes persisted to an age of 3 months. Brain growth rate, however, did not seem to differ between neonates with CHD and healthy controls in 1 study.\textsuperscript{40}

Brain metabolism and microstructural development were also in accordance with delayed cerebral development. White matter fractional anisotropy\textsuperscript{44–47} and NAA/Cho\textsuperscript{45–47} were lower, and mean average diffusivity,\textsuperscript{45–47} lactate/choline (Lac/Cho),\textsuperscript{45–47} Cho/Cr,\textsuperscript{48} and myo-inositol/creatinine\textsuperscript{48} were higher. The mean total maturation scores were significantly lower than reported normative data in neonates without CHD and corresponded to a delay of ∼4 weeks in structural brain development.\textsuperscript{49} In infants with TGA, the altered metabolism was
<table>
<thead>
<tr>
<th>Study (First Author, Journal, Year of Publication)</th>
<th>Study Design, No. Infants</th>
<th>CHD Antenatal Diagnosis</th>
<th>Methods</th>
<th>Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brossard-Racine et al, ANJR Am J Neuroradiol, 2016</td>
<td>Cohort study, N = 103</td>
<td>Mixed 100% MRI (structural)</td>
<td>32% brain injury (28% acquired)</td>
<td>WMI most common injury (5 mild and 10 moderate or severe) WMI located in the periventricular white matter; centrum semiovale, and frontal white matter Second most common injury: nonhemorrhagic parenchymal injury</td>
</tr>
<tr>
<td>McCarthy et al, Pediatr Res, 2015</td>
<td>Retrospective study, N = 72</td>
<td>Mixed U MRI (structural)</td>
<td>The majority of PVL classified as moderate</td>
<td>23% WMI or stroke, 47% intracranial hemorrhage (subdural hematoma or choroid plexus) Low Spo₂ risk factor for brain injury, BAS not associated with brain injury Brain injury associated with poorer neurologic functioning (82% abnormal assessment)</td>
</tr>
<tr>
<td>Bertholdt et al, Eur J Cardiothorac Surg, 2014</td>
<td>Case-control study, N = 30/20</td>
<td>Mixed 17% MRI (structural)</td>
<td>Brain immaturity and male sex independent strong predictors of PVL</td>
<td></td>
</tr>
<tr>
<td>Owen et al⁴, J Pediatr, 2014</td>
<td>Cohort study, N = 35</td>
<td>Mixed 51% MRI (structural)</td>
<td>46% evidence of injury or immaturity on MRI (most common: hemorrhage) 71% suspect or abnormal neurobehavioral assessment (18 suspect, 9 abnormal)</td>
<td></td>
</tr>
<tr>
<td>Goff et al, J Thorac Cardiovasc Surg, 2014</td>
<td>Cohort study, N = 57</td>
<td>HLHS 86% MRI (structural)</td>
<td>19% PVL preoperatively</td>
<td></td>
</tr>
<tr>
<td>Andropoulos et al⁵, Paediatr Anaesth, 2014</td>
<td>Retrospective study, N = 39</td>
<td>Mixed U MRI (structural)</td>
<td>46% preoperative brain injury</td>
<td>WMI most common injury (31%, 8 mild, 3 moderate, 1 severe)</td>
</tr>
<tr>
<td>Beca et al⁶, Circulation, 2013</td>
<td>Cohort study, N = 153</td>
<td>Mixed 59% MRI (structural)</td>
<td>26% brain injury (20% WMI, 5% stroke, 4% hemorrhage) WMI associated with brain immaturity but not with BAS, diagnostic group, or GA at birth WMI and stroke not associated with postoperative brain injury 47% ≥1 type of brain injury, 26% 2–4 injury types 26% brain injury if hemorrhage was excluded Lower Apgar score at 5 min associated with brain injury Reduced cortical surface area and gyriﬁcation index for left and right hemispheres 46% focal signal abnormalities in the white matter 24% white matter injury Infants with TGA and blood stream infection might have a higher risk of developing WMI (not signiﬁcant in the whole group but signiﬁcant when stroke was excluded)</td>
<td></td>
</tr>
<tr>
<td>Mulkey et al, Pediatr Cardiol, 2013</td>
<td>Retrospective study, N = 73</td>
<td>Mixed 32% MRI (structural)</td>
<td></td>
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</tr>
<tr>
<td>Ortinau et al, J Pediatr, 2013</td>
<td>Case-control study, N = 15/12</td>
<td>Mixed U MRI (structural)</td>
<td>43% brain injury (23 stroke, 21 WMI, and 7 IVH) BAS doubled the risk for brain injury Higher Spo₂ protective factor for brain injury (OR = 0.96) 28% brain injury (single ventricle and 2 ventricles) Brain immaturity associated with preoperative WMI and late death 58% of lesions partially or completely resolved at late MRI scan (3–6 mo)</td>
<td></td>
</tr>
<tr>
<td>Glass et al, Cardiol Young, 2011</td>
<td>Cohort study, N = 127</td>
<td>Mixed U MRI (structural)</td>
<td>46% focal signal abnormalities in the white matter 24% white matter injury</td>
<td></td>
</tr>
<tr>
<td>Block et al, J Thorac Cardiovasc Surg, 2010</td>
<td>Cohort study, N = 92</td>
<td>TGA U MRI (structural)</td>
<td>30% brain injury (27% WMI and 5% stroke) No differences between cardiac diagnoses No association between BAS and brain injury 38% PVL, 0 strokes</td>
<td></td>
</tr>
<tr>
<td>Andropoulos et al, J Thorac Cardiovasc Surg, 2010</td>
<td>Cohort study, N = 67</td>
<td>Mixed 44% MRI (structural)</td>
<td>41% brain injury (5 stroke, 2 WMIs, 1 IVH, 4 combination of lesions) Brain immaturity and male sex independent strong predictors of PVL</td>
<td></td>
</tr>
<tr>
<td>Beca et al, J Am Coll Cardiol, 2009</td>
<td>Cohort study, N = 64</td>
<td>Mixed 32% MRI (structural)</td>
<td>28% brain injury if hemorrhage was excluded Lower Apgar score at 5 min associated with brain injury Reduced cortical surface area and gyriﬁcation index for left and right hemispheres 46% focal signal abnormalities in the white matter 24% white matter injury Infants with TGA and blood stream infection might have a higher risk of developing WMI (not signiﬁcant in the whole group but signiﬁcant when stroke was excluded)</td>
<td></td>
</tr>
<tr>
<td>Petit et al, Circulation, 2009</td>
<td>Retrospective study, N = 26</td>
<td>TGA U MRI (structural)</td>
<td>Arterial oxygen saturation and time to surgery risk factors for brain injury No association between BAS and brain injury</td>
<td></td>
</tr>
<tr>
<td>Licht et al, J Thorac Cardiovasc Surg, 2009</td>
<td>Cohort study, N = 42</td>
<td>TGA 83% HLHS MRI (structural)</td>
<td>21% PVL, 9.5% stroke, 86% incomplete closure of the opercular space (brain immaturity) Lower total maturation scores (10.15), ~1 mo younger than their actual GA 41% brain injury (5 stroke, 2 WMIs, 1 IVH, 4 combination of lesions) Brain immaturity and male sex independent strong predictors of PVL</td>
<td></td>
</tr>
<tr>
<td>McQuillen et al, Circulation, 2006</td>
<td>Cohort study, N = 29</td>
<td>TGA U MRI (structural)</td>
<td>5 min Apgar score, lowest Spo₂, and BAS (12 of 19 infants with BAS had brain injury, 0 of 10 without BAS had brain injury) are risk factors for brain injury</td>
<td></td>
</tr>
<tr>
<td>Durandy et al, Artif Organs, 2011</td>
<td>Cohort study, N = 21</td>
<td>TGA 57% MRI (structural)</td>
<td>42% brain injury (4 infant, 4 WMIs, and 5 hemorrhages in 9 infants) 55% brain injury in antenatal diagnosis compared with 33% in postnatal diagnosis</td>
<td></td>
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</tbody>
</table>
### Table 2 Continued

<table>
<thead>
<tr>
<th>Study (First Author, Journal, Year of Publication)</th>
<th>Study Design, No. Infants</th>
<th>CHD Antenatal Diagnosis</th>
<th>Methods</th>
<th>Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)</th>
</tr>
</thead>
</table>
| Tavani et al, *Neuroradiology, 2003*<sup>10</sup> | Cohort study, *N* = 24 | Mixed | MRI (structural) | 62% of infants delivered vaginally had hemorrhage on MRI (structural)  
11 subdural hematomas  
6 blood in the subdural space along the tentorium and falx or more laterally  
7 blood in the choroid plexus  
No relation between intracranial hemorrhage and abnormal neurologic examination |
Smallest difference: mesencephalon 7.7% smaller  
Biggest difference: cortical gray matter 29.5% smaller and occipital lobes 28.5% smaller |
Brain growth rate not different  
Differences in volume persisted at 3 mo, except for cerebellar measures  
Somatic growth the greatest predictor of brain growth |
Smaller frontal, parietal, cerebellar, and brain stem  
Frontal and brain stem most affected  
Delayed maturation at the microstructural level |
Lower FA splenium corpus callosum |
| Hagmann et al, *J Child Neurol, 2016* | Case-control study, *N* = 22/22 | Mixed | MRI (volume, DTI) | Corpus callosum 25% (splenium) to 35% (genu) smaller  
Total corpus callosum and splenium significantly smaller  
Splenium lower FA, higher radial diffusion, diffusion coefficient not significant |
52% brain injury (WMI or stroke)  
Lower FA in multiple major white matter tracts in infants with brain injury compared with infants without brain injury  
28% brain injury (focal or multifocal)  
Brain injury associated with less change in FA over time in the pyramidal tract compared with newborns with 2 normal MRI scans |
| Partridge et al, *Ann Neurol, 2006* | Cohort study, *N* = 25 | Mixed | MRI (structural, DTI) | Infants with brain injury had the least dramatic changes with age detected by DTI  
Trend in FA maturation rates across the 3 injury groups: newborns with normal scans had the most rapid changes, those with postoperative injury had intermediate maturation rates, and those with preoperative injury had the least rapid changes  
No differences in directionally averaged diffusion coefficients |
Higher mean average diffusivity for gray matter and lower FA in the white matter regions  
Lower mean NAA/Cho ratios and higher mean Lac/Cho ratios  
Delayed microstructural brain development  
No abnormal findings on preoperative MRI  
Altered metabolism in parietal white matter (increased Cho/Cr) and occipital gray matter (increased Cho/Cr and Ino/Cr)  
Altered metabolism persisted 1 y after ASO in parietal white matter and normalized for occipital gray matter  
40% brain injury (stroke or hemorrhage)  
Higher Lac/Cho |
| Park et al<sup>a</sup>, *Pediatr Cardiol, 2006* | Case-control study, *N* = 18/15 | TGA | MRI (structural, MRS) | No abnormal findings on preoperative MRI  
Altered metabolism persisted 1 y after ASO in parietal white matter and normalized for occipital gray matter  
Similar NAA/Cho between TGA and healthy controls, but those with brain injury on MRI had lower NAA/Cho  
0% focal deficits on neurologic examination  
Abnormalities in tone or reflexes common in newborns with and without brain injury |

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<sup>a</sup> Indicates a single-center, single-institution study.
<table>
<thead>
<tr>
<th>Study (First Author, Journal, Year of Publication)</th>
<th>Study Design, No. Infants</th>
<th>CHD Antenatal Diagnosis</th>
<th>Methods Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahle et al, <em>Circulation,</em> 2002</td>
<td>Cohort study, N = 24</td>
<td>Mixed 63% MRI (structural, MRS)</td>
<td>25% ischemic lesions (small cortical watershed infarct, small infarct of the caudate, PVL) 4% hemorrhagic injury 16% elevated lactate with diffuse distribution, 25% lactate localized to the basal ganglia, 4% lactate in the peri-insular region Elevation of brain lactate associated with brain injury</td>
</tr>
<tr>
<td>Dimitropoulos et al, <em>Neurology,</em> 2013</td>
<td>Cohort study, N = 120</td>
<td>Mixed 33% MRI (structural, DTI, MRS)</td>
<td>Lower WM FA and lower NAA/Cho associated with higher injury severity preoperatively Higher SNAP-PE, lower SpO2, hypotension, and BAS predictive for higher injury severity</td>
</tr>
<tr>
<td>Shedeed and Elfaytouri, <em>Pediatr Cardiol,</em> 2011</td>
<td>Case-control study, N = 38/20</td>
<td>MRI (structural, DTI, MRS)</td>
<td>24% white matter injury (PVL and stroke) Lower NAA/Cho ratio (0.55 vs 0.67) Higher Lac/Cho ratio (0.14 vs 0.09) Higher average diffusivity (1.41 vs 1.27) Lower white matter FA (0.19 vs 0.25)</td>
</tr>
<tr>
<td>Miller et al, <em>N Engl J Med,</em> 2007</td>
<td>Case-control study, N = 41/16</td>
<td>MRI (structural, DTI, MRS)</td>
<td>Decreased NAA/Cho (10%), increased average diffusivity (4%), decreased FA (12%), increased Lac/Cho (28%)</td>
</tr>
<tr>
<td>Nagaraj et al, <em>J Pediatr,</em> 2015</td>
<td>Case-control study, N = 43/58</td>
<td>MRI (structural, ASL)</td>
<td>32.6% brain injury (64.3% WMI) compared with 0.6% in controls All cerebral blood flow parameters lower but not significantly different Lower global cerebral blood flow and regional cerebral blood flow in SVA Lower regional thalamic cerebral blood flow in cyanotic CHD and lower cerebral blood flow in thalami, occipital white matter, and basal ganglia compared with acyanotic CHD</td>
</tr>
<tr>
<td>Licht et al, <em>J Thorac Cardiovasc Surg,</em> 2004</td>
<td>Cohort study, N = 25</td>
<td>MRI (volume, ASL)</td>
<td>Mean cerebral blood flow 19.7 ± 9.1 mL/100 g per min compared with 50 ± 3.4 mL/100 g per min in controls 5 neonates cerebral blood flow &lt;10 mL/100 g per min (moderate ischemic changes in piglets) 24% microcephaly Low Hb associated with higher baseline cerebral blood flow 28% PVL, associated with lower cerebral blood flow and less reactivity to hypercarbia</td>
</tr>
<tr>
<td>Van der Laan et al, <em>Pediatr Res,</em> 2013</td>
<td>Retrospective study, N = 21 (12 BAS)</td>
<td>U NIRS</td>
<td>Predectual SpO2 increased immediately after BAS (72%–85%) and stabilized afterward (86%) rTPS02 increased immediately after BAS and continued increasing during 24 h after BAS (42%–48% 2 h after BAS to 64% 24 h after BAS) Lower baseline rTPS02 in the BAS group, whereas post-BAS rTPS02 was higher compared with infants who did not undergo BAS (64% vs 58%) 10 h before surgery, HLHS infants had higher rTPS02 than TGA infants (61% vs 56%) In HLHS infants, rTPS02 decreased after CPB and recovered to preoperative values within 48 h after CPB In TGA infants, rTPS02 decreased after CPB and increased ~20% above preoperative values within 48 h after CPB</td>
</tr>
<tr>
<td>Uebing et al, <em>J Thorac Cardiovasc Surg,</em> 2011</td>
<td>Cohort study, N = 53</td>
<td>U NIRS</td>
<td>Lower rTPS02 (immediately before surgery in the operating room, 1 min recordings) Infant with PA had lowest rTPS02 values (58% ± 8%)</td>
</tr>
<tr>
<td>Kurth et al, <em>Ann Thorac Surg,</em> 2001</td>
<td>Case-control study, N = 91/19</td>
<td>Mixed U NIRS</td>
<td>29% brain injury (16% brain edema, 6% PVL, 4% ventricular dilatation, 3% IVH grade I) Clinical variables not associated with brain injury BAS associated with brain edema (32% vs 6%)</td>
</tr>
<tr>
<td>Latal et al4, <em>Dev Med Child Neurol,</em> 2015</td>
<td>Cohort study, N = 77</td>
<td>Mixed 27% CUS</td>
<td>53% EA, commonly left-sided, predominantly occurring during CPB 0% preoperative EA 3% preoperative EA</td>
</tr>
<tr>
<td>Gunn et al4, <em>Intensive Care Med,</em> 2012</td>
<td>Cohort study, N = 150</td>
<td>U aEEG</td>
<td>3% preoperative EA</td>
</tr>
</tbody>
</table>
### TABLE 2 Continued

<table>
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<tr>
<th>Study (First Author, Journal, Year of Publication)</th>
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<th>Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Te Pas et al, Acta Paediatr, 2005</td>
<td>Retrospective study, N = 50</td>
<td>Mixed</td>
<td>U</td>
<td>CUS 42% abnormal CUS (26% widening ventricles or subarachnoidal space, 8% ischemic changes, 6% lenticulostriate vascopathy) Abnormalities on CUS tended to occur more frequently in HLHS or CoA (63%) than TGA (14%)</td>
</tr>
<tr>
<td>Sigler et al, Ann Thorac Surg, 2001</td>
<td>Cohort study, N = 35</td>
<td>TGA</td>
<td>U</td>
<td>CUS 3% preoperative brain injury (enhanced subependymal echogenicity) 65% resolved within 2 wk after operation Neuron specific enolase not associated with brain injury</td>
</tr>
<tr>
<td>Combination of techniques</td>
<td></td>
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</tr>
<tr>
<td>Mulkey et al, Pediatr Neurol, 2015</td>
<td>Cohort study, N = 24</td>
<td>Mixed</td>
<td>100%</td>
<td>aEEG MRI (structural) 63% abnormal aEEG (42% mildly abnormal, 21% severely abnormal) Abnormal aEEG associated with lower Apgar score at 5 min, CHD surgery at an older age, and male sex 50% brain injury (infarct and/or white matter injury) Infants with brain injury higher odds of having abnormal aEEG (OR = 3.0) 33% brain atrophy Severely abnormal aEEG background pattern associated with brain atrophy (OR = 15.0)</td>
</tr>
<tr>
<td>Dehaes et al, Biomed Opt Express, 2015</td>
<td>Case-control study, N = 11/13</td>
<td>SVA</td>
<td>U</td>
<td>NIRS Lower cerebral oxygen metabolism index, cerebral blood flow index, cerebral oxygen saturation index, and hemoglobin Higher cerebral oxygen extraction Lower resting state oxygen extraction fraction, cerebral blood flow, and cerebral metabolic rate for oxygen 22% PVL</td>
</tr>
<tr>
<td>Jain et al, J Cereb Blood Flow Metab, 2014</td>
<td>Cohort study, N = 32</td>
<td>Mixed</td>
<td>U</td>
<td>MRI DCS (structural) 3% brain injury ultrasound (4 hemorrhage, 1 PVL) 26% brain injury MRI (WMI most common) 4 infants with hemorrhage on CUS had normal MRI suggesting 80% false positives and a positive predictive value for brain injury of only 20% for HUS before surgery 33% brain injury Mean preoperative r_So2 56.5% (53.0%–61.9%) r_So2 &lt; 45% area under the curve 9 (0–191) min MCA-PI &gt; 0.75 TGA, &gt; 2.01 TOF, &gt; 2.4 HLHS CPR &lt; 1 40% TGA, 67% TOF, 60% HLHS MCA-PI positive correlation with neonatal EEG left frontal polar and left frontal β power</td>
</tr>
<tr>
<td>Lynch et al, J Thorac Cardiovasc Surg, 2014</td>
<td>Cohort study, N = 37</td>
<td>HLHS</td>
<td>U</td>
<td>MRI DCS (structural) 33% brain injury (27%–52%) 12 h before CPB 56% SWC within 72 h In acyanotic CHD, SWC more frequent in CoA than in HLHS (92% vs 48%) 9% ischemia on HUS Trend for more severely abnormal background patterns in abnormal HUS (OR 5.4) Severe abnormal background pattern and EA associated with more profound acidosis (low pH, more negative base excess, higher lactate) 39% preoperative brain injury (18% WMH, 21% stroke, 8% IVH) Risk factors for preoperative brain injury: BAS and 5 min Apgar score Preoperative brain injury more common in 2 ventricle anomalies Lower r_So2 (27%–52%) 12 h before CPB 100% normal aEEG, 0% EA No difference in duration to normalization in aEEG after surgery between preoperative low or high r_So2</td>
</tr>
<tr>
<td>Rios et al, Pediatrics, 2013</td>
<td>Cohort study, N = 167</td>
<td>Mixed</td>
<td>U</td>
<td>MRI CUS 3% preoperative brain injury associated with postoperative PVL Longer time to surgery associated with lower r_So2 and higher blood flow index associated with postoperative PVL Longer time to surgery associated with lower r_So2 and higher FTOE 3% brain injury ultrasound (4 hemorrhage, 1 PVL)</td>
</tr>
<tr>
<td>Andropoulos et al, Ann Thorac Surg, 2012</td>
<td>Cohort study, N = 30</td>
<td>Mixed</td>
<td>43%</td>
<td>MRI NIRS Ultrasound (Doppler) EEG Mean preoperative r_So2 56.5% (53.0%–61.9%) r_So2 &lt; 45% area under the curve 9 (0–191) min MCA-PI &gt; 0.75 TGA, &gt; 2.01 TOF, &gt; 2.4 HLHS</td>
</tr>
<tr>
<td>Williams et al, Ultrasound Obstet Gynecol, 2012</td>
<td>Pilot study, N = 13</td>
<td>Mixed</td>
<td>100%</td>
<td>MRI NIRS Ultrasound (Doppler) EEG CPR &lt; 1 40% TGA, 67% TOF, 60% HLHS MCA-PI positive correlation with neonatal EEG left frontal polar and left frontal β power</td>
</tr>
<tr>
<td>Ter Horst et al, Early Hum Dev, 2010</td>
<td>Cohort study, N = 62</td>
<td>Mixed</td>
<td>15%</td>
<td>aEEG CUS 19% EA, more frequently observed in acyanotic CHD (OR 3.9) 58% SWC within 72 h In acyanotic CHD, SWC more frequent in CoA than in HLHS (92% vs 48%) 9% ischemia on HUS Trend for more severely abnormal background patterns in abnormal HUS (OR 5.4) Severe abnormal background pattern and EA associated with more profound acidosis (low pH, more negative base excess, higher lactate) 39% preoperative brain injury (18% WMH, 21% stroke, 8% IVH) Risk factors for preoperative brain injury: BAS and 5 min Apgar score Preoperative brain injury more common in 2 ventricle anomalies Lower r_So2 (27%–52%) 12 h before CPB 100% normal aEEG, 0% EA No difference in duration to normalization in aEEG after surgery between preoperative low or high r_So2</td>
</tr>
<tr>
<td>McQuillen et al, Stroke, 2007</td>
<td>Cohort study, N = 62</td>
<td>Mixed</td>
<td>U</td>
<td>MRI NIRS aEEG 39% preoperative brain injury (18% WMH, 21% stroke, 8% IVH) Risk factors for preoperative brain injury: BAS and 5 min Apgar score Preoperative brain injury more common in 2 ventricle anomalies Lower r_So2 (27%–52%) 12 h before CPB 100% normal aEEG, 0% EA No difference in duration to normalization in aEEG after surgery between preoperative low or high r_So2</td>
</tr>
<tr>
<td>Toet et al, Exp Brain Res, 2005</td>
<td>Cohort study, N = 20</td>
<td>TGA</td>
<td>U</td>
<td>NIRS aEEG 39% preoperative brain injury (18% WMH, 21% stroke, 8% IVH) Risk factors for preoperative brain injury: BAS and 5 min Apgar score Preoperative brain injury more common in 2 ventricle anomalies Lower r_So2 (27%–52%) 12 h before CPB 100% normal aEEG, 0% EA No difference in duration to normalization in aEEG after surgery between preoperative low or high r_So2</td>
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</tbody>
</table>
still present in the white matter and disappeared in the gray matter 1 year after the arterial switch operation.\textsuperscript{48}

Apart from delayed cerebral development, the most commonly observed lesions on MRI were (punctate) white matter injury, periventricular leukomalacia, and stroke. Such brain lesions were reported in 19\% to 52\% of the cases.\textsuperscript{31,46,50–69} Although the type of CHD was associated with the occurrence of developmental delay or brain injury on MRI, most studies did not specify these differences.\textsuperscript{39–41,65}

There were multiple clinical factors associated with preoperative brain injury. Risk factors for preoperative brain injury included brain immaturity,\textsuperscript{53,54,59,64,70} lower arterial oxygen saturation values,\textsuperscript{53,63,71,72} lower Apgar scores at 5 minutes,\textsuperscript{56,61,70} abnormal amplitude-integrated electroencephalography (aEEG) background pattern,\textsuperscript{65} longer time to surgery,\textsuperscript{72} male sex,\textsuperscript{73} and presence of brain lactate.\textsuperscript{74} A higher Score for Neonatal Acute Physiology–Perinatal Extension, hypotension, lower white matter fractional anisotropy, and lower NAA/Cho were associated with higher brain injury severity.\textsuperscript{53} Balloon atrial septostomy (BAS) was found to be an independent risk factor for brain injury in 4 studies,\textsuperscript{53,59,61,70} whereas 4 other studies did not find an association between BAS and brain injury.\textsuperscript{54,60,71,72}

**Near-Infrared Spectroscopy**

Only a few studies examined regional cerebral oxygen saturation ($r_{SO_2}$) by means of near-infrared spectroscopy (NIRS) before surgery. Neonates with CHD had significantly lower preoperative $r_{SO_2}$ compared with healthy controls.\textsuperscript{75–77} Neonates with HLHS had higher $r_{SO_2}$ than neonates with TGA,\textsuperscript{78} and neonates with a pulmonary atresia (PA) had the lowest $r_{SO_2}$.\textsuperscript{75} In HLHS, neonates in whom cerebral oxygen saturation was monitored by NIRS had higher arterial oxygen saturation, were less often mechanically ventilated, and were less often intubated for a presumed circulatory mismatch.\textsuperscript{79} In TGA, $r_{SO_2}$ increased immediately after BAS and continued increasing during the 24 hours after BAS. Neonates in need of BAS had lower baseline $r_{SO_2}$ but higher post-BAS $r_{SO_2}$ compared with neonates who did not undergo BAS.\textsuperscript{80}

**Other Techniques**

Brain injury on transcranial ultrasound was reported in up to 42\% of the cases. The positive predictive value of transcranial ultrasound for the presence of brain injury, however, was very low with a value of 20\%.\textsuperscript{81–84}

Up to 63\% of the neonates had an abnormal preoperative aEEG recording (42\%–45\% mildly abnormal and 15\%–21\% severely abnormal).\textsuperscript{65,85–87} In 0\% to 19\% of the cases, epileptic activity (EA) was registered\textsuperscript{5,85–87} before surgery. EA was more frequently observed in neonates with acyanotic CHD.\textsuperscript{85} An abnormal aEEG recording was associated with lower Apgar scores at 5 minutes, surgery at an older age, and male sex.\textsuperscript{65} Furthermore, neonates with brain injury had higher odds of having abnormal aEEG recordings.\textsuperscript{65}

**Neurodevelopmental Outcome in Infants With CHD**

Sixteen prenatal or preoperative postnatal studies reported on NDO in infants with CHD. Fourteen of these studies used the BSID II or Bayley III at an age of 6 to 48 months. Thirteen studies assessed the association between prenatal or preoperative postnatal cerebral findings and NDO and were included in Table 3. Although scores were frequently within the normal range reported in healthy term infants (mean, SD 100 ± 15), almost all studies reported poorer NDO scores in infants with CHD compared with healthy controls or normative data. For the BSID II, the psychomotor developmental index (PDI) was more affected than the mental developmental index (MDI). Mean composite scores for the PDI ranged from 69.0 to 103.0 in infants with CHD\textsuperscript{14,24,81,88,89} and for the MDI from 85.2 to 103.5.\textsuperscript{14,24,81,88,89} The mean composite scores for the Bayley III were slightly higher compared with the composite scores for the BSID II. Mean cognitive scores ranged from 91.0 to 104.8, mean language scores ranged from 87.8 to 97.0, and mean motor scores ranged from 86.0 to 97.0.\textsuperscript{37,52,54,62,85,86} There were many prenatal and postnatal preoperative factors
<table>
<thead>
<tr>
<th>Study (First Author, Journal, Year of Publication)</th>
<th>Study Design, No. Infants</th>
<th>CHD Age at NDO Testing, Mo</th>
<th>Methods</th>
<th>Outcome</th>
<th>Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)</th>
<th>Relation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ultrasound</strong>&lt;br&gt;Hahn et al, <em>Ultrasound Obstet Gynecol</em>, 2016</td>
<td>Retrospective study, <em>N</em> = 133</td>
<td>SVA 14</td>
<td>Ultrasound (Doppler and biometry)</td>
<td>BSID II</td>
<td>MDI 88.5 ± 16.6 and PDI 76.4 ± 19.8&lt;br&gt;First MCA-PI negatively associated with PDI HC/AC negatively associated with PDI</td>
<td>±</td>
</tr>
<tr>
<td><strong>Zeng et al, Ultrasound Obstet Gynecol, 2015</strong></td>
<td>Case-control study, <em>N</em> = 112/112</td>
<td>Mixed 12</td>
<td>Ultrasound (three dimensional, Doppler)</td>
<td>BSID II</td>
<td>Lower MDI (85.2 vs 99.1) and PDI (72.8 vs 99.4)&lt;br&gt;No correlation between MCA-PI and NDO&lt;br&gt;Total intracranial flow index positively correlated with PDI and MDI</td>
<td>±</td>
</tr>
<tr>
<td><strong>Williams et al, Am Heart J, 2013</strong></td>
<td>Cohort study, <em>N</em> = 134</td>
<td>SVA 14</td>
<td>Ultrasound (Doppler)</td>
<td>BSID II</td>
<td>MDI 88.5 ± 16.6 and PDI 76.4 ± 19.8&lt;br&gt;62% PDI &lt; 85 and 35% MDI &lt; 85&lt;br&gt;MCA-PI correlated negatively with PDI but not with MDI&lt;br&gt;MCA-PI &lt; −2.0, on average, with 11-point-higher PDI scores compared with MCA-PI &gt; −2.0 (84.7 vs 73.6)</td>
<td>+</td>
</tr>
<tr>
<td><strong>Latal et al, Dev Med Child Neurol, 2015</strong></td>
<td>Cohort study, <em>N</em> = 77</td>
<td>Mixed 12</td>
<td>HUS</td>
<td>BSID II</td>
<td>MDI 89 (49–107) and PDI 69 (49–113)&lt;br&gt;Isolated CHD: MDI 91 (50–107) and PDI 70 (49–113)&lt;br&gt;No association between brain injury on ultrasound and NDO</td>
<td>−</td>
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<tr>
<td><strong>MRI</strong>&lt;br&gt;Masoller et al, <em>Ultrasound Obstet Gynecol</em>, 2016</td>
<td>Case-control study, <em>N</em> = 58/58</td>
<td>Mixed 6</td>
<td>MRI</td>
<td>Bayley III</td>
<td>Lower cognitive (91 vs 103), language (97 vs 108), motor (86 vs 100), social-emotional (85 vs 106), and adaptive (89 vs 97) score&lt;br&gt;Average Bayley III score associated with total blood volume, left and right singulate depth, frontal Ino/Cho ratio, and NAA/Cho ratio</td>
<td>+</td>
</tr>
<tr>
<td><strong>Andropoulos et al, Paediatr Anaesth, 2014</strong></td>
<td>Retrospective study, <em>N</em> = 59</td>
<td>Mixed 12</td>
<td>MRI</td>
<td>Bayley III</td>
<td>Composite scores: cognitive 102 ± 13.3, language 87.8 ± 12.5, motor 89.6 ± 14.1&lt;br&gt;Preoperative brain injury not associated with NDO&lt;br&gt;Preoperative rSCo2 values associated with cognitive and motor score</td>
<td>±</td>
</tr>
<tr>
<td>Study (First Author, Journal, Year of Publication)</td>
<td>Study Design, No. Infants</td>
<td>CHD Age at NDO Testing, Mo</td>
<td>Methods</td>
<td>Outcome</td>
<td>Findings (Compared With Healthy Controls and/or Reference Values, Unless Otherwise Stated)</td>
<td>Relation</td>
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<tr>
<td>Beca et al., <em>Circulation</em>, 2013</td>
<td>Cohort study, N = 153</td>
<td>Mixed</td>
<td>MRI</td>
<td>Bayley III</td>
<td>Composite scores: cognitive 94 ± 15, language 94 ± 16, motor 97 ± 12 Delay in maturation of the posterior limb of the internal capsule on the first MRI associated with lower motor scores Lower brain maturity associated with reduced performance on all domains</td>
<td>+</td>
</tr>
<tr>
<td>Gunn et al., Ann Thorac Surg, 2012</td>
<td>Cohort study, N = 39</td>
<td>SVA</td>
<td>aEEG</td>
<td>Bayley III</td>
<td>Composite scores: cognitive 92.4 ± 13.5, language 94.3 ± 17.7, motor 93.8 ± 10.6 Seizures associated with mortality but not associated with NDO Recovery of background pattern within 48 h: 14 points increase in motor score</td>
<td>±</td>
</tr>
<tr>
<td>Gunn et al., Intensive Care Med, 2012</td>
<td>Cohort study, N = 150</td>
<td>Mixed</td>
<td>aEEG</td>
<td>Bayley III</td>
<td>Composite scores: cognitive 93.2 ± 13.7, language 93.5 ± 16.2, motor 96.7 ± 12.7 Preoperative background pattern not associated with NDO</td>
<td>−</td>
</tr>
<tr>
<td>Combination of techniques Andropoulos et al., Ann Thorac Surg, 2012</td>
<td>Cohort study, N = 30</td>
<td>TGA</td>
<td>NIRS</td>
<td>Bayley III</td>
<td>Composite scores: cognitive 104.8 ± 15, language 90.0 (83.0–94.0), motor 92.3 ± 14.2 Lower preoperative ( r_s ) associated with lower cognitive score Preoperative brain injury associated with lower language score Preoperative brain injury, lower preoperative ( r_s ) associated with lower motor score</td>
<td>+</td>
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</table>
associated with neurodevelopmental outcome in infants with CHD. Two articles found a negative correlation between MCA-PI and NDO.\textsuperscript{24,88} MCA-PI < 2.0 was associated with an increase of PDI of 11 points.\textsuperscript{88} One article found a positive correlation between MCA-PI and Bayley III cognitive scores\textsuperscript{16} and with lower BSID II scores.\textsuperscript{76} Preoperative brain injury on MRI was associated with lower language and motor scores,\textsuperscript{62} whereas brain injury on preoperative ultrasound was not associated with NDO.\textsuperscript{81} Lower preoperative r\textsubscript{SO\textsubscript{2}} was associated with lower cognitive scores and lower motor scores\textsuperscript{62} and with lower BSID II scores.\textsuperscript{76} There was little evidence on the association between preoperative EEG or aEEG and NDO. One study found a positive association between preoperative left frontal polar and left frontal β power and cognitive scores.\textsuperscript{16} Three other studies did find an association between intraoperative or postoperative aEEG and NDO, but not between preoperative aEEG and NDO outcome.\textsuperscript{85,86,88}

**DISCUSSION**

This systematic review demonstrates that prenatal and postnatal preoperative brain injury are common in infants with CHD. More importantly, this review demonstrates that abnormal cerebral findings during these periods might be associated with poorer neurodevelopmental outcomes in later life.
One major finding of this review was the presence of cerebral developmental delay in many infants with CHD during both the prenatal as well as the postnatal preoperative period. All cerebral regions were affected and a delay of up to 4 weeks compared with healthy controls was described.49 It has been well established that preterm-born infants are at risk for developing brain injury because of the complex mechanisms of destructive events and developmental issues. The preterm brain is associated with vulnerable white matter, immature vasculature, and impaired autoregulation.90 Moreover, signs of cerebral developmental delay are associated with adverse NDO in preterm infants. In infants with CHD, cerebral developmental delay was associated with the occurrence of brain injury on preoperative MRI and also with the severity of brain injury.53,59,64 We speculate, therefore, that cerebral developmental delay might lead to an increased vulnerability of the brain and could therefore be an important contributor to brain injury in infants with CHD.

Another major finding was that many fetuses with CHD had abnormal Doppler parameters. PI of the middle cerebral artery and CPR were low, whereas UA-PI was high compared with healthy fetuses in the majority of studies that reported on Doppler parameters. These findings are in accordance with redistribution of blood flow to enhance cerebral perfusion, also called the brain-sparing effect.30 Brain sparing might be a consequence of low cerebral oxygen content (hypoxemia) or low cerebral blood volume (ischemia). In fetuses with intrauterine growth restriction, brain sparing is a sign of severely impaired oxygen and/or nutrient supply and is associated with mortality and poor outcome.91 In fetuses with CHD, this association seems to be less clear8,14,16,24,88 and might even be a protective factor.24,88 Moreover, it has been reported that up to 23.8% of fetuses with CHD are also growth restricted,92–94 and variable degrees of impaired placental function may concurrently modulate cerebral vascular resistance. Brain sparing in fetuses with CHD could be an adaptive mechanism to compensate for either hypoxemia (low Po2 because of placental insufficiency), hypoxia (low oxygen saturation because of intra- and extracardiac mixing), or ischemia.93 In all 3 situations, changes in cerebral vascular resistance may occur to compensate for poor oxygenation and to meet cerebral metabolic demands.14 Unfortunately, to date there are no studies looking systematically at uteroplacental (UA) and fetal (MCA, ductus venosus) flow to clarify if and to what extent brain sparing is determined by the effect of the cardiac lesion on oxygen saturation in fetuses with CHD.

Postnatally, brain injury was frequently reported (up to 52%) before cardiac surgery in infants with CHD. The most commonly observed lesions were all associated with decreased cerebral blood flow (ischemia) and included (punctate) white matter injury, periventricular leukomalacia, and stroke.30 Another indicator of an ischemic state was the presence of cerebral lactate in some infants with CHD.34,74 In addition to ischemia, hypoxia might also play a role in the development of early acquired brain injury in infants with CHD. Multiple studies found low arterial oxygen saturation values to be an independent risk factor for preoperative brain injury and high arterial oxygen saturation values to be a protective factor for preoperative brain injury.53,58,61,71,72

In general, infants with CHD scored lower on neurodevelopmental tests compared with healthy infants. Their mean scores, however, were frequently within the normal ranges reported in healthy term infants (mean, SD 100 ± 15). A possible explanation for these normal scores might be that most infants were examined during early childhood (6–48 months). Certain capacities and skills such as memory function and abstract-logic thinking mature during the course of childhood, and problems might only become apparent at an older age.96 Children with CHD at school age on average score lower on motor skills, higher-order language, visual-spatial skills, vigilance, and sustained attention. These deficits often persist through adolescence into adulthood. Furthermore, children and adolescents with complex CHD often have difficulties with social cognition and executive functioning, which might lead to psychosocial disorders and a lower quality of life.97

We found numerous associations between prenatal and postnatal preoperative cerebral findings and neurodevelopmental outcome in infants with CHD. Both prenatally as well as postnatally we were unable to identify specific cerebral findings that were responsible for poorer neurodevelopmental functioning in infants with CHD. We speculate, therefore, that neurodevelopmental impairment in CHD is the cumulative effect of delayed microstructural development in combination with multiple hypoxic and/or ischemic events during prenatal and postnatal preoperative life rather than being caused by a single independent factor.

Research to further clarify the actual mechanisms responsible for neurodevelopmental impairment in infants with CHD is essential. Nowadays, the adult population with CHD is larger than the pediatric population with CHD. Many adults with CHD still experience psychosocial and cognitive challenges that may impact emotional functioning, academic achievement, and even
quality of life. To explore pathophysiological mechanisms and to optimize treatment protocols, large (multicenter) prospective trials should be conducted that include the prenatal to the postoperative period with an adequate duration of follow-up. Furthermore, increasing awareness of the vulnerability of the young developing brain of an infant with CHD is also essential among physicians and other caregivers that are involved in the treatment to prevent neurodevelopmental impairment later in life.

This systematic review has several limitations. First, most studies included in this review were observational studies. This type of study is unequivocally associated with a risk of bias of under- or overestimating outcome measures. The vast majority of studies, however, were of reasonable to very good quality according to the Newcastle-Ottawa Quality Assessment Scale. Second, comparisons between studies were difficult because various techniques and methods were used to assess cerebral abnormalities in infants with complex CHD. Reference values for antenatal Doppler parameters, for example, were different from one study to another. In addition to various techniques and methods, numerous different types of CHD were included with different pathophysiology, circulatory effects, and treatment protocols. This also made comparisons between studies more difficult. Future studies should differentiate between cardiac lesions to make risk stratification of infants with CHD possible and counseling perhaps a little more specific. Finally, an effect of chromosomal abnormalities on cerebral development and NDO cannot be ruled out completely since not all studies stated whether they included infants with chromosomal abnormalities with CHD. For future studies, it would also be interesting to assess differences in cerebral abnormalities and NDO between infants with isolated CHD and infants with nonisolated CHD.

CONCLUSIONS
The current systematic review suggests that prenatal and postnatal preoperative abnormal cerebral findings may play an important role in neurodevelopmental impairment in infants with CHD. Physicians and other caregivers should be more aware of this vulnerability of the brain and of the possible effect repeated episodes of hypoxia and/or ischemia during early life may have in infants with CHD. Prenatal and postnatal counseling remains challenging when CHD is diagnosed. Targeted investigation in each individual case may help clarify which injuries are already present prenatally and which are due to the postnatal course of the condition.

Prof Dr Bilardo and Prof Dr Bos conceptualized and designed the study and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

ABBREVIATIONS
aEEG: amplitude-integrated electroencephalography
BAS: balloon atrial septostomy
Bayley III: Bayley Scales of Infant and Toddler Development III
BSID II: Bayley Scales of Infant Development II
CHD: congenital heart disease
Cho/Cr: choline/creatinine
CPR: cerebroplacental ratio
EA: epileptic activity
HC: head circumference
HLHS: hypoplastic left heart syndrome
Ino/Cho: myo-inositol/choline
Lac/Cho: lactate/choline
MCA: middle cerebral artery
MCA-PI: pulsatility index of the middle cerebral artery
MDI: mental developmental index
NAA/Cho: n-acetylaspartate/choline
NDO: neurodevelopmental outcome
NIRS: near-infrared spectroscopy
PA: pulmonary atresia
PDI: psychomotor developmental index
PI: pulsatility index
r SO2: cerebral oxygen saturation
TGA: transposition of the great arteries
UA: umbilical artery
UA-PI: pulsatility index of the umbilical artery

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