



Universiteit
Leiden

The Netherlands

Imaging the prenatal brain in congenital heart defects

Everwijn, S.M.P.

Citation

Everwijn, S. M. P. (2023, December 13). *Imaging the prenatal brain in congenital heart defects*. Retrieved from <https://hdl.handle.net/1887/3672336>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3672336>

Note: To cite this publication please use the final published version (if applicable).

PART II

The HAND-study: The assessment of different techniques of brain development in fetuses with isolated congenital heart defects.

Fetal brain imaging
in isolated congenital heart
defects – a systematic
review and meta-analysis

CHAPTER

3

*Published in: Prenatal
Diagnosis 2016, 36, 601–613*

Sheila M.P. Everwijn
Fenna A.R. Jansen
Robert Scheepjens
Theo Stijnen
Cacha M.P.C.D. Peeters-
Scholte
Jan M.M. van Lith
Monique C. Haak

ABSTRACT

INTRODUCTION: Congenital heart defects (CHD) are associated with neurodevelopmental (ND) delay. This study aims to assess evidence for impaired prenatal brain development, in fetuses with CHD.

METHODS: A systematical search was performed and 34 studies evaluating the fetal brain (MRI or ultrasound) in isolated CHD were included (1990-2015). Data regarding cerebral abnormalities, head circumference (HC) growth and middle cerebral artery (MCA) flow were extracted.

RESULTS: natal MRI was studied in 10 articles (445 fetuses), resulting in a pooled prevalence of 18% (95%CI -6% to 42%) for combined structural and acquired cerebral abnormalities. Prenatal HC was studied in 13 articles (753 fetuses), resulting in a pooled z-score of -0.51 (95%CI -0.84;-0.18). Doppler was studied in 21 articles (1412 fetuses), resulting in a lower MCA pulsatility index (z-score -0.70 95%CI -0.99;-0.41) in left sided CHD only.

CONCLUSIONS: We conclude that prenatal MRI and ultrasound demonstrate brain abnormalities, delay in head growth and brainsparing in subgroups of CHD. However, large MRI studies are scarce and ultrasound data are biased towards severe and left-sided CHD. Long term follow-up studies correlating prenatal findings with postnatal ND outcome are limited and data is lacking to support counselling families regarding ND outcome based on prenatal findings suggestive of altered brain development.

BACKGROUND

Congenital heart disease (CHD) is the most common congenital malformation, affecting six to eight per 1000 newborns. Although the survival rates of these children have increased over the last decades, there is a significant risk for adverse neurodevelopmental (ND) outcome, even in the absence of associated chromosomal or syndromic abnormalities¹⁻⁴. ND sequelae, like developmental delay and low IQ, are mainly encountered in children with severe CHD, who require surgery in the first year of life⁵. Until recently, these ND sequelae were assumed to be the result of perioperative conditions resulting in cerebral hypoxia and thromboembolic events⁶.

Recent studies demonstrated signs of abnormal neurological development already present at birth, prior to surgery. These studies demonstrated abnormal results of early neurological examination and abnormal imaging findings such as periventricular leukomalacia, white matter injury and cerebral atrophy^{7;8}. Some studies related these findings to a poor neurological development later in life^{9;10}. The characteristics of certain pre-operative neurological abnormalities, such as cerebral atrophy and delayed maturation, suggest that these abnormalities originate in utero. A second finding indicating towards a fetal origin is a smaller head circumference (HC), found in neonates with severe isolated CHD. Smaller HC is mainly reported in neonates with transposition of the great arteries (TGA), tetralogy of Fallot (ToF) and hypoplastic left heart syndrome (HLHS)¹¹⁻¹⁴ and is associated with a higher risk for ND outcome¹⁵. When a CHD is identified before birth, basic fetal ultrasound (US) can be used to identify delayed fetal head growth and abnormal cerebral flow. Dedicated fetal neurosonography or fetal brain magnetic resonance imaging (MRI) can be used to identify more subtle signs impaired fetal cerebral development^{16;17;18}. The aim of this study was to systematically review existing evidence for impaired brain development *in utero*, in fetuses with isolated CHD. More specifically, we aimed to objectify the presence of fetal hemodynamic brain-sparing effects, delay in fetal brain growth or fetal brain abnormalities in general, in these cases. Furthermore we attempted to stratify the findings to the type of CHD.

Methods

Search strategy

A systematic search was conducted in PubMed, Embase, Web of Science and Cochrane databases in October 2015. Publications from 1 January 1990 to 28 October 2015, containing the search terms *imaging (ultrasonography or MRI), fetology, congenital heart disease and neurodevelopment* were included. The complete search string is available in Supplement 1. Studies on genetic syndromes asso-

ciated with CHD, such as Trisomy 21, Noonan syndrome and 22q11.2 microdeletion syndrome were excluded, as well as functional CHD, arrhythmias and lethal abnormalities. The extracted articles were evaluated for relevance by 3 independent researchers (FJ, SE, MH). Studies were eligible for inclusion if MRI and/or US was performed *before birth*, assessing cerebral maturation, brain volume or growth, measuring Doppler flow patterns in the middle cerebral artery (MCA), and/or measuring head biometry, in fetuses with isolated CHD. To maximize the sample size, selected articles were cross-referenced. We assessed study quality and risk of bias by rating the articles based on the Strobe criteria¹⁹. Disagreement was resolved by consensus. Low methodological quality was not an exclusion criterion. The consensus statement on reporting in meta-analysis of observational studies in epidemiology (MOOSE-statement), was followed when possible and appropriate²⁰.

Data extraction and processing

The number and type of identified cerebral abnormalities were extracted from the MRI studies. Reported abnormalities were assessed by a paediatric neurologist (CP) and subdivided into four categories: 1) structural malformations, such as callosal agenesis, 2) cystiform anomalies including arachnoid, subependymal and germinolytic cysts, 3) ventricular anomalies including asymmetrical appearing ventricles and intraventricular haemorrhage, and 4) lesions possibly caused by hemodynamic changes, such as cerebral atrophy, white matter injury and delay in maturation. The prevalence of the abnormalities was pooled per category, based on the available data.

Biometrical values of head circumference (HC) and MCA-pulsatility indices (MCA PIs) were extracted from the US studies, as mean or median z-scores, percentiles or absolute values. If z-scores or percentiles were reported, the used reference population was noted. Reported percentiles, absolute values or median PI z-scores with range intervals were transformed to mean z-scores to correct for differences in gestational age (GA) at sampling (Supplement 2). To transform the HC outcome measures into z-scores, the population parameters by Hadlock were used²¹. To transform the MCA-PI outcome measures into z-scores, the population parameters by Arduini were used²². Furthermore, we extracted the gestational age of assessment, the type of included CHD, the used exclusion criteria and the centres and time span of data-collection. Also, if included, the used control group was noted, as well as the method of postnatal neurodevelopmental assessment, if performed. An e-mail request was sent to authors if data were not extractable from the original article.

Meta-analysis models

The metafor package (Viechtbauer 2010, version 1.9-4) for the statistical program R (R Development Core Team 2010), was used to conduct the meta-analyses. For the HC and MCA PI measurements, meta-analysis models were constructed for all CHD combined (mixed types of CHD). For the MCA PI measurements meta-analysis models were also constructed for the following subgroups: 1) left sided obstructive lesions (LSOL) such as hypoplastic left heart syndrome and coarctation of the aorta, 2) right sided obstructive lesions (RSOL), such as tricuspid atresia, pulmonary stenosis, Ebstein's anomaly and tetralogy of Fallot, and 3) transposition of great arteries (TGA). If combined effect sizes for a mixture of CHDs were not reported in a study, missing combined effect sizes were calculated from documented subgroup effect sizes (Supplement 2).

For each meta-analysis model the following parameters were calculated using a random effect model: the estimated overall effect size with its standard error, the statistical significance of the estimated effect and several parameters describing the heterogeneity (between studies variance (τ^2), Cochran's Q-test and I^2). The variance between studies was calculated with the restricted maximum likelihood method. A forest plot and a funnel plot were created additionally for each fitted model. Sensitivity analyses were performed to check whether the meta-analysis models should be corrected for two possible origins of estimation biases: bias related to overlapping cohorts between studies (duplicate/secondary publication) and missing effect sizes of control groups.

Results

The search resulted in 34 included articles (1983 fetuses, Figure 1). The study characteristics are summarized in Tables 1a (MRI studies) and 1b (US studies). Quality assessment is summarized in Figures 2a (MRI studies) and 2b (US studies). The included types of CHD per cohort are delineated in Tables 1a and 1b. CHD characteristics were not always described thoroughly. Several authors divided the cohort into LSOL, RSOL and mixed lesions. Others only included certain types of CHD (TGA, TOF, HLHS). Variation was found in the description of HLHS and LSOL: some only included those with retrograde aortic arch flow, others included cases of aortic stenosis, coarctation of the aorta and/or interrupted arch as well in the LSOL group. In this meta-analysis, all types of LSOL were combined in one group.

MAGNETIC RESONANCE IMAGING

The search resulted in ten studies (445 fetuses) addressing fetal cerebral MRI. In Table 2 the main conclusions and extracted data regarding cerebral abnormalities are summarized. We noted variation in reported cerebral data: some studies reported

fetal brain volumes or brain weights, but the methods to calculate the variables differed²³⁻²⁸. Others reported on metabolic aspects^{23;28;29}, cerebral maturation indices^{27;28} or derived cerebral oxygenation parameters^{24;26}. Most authors also described cerebral malformations or acquired cerebral lesions. Possible duplicate cohorts were identified in three publications^{23;25;27}. The data of five articles (duplicate cohorts not included) were summarized to a prevalence estimate of cerebral abnormalities of 18% (95% CI -6; 42)²⁸⁻³². Structural brain anomalies were present in 3% (95% CI -1; 8). The subdivision in the three other categories was feasible in two articles without possible overlap; the estimated prevalence is displayed in Table 2 (cystiform abnormalities 4%, ventricular abnormalities 12% and other (acquired) lesions 6%)^{30;31}. The data were reported as mixed CHD group, however most authors included severe CHD only. The data did not allow further subdivision into in specific CHD.

ULTRASOUND STUDIES

Head circumference

The search resulted in 13 studies (753 fetuses) addressing fetal head biometry values. Eight studies included larger groups of mixed CHD^{28;33-39} and five only included HLHS⁴⁰⁻⁴⁴. Eight studies calculated z-scores or percentiles to correct for the effect of gestational age, using various normal reference populations (Table 1b)^{28;33-36;40-42}. One study reported absolute values at 34 weeks of gestation³⁷. Data from five articles were excluded from the meta-analysis because of incomparable data (BPD³⁶ or head/weight ratio^{38;43}), or because data were not displayed^{39;44}. Four meta-analysis models were fitted, including three models for sensitivity analysis (Supplement 3). Three articles contained possible duplicates and were excluded from the final meta-analysis model^{28;41;42}. The final model (Figure 3) includes the data of five articles, of which three included a control group^{34;35;37}. The results were analyzed as data of a mixed CHD group, but LSOL and single ventricle defects cases are overrepresented. The HC has a pooled z-score of -0.51 (95% CI -0.84; -0.18), indicating a smaller HC in CHD fetuses of 0,5 SD below the population mean. The data did not allow further subdivision into in specific CHD, because of small numbers in each category. Funnel plots and information on statistical heterogeneity are available in Supplement 4.

Several authors reported the percentage of fetuses with "abnormal" HC values, meaning cases with a HC below the third percentile or a z-score below -2, at various gestational ages^{28;41;42}. Only a few studies explored the HC/abdominal circumference or HC/fetal weight ratio as well^{37;38;41;43}, but the data were not suitable for pooling.

Doppler flow

Data regarding middle cerebral artery (MCA) flow were available in 21 articles (1412 fetuses). Most studies ($n=14$) calculated z-scores or percentiles to correct for the effect of the gestational age, using various normal reference populations (Table 1b)^{28;33;35;40;45-54}. Seven studies reported absolute values at a specific gestational age^{36-39;42;55;56}. Three articles were excluded from the meta-analysis because the pulsatility indices (PIs) were not available^{23;36;38}. In three studies the combined effect size for a group of mixed CHDs was not reported, but could be calculated from documented subgroup effect sizes^{46;52;53} (Supplement 2). Sixteen meta-analysis models were fitted, including twelve models for sensitivity analyses (Supplement 3). Several studies were identified to report overlapping populations^{28;39;42;52;54;56}, and 13 studies included a control group. Only the largest and/or the most recent cohorts, including a control group, were used in the final meta-analyses displayed in Figures 4a-d; either as a mixed CHD group (nine articles, Figure 4a) or for specific CHD: LSOL (six articles, Figure 4b); RSOL (seven articles, Figure 4c) or TGA (four articles, Figure 4d). A significant lower MCA PI z-score was found in the mixed CHD group (-0.33; 95% CI -0.50 to -0.16) and the LSOL group (-0.70; 95% CI -0.99 to -0.41). Only two studies reported a subgroup with ToF^{49;50}. These numbers were too small for a subgroup meta-analysis. Funnel plots and information on statistical heterogeneity are available in Supplement 4.

Several authors reported the percentage of fetuses with "abnormal" values. The definitions of abnormal varied (MCA PI, or RI, below the fifth or 2,3rd percentile or a z-score below -2, at least once in pregnancy or at a certain gestational age)^{27;34-37;40;42;46-48;50;52;56}. Reports on the prevalence of CPR below 1.0 (labeled as "brain-sparing") varied, ranging from 11% (in the third trimester) to 56% (in the second trimester) and 44% at any time in pregnancy^{36;38;49}. A higher prevalence of CPR below the fifth percentile was reported in CHD fetuses⁴⁷, and CPR z-scores below -2 were reported more frequently in HLHS fetuses⁵⁰. These data were not suitable for pooling.

CORRELATION WITH NEURODEVELOPMENTAL OUTCOME

In eight articles (331 fetuses, Table 3), postnatal ND outcome was assessed. The correlation with fetal data was studied in seven articles^{28;33;34;42;49;53;54}. One study was identified as a possible duplicate⁵⁴. Results varied between studies. Three articles focused on correlating ND outcome to fetal cerebral flows, but had conflicting results^{49;53;54}. The largest of the studies correlated brain-sparing with a favourable ND outcome⁵⁴. Three articles focused on correlating ND outcome to fetal biometry, possibly showing a trend towards worse ND outcome in fetuses with lower age-adjusted weight in general^{33;34;42}. Relative small fetal HC compared to weight (small

HC/weight or HC/abdomen ratio) was not unanimously identified as a predictor for adverse ND outcome.

Discussion

This review and meta-analysis show that fetuses with CHD demonstrate signs of impaired brain development, identified either with fetal US or MRI. The most studied parameter is the middle cerebral artery (MCA), which demonstrates a slightly increased end-diastolic blood flow in CHD fetuses. This effect appears to be predominantly present in LSOL. The MCA-flow appears not to be altered in TGA or RSOL. Although one of the larger studies focusing solely on TGA showed a significant lower MCA PI⁵⁵, this effect is contradicted by the three other studies that included a TGA subgroup.

Combining all types of CHD, a smaller HC throughout gestation is encountered^{21;57;58}, but pre-selected CHD cases, mainly LSOL, are overrepresented in these data. In postnatal studies, neonates with HLHS, TGA and ToF have been associated with a smaller HC and subsequent adverse ND outcome¹²⁻¹⁵. Recently, a large population-based study reported a smaller neonatal HC in less severe CHD such as ventricular septal defects⁵⁹, but this has not been confirmed in prenatal studies yet. Reported US data are limited to the measurement of flows or biometry at specific gestational ages. The effect of growth throughout gestation has not been investigated thoroughly, thus the timing of (ND) deterioration is difficult to determine. The small HC might already be present at midgestation in specific types of CHD³⁵. The MCA PI appears to diminish with advancing GA⁵².

We did not encounter any fetal US studies assessing detailed cerebral characteristics, such as cortical thickness, cerebral maturation or spinal fluid amount, even though neonatal studies report delayed brain maturation and cerebral atrophy in newborns with CHD^{7;8} and dedicated neurosonography has the capacity to detect most of the reported anomalies¹⁶. Fetal brain volume was addressed in one ultrasound study, showing reduced cerebral volume growth in fetuses with HLHS, TGA, aortic arch hypoplasia and ToF³⁹. As demonstrated in our review, ND details and cerebral metabolism are increasingly being studied in CHD using fetal MRI. The reported variables in the included MRI studies are however very heterogeneous and were assessed at different gestational ages. Normal values are not available for comparison, and methods of data reporting vary between studies, hampering meta-analysis. Studies including a control group do consistently report smaller fetal brain volumes in different types of CHD^{23-25;27;28;32;60}. Reports on this topic are emerging rapidly, but the analysis of fetal cerebral volume, metabolism and maturation appears to be limited to research settings and have not permeated to daily clinical practice yet. Also, the definition of (the pathogenicity of) MRI lesions varies between studies. For example,

subependymal cysts are generally considered to be physiological variants⁶¹, but are reported as abnormalities by some authors^{23;30;60}. Furthermore, genetic abnormalities and severe structural lesions, such as holoprosencephaly, were not excluded in certain studies^{26;30}, resulting in an overrating of found anomalies.

Several theories were postulated to explain the correlation of CHD with prenatal cerebral findings, but exact pathophysiologic mechanisms remain unclear. A high prevalence of children small for gestational age in CHD⁶²⁻⁶⁴ prompted several authors to investigate the relationship between fetal CHD and placental development^{26;60;65}. Placental insufficiency and subsequent growth restriction usually presents with a relative large HC/abdomen ratio in fetuses without CHD⁶⁶. Most of the fetal biometry reports addressing HC growth in CHD fetuses did, however, not include the abdominal growth, fetal weight or HC/abdomen ratios. Therefore, we are unable to determine a possible correlation between the found smaller HC and fetal weight. Postnatal studies have indicated that most of the neonates with CHD and smaller HC are also small for gestational age at birth; but HC/weight ratios have not been extensively investigated^{11;14}.

Secondly, a correlation between cerebral hemodynamics and fetal neurodevelopment in CHD has been suggested³⁸. It seems plausible that the restriction of flow to the carotid arteries, in cases of reversed aortic arch flow, can induce vasodilatation in the cerebral circulatory system to facilitate and secure transport of oxygen and nutrients. This is not proven in an in-vivo setting yet. In this review, heterogeneity in the reported data resulted in an impossibility to pool the data on the cerebroplacental ratio, hampering a definite conclusion regarding a possible brainsparing effect in CHD. Moreover, research concerning the brainsparing effect has mainly been performed in placental insufficiency, in which it is considered a mechanism to prevent fetal brain hypoxia rather than a sign of impending brain damage⁶⁷. Because of the totally different pathophysiological and hemodynamic circumstances in CHD versus growth restriction, conclusions are not interchangeable. Brainsparing is correlated with worse ND outcome in growth restricted fetuses⁶⁸. Even though available data suggests that brainsparing correlates with altered brain development in CHD^{27;28}, a correlation with long-term outcome has not been established. On the contrary, it has even been suggested that brainsparing is associated with more favourable ND outcome in CHD⁵⁴.

Another explanation for the cerebral variations in neonates with CHD could be a common genetic pathway, causing fetal CHD and ND delay^{69;70}. The fact that fetuses and neonates with types of CHD that do not have a significant effect on fetal hemodynamics (minor CHD), also demonstrate cerebral anomalies, a smaller HC and low birth weight⁵⁹ supports this theory. The development of the fetal brain in less severe

CHD, such as ventricular septal defects, has however not been reported separately. In future research, the inclusion of minor CHD will be necessary to investigate this. Furthermore, a thorough genetic assessment in fetal CHD studies is necessary to exclude the effect of confounding genetic factors. Prenatal genetic testing is generally limited to array CGH with a reasonable resolution⁷¹, but it is known that smaller (point) mutations can play a role in CHD or neurodevelopment⁷²⁻⁷⁴.

To our knowledge, this review and meta-analysis is the first to perform a meta-analysis of fetal cerebral flow abnormalities in fetuses with (severe) CHD. A narrative review published in 2010 and a recent systematic review on MRI findings are available^{75,76}. Certain included publications overlap, but our study includes a larger sample size with regard to cerebral flow, facilitating meta-analyses and subgroup assessment. Furthermore, exclusion of certain duplicate MRI cohorts results in a lower prevalence of MRI abnormalities in our review, which did not reach statistical significance. Two reviews focusing on postnatal findings are available for comparison, reporting high rates of cerebral damage in fetuses with CHD prior to surgery^{7,8}. However, these reviews probably included children with CHD that were undetected prior to birth, thus possibly including postnatally developed abnormalities, possibly due to asphyxia because of a delayed diagnosis.

In our meta-analyses we compared z-scores. A z-score is a statistical tool to compare the results from cases with a standardized population, eliminating the influence of gestational age. We have tried to maximize our sample size by transforming divergent outcome measures to mean z-scores, which also has some drawbacks. Grouped effect sizes would have been more accurate when individual measurements were corrected for individual gestational age, but these data are not available and assumptions on a higher data aggregation level are made. Another source of bias can be the various used normal values, which causes difficulty comparing the studies with each other. In the sensitivity analyses we determined that the use of population references, compared to the use of a control group, leads to a different outcome. In most studies it lead to a larger difference in effect size. To eliminate the effect of the various used standard populations we have chosen to use the studies reported control group as reference value.

Conclusion

This meta-analysis shows that fetuses with isolated, severe CHD demonstrate signs of impaired fetal cerebral development, demonstrated by fetal ultrasound or MRI. Our findings underline the importance of fetal neurological evaluation in CHD. However, reports correlating postnatal ND outcome to fetal findings remain incon-

clusive. Therefore, it is too early to conclude that aberrations revealed by neuroimaging involve a high risk of ND delay. To define the clinical meaning of prenatal cerebral variations in CHD, prospective large and long-term cohort studies are required, combining pre- and postnatal data. Such studies should include thorough genetic assessment and compare the findings to healthy controls. Parents should be counselled about the correlation of (specific types of) CHD with ND delay⁷⁷, but until a correlation with ND outcome has been ascertained, there is insufficient data to support counselling families regarding ND outcome, or as a rationale for fetal therapy, based on prenatal findings suggestive of altered brain development.

Supplemental material:

S1: complete search string

S2: transformation of extracted data to z-scores

S3: results of sensitivity analyses

S4: estimation of heterogeneity and funnel plots

These materials can be accessed online via: <https://obgyn.onlinelibrary.wiley.com/journal/10970223>

References

- 1 Bellinger DC, Jonas RA, Rappaport LA et al. Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *N Engl J Med* 1995;332:549-555.
- 2 Stieh J, Kramer HH, Harding P, Fischer G. Gross and fine motor development is impaired in children with cyanotic congenital heart disease. *Neuropediatrics* 1999;30:77-82.
- 3 Marino B, Digilio MC. Congenital heart disease and genetic syndromes: specific correlation between cardiac phenotype and genotype. *Cardiovasc Pathol* 2000;9:303-315.
- 4 Marino BS, Lipkin PH, Newburger JW et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation* 2012;126:1143-1172.
- 5 McQuillen PS, Miller SP. Congenital heart disease and brain development. *Ann N Y Acad Sci* 2010;1184:68-86.
- 6 du Plessis AJ. Mechanisms of brain injury during infant cardiac surgery. *Semin Pediatr Neurol* 1999;6:32-47.
- 7 Owen M, Shevell M, Majnemer A, Limperopoulos C. Abnormal brain structure and function in newborns with complex congenital heart defects before open heart surgery: A review of the evidence. *Journal of Child Neurology* 2011;26:743-755.

- 8 Khalil A, Suff N, Thilaganathan B, Hurrell A, Cooper D, Carvalho JS. Brain abnormalities and neurodevelopmental delay in congenital heart disease: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2014;43:14-24.
- 9 Majnemer A, Limperopoulos C, Shevell MI, Rohlicek C, Rosenblatt B, Tchervenkov C. A new look at outcomes of infants with congenital heart disease. *Pediatr Neurol* 2009;40:197-204.
- 10 Donofrio MT, Duplessis AJ, Limperopoulos C. Impact of congenital heart disease on fetal brain development and injury. *Current Opinion in Pediatrics* 2011;23:502-511.
- 11 Rosenthal GL. Patterns of prenatal growth among infants with cardiovascular malformations: possible fetal hemodynamic effects. *Am J Epidemiol* 1996;143:505-513.
- 12 Manzar S, Nair AK, Pai MG, Al-Khhusaiby SM. Head size at birth in neonates with transposition of great arteries and hypoplastic left heart syndrome. *Saudi Medical Journal* 2005;26:453-456.
- 13 Shillingford AJ, Ittenbach RF, Marino BS et al. Aortic morphometry and microcephaly in hypoplastic left heart syndrome. *Cardiol Young* 2007;17:189-195.
- 14 Barbu D, Mert I, Kruger M, Bahado-Singh RO. Evidence of fetal central nervous system injury in isolated congenital heart defects: microcephaly at birth. *Am J Obstet Gynecol* 2009;201:43-47.
- 15 Limperopoulos C, Majnemer A, Shevell MI et al. Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects. *J Pediatr* 2002;141:51-58.
- 16 Pistorius LR, Stoutenbeek P, Groenendaal F et al. Grade and symmetry of normal fetal cortical development: a longitudinal two- and three-dimensional ultrasound study. *Ultrasound Obstet Gynecol* 2010;36:700-708.
- 17 Rossi AC, Prefumo F. Additional value of fetal magnetic resonance imaging in the prenatal diagnosis of central nervous system anomalies: a systematic review of the literature. *Ultrasound Obstet Gynecol* 2014;44:388-393.
- 18 Frick N, Fazelnia C, Kanzian K et al. The reliability of fetal MRI in the assessment of brain malformations. *Fetal Diagn Ther* 2015;37:93-101.
- 19 von EE, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370:1453-1457.
- 20 Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-2012.
- 21 Hadlock FP. Computer-assisted, multiple-parameter assessment of fetal age and growth. *Semin Ultrasound CT MR* 1989;10:383-395.
- 22 Arduini D, Rizzo G. Normal values of Pulsatility Index from fetal vessels: a cross-sectional study on 1556 healthy fetuses. *J Perinat Med* 1990;18:165-172.
- 23 Limperopoulos C, Tworetzky W, McElhinney DB et al. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation* 2010;121:26-33.

- 24 Al NB, van Amerom JF, Forsey J et al. Fetal circulation in left-sided congenital heart disease measured by cardiovascular magnetic resonance: a case-control study. *J Cardiovasc Magn Reson* 2013;15:65.
- 25 Schellen C, Ernst S, Gruber GM et al. Fetal MRI detects early alterations of brain development in Tetralogy of Fallot. *Am J Obstet Gynecol* 2015;213:392-397.
- 26 Sun L, Macgowan CK, Sled JG et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. *Circulation* 2015;131:1313-1323.
- 27 Clouchoux C, du Plessis AJ, Bouyssi-Kobar M et al. Delayed cortical development in fetuses with complex congenital heart disease. *Cereb Cortex* 2013;23:2932-2943.
- 28 Masoller N, Sanz-Cortes M, Crispi F et al. Severity of Fetal Brain Abnormalities in Congenital Heart Disease in Relation to the Main Expected Pattern of in utero Brain Blood Supply. *Fetal Diagn Ther* 2016; 39: 269– 78.
- 29 Berman JI, Hamrick SE, McQuillen PS et al. Diffusion-weighted imaging in fetuses with severe congenital heart defects. *AJNR Am J Neuroradiol* 2011;32:E21-E22.
- 30 Mlczoch E, Brugger P, Ulm B et al. Structural congenital brain disease in congenital heart disease: Results from a fetal MRI program. *Eur J Paediatr Neurol* 2013; 17: 153– 60.
- 31 Brossard-Racine M, du Plessis AJ, Vezina G et al. Prevalence and spectrum of in utero structural brain abnormalities in fetuses with complex congenital heart disease. *AJNR Am J Neuroradiol* 2014;35:1593-1599.
- 32 Paladini, Alfrevic Z, Carvalho JS, et al. Prenatal counselling for neurodevelopmental delay in congenital heart disease. The results of a worldwide survey of experts' attitudes advise caution. *Ultrasound Obstet Gynecol* 2016.
- 33 Hahn E, Szwast A, Cnota J et al. The association of fetal growth, cerebral blood flow, and neurodevelopmental outcome in single ventricle fetuses. *Ultrasound Obstet Gynecol* 2016; 47(4): 460– 5.
- 34 Williams IA, Fifer WP, Andrews H. Fetal Growth and Neurodevelopmental Outcome in Congenital Heart Disease. *Pediatr Cardiol* 2015;(6): 1135– 44.
- 35 Masoller N, Martinez JM, Gomez O et al. Evidence of second-trimester changes in head biometry and brain perfusion in fetuses with congenital heart disease. *Ultrasound Obstet Gynecol* 2014;44:182-187.
- 36 Itsukaichi M, Kikuchi A, Yoshihara K, Serikawa T, Takakuwa K, Tanaka K. Changes in fetal circulation associated with congenital heart disease and their effects on fetal growth. *Fetal Diagn Ther* 2011;30:219-224.
- 37 Arduini M, Rosati P, Caforio L et al. Cerebral blood flow autoregulation and congenital heart disease: possible causes of abnormal prenatal neurologic development. *J Matern Fetal Neonatal Med* 2011;24:1208-1211.
- 38 Donofrio MT, Bremer YA, Schieken RM et al. Autoregulation of cerebral blood flow in fetuses with congenital heart disease: the brain sparing effect. *Pediatr Cardiol* 2003;24:436-443.

- 39 Zeng S, Zhou QC, Zhou JW, Li M, Long C, Peng QH. Volume of intracranial structures on three-dimensional ultrasound in fetuses with congenital heart disease. *Ultrasound Obstet Gynecol* 2015;46:174-181.
- 40 McElhinney DB, Benson CB, Brown DW et al. Cerebral blood flow characteristics and biometry in fetuses undergoing prenatal intervention for aortic stenosis with evolving hypoplastic left heart syndrome. *Ultrasound Med Biol* 2010;36:29-37.
- 41 Hinton RB, Andelfinger G, Sekar P et al. Prenatal head growth and white matter injury in hypoplastic left heart syndrome. *Pediatr Res* 2008;64:364-369.
- 42 Hangge PT, Cnota JF, Woo JG et al. Microcephaly is associated with early adverse neurologic outcomes in hypoplastic left heart syndrome. *Pediatr Res* 2013;74:61-67.
- 43 Miller TA, Joss-Moore L, Menon SC, Weng C, Puchalski MD. Umbilical artery systolic to diastolic ratio is associated with growth and myocardial performance in infants with hypoplastic left heart syndrome. *Prenat Diagn* 2014;34:128-133.
- 44 Cnota JF, Hangge PT, Wang Y et al. Somatic growth trajectory in the fetus with hypoplastic left heart syndrome. *Pediatr Res* 2013;74:284-289.
- 45 Meise C, Germer U, Gembruch U. Arterial Doppler ultrasound in 115 second- and third-trimester fetuses with congenital heart disease. *Ultrasound Obstet Gynecol* 2001;17:398-402.
- 46 Kaltman JR, Di H, Tian Z, Rychik J. Impact of congenital heart disease on cerebrovascular blood flow dynamics in the fetus. *Ultrasound Obstet Gynecol* 2005;25:32-36.
- 47 Modena A, Horan C, Visintine J, Chanthasenanont A, Wood D, Weiner S. Fetuses with congenital heart disease demonstrate signs of decreased cerebral impedance. *Am J Obstet Gynecol* 2006;195:706-710.
- 48 Guorong L, Shaohui L, Peng J et al. Cerebrovascular blood flow dynamic changes in fetuses with congenital heart disease. *Fetal Diagn Ther* 2009;25:167-172.
- 49 Williams IA, Tarullo AR, Grieve PG et al. Fetal cerebrovascular resistance and neonatal EEG predict 18-month neurodevelopmental outcome in infants with congenital heart disease. *Ultrasound Obstet Gynecol* 2012;40:304-309.
- 50 Berg C, Gembruch O, Gembruch U, Geipel A. Doppler indices of the middle cerebral artery in fetuses with cardiac defects theoretically associated with impaired cerebral oxygen delivery in utero: is there a brain-sparing effect? *Ultrasound Obstet Gynecol* 2009;34:666-672.
- 51 Yamamoto Y, Khoo NS, Brooks PA, Savard W, Hirose A, Hornberger LK. Severe left heart obstruction with retrograde arch flow influences fetal cerebral and placental blood flow. *Ultrasound Obstet Gynecol* 2013;42:294-299.
- 52 Szwast A, Tian Z, McCann M, Soffer D, Rychik J. Comparative analysis of cerebrovascular resistance in fetuses with single-ventricle congenital heart disease. *Ultrasound Obstet Gynecol* 2012;40:62-67.
- 53 Zeng S, Zhou J, Peng Q et al. Assessment by three-dimensional power Doppler ultrasound of cerebral blood flow perfusion in fetuses with congenital heart disease. *Ultrasound Obstet Gynecol* 2015;45:649-656.

- 54 Williams IA, Fifer C, Jaeggi E, Levine JC, Michelfelder EC, Szwaast AL. The association of fetal cerebrovascular resistance with early neurodevelopment in single ventricle congenital heart disease. *Am Heart J* 2013;165:544-550.
- 55 Jouannic JM, Benachi A, Bonnet D et al. Middle cerebral artery Doppler in fetuses with transposition of the great arteries. *Ultrasound Obstet Gynecol* 2002;20:122-124.
- 56 Chen Y, Lv G, Li B, Wang Z. Cerebral vascular resistance and left ventricular myocardial performance in fetuses with Ebstein's anomaly. *Am J Perinatol* 2009;26:253-258.
- 57 Kurmanavicius J, Wright EM, Royston P et al. Fetal ultrasound biometry: 1. Head reference values. *Br J Obstet Gynaecol* 1999;106:126-135.
- 58 Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. *Pediatrics* 2010;125:e214-e224.
- 59 Matthiesen NB, Henriksen TB, Gaynor JW et al. Congenital Heart Defects and Indices of Fetal Cerebral Growth in a Nationwide Cohort of 924 422 Liveborn Infants. *Circulation* 2016;133:566-575.
- 60 Andescavage N, Yarish A, Donofrio M et al. 3-D volumetric MRI evaluation of the placenta in fetuses with complex congenital heart disease. *Placenta* 2015;36:1024-1030.
- 61 Pappalardo EM, Militello M, Rapisarda G et al. Fetal intracranial cysts: prenatal diagnosis and outcome. *J Prenat Med* 2009;3:28-30.
- 62 Kramer HH, Trampisch HJ, Rammos S, Giese A. Birth weight of children with congenital heart disease. *Eur J Pediatr* 1990;149:752-757.
- 63 Rosenthal GL, Wilson PD, Permutt T, Boughman JA, Ferencz C. Birth weight and cardiovascular malformations: a population-based study. The Baltimore-Washington Infant Study. *Am J Epidemiol* 1991;133:1273-1281.
- 64 Spiers PS. Does growth retardation predispose the fetus to congenital malformation? *Lancet* 1982;1:312-314.
- 65 Huhta J, Linask KK. Environmental origins of congenital heart disease: the heart-placenta connection. *Semin Fetal Neonatal Med* 2013;18:245-250.
- 66 Kramer MS, McLean FH, Olivier M, Willis DM, Usher RH. Body proportionality and head and length 'sparing' in growth-retarded neonates: a critical reappraisal. *Pediatrics* 1989;84:717-723.
- 67 Scherjon SA, Smolders-DeHaas H, Kok JH, Zondervan HA. The "brain-sparing" effect: antenatal cerebral Doppler findings in relation to neurologic outcome in very preterm infants. *Am J Obstet Gynecol* 1993;169:169-175.
- 68 Hernandez-Andrade E, Serralde JA, Cruz-Martinez R. Can anomalies of fetal brain circulation be useful in the management of growth restricted fetuses? *Prenat Diagn* 2012;32:103-112.
- 69 Connor JA, Hinton RB, Miller EM, Sund KL, Ruschman JG, Ware SM. Genetic testing practices in infants with congenital heart disease. *Congenit Heart Dis* 2014;9:158-167.
- 70 Levenson D. Genetic testing using array comparative genomic hybridization may benefit newborns with congenital heart disease: study shows aCGH more effective at detecting potential genetic causes of CHD than other methods. *Am J Med Genet A* 2014;164A:ix.

- 71 Wapner RJ, Martin CL, Levy B et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. *N Engl J Med* 2012;367:2175-2184.
- 72 Fahed AC, Gelb BD, Seidman JG, Seidman CE. Genetics of congenital heart disease: the glass half empty. *Circ Res* 2013;112:707-720.
- 73 Hartman RJ, Rasmussen SA, Botto LD et al. The contribution of chromosomal abnormalities to congenital heart defects: a population-based study. *Pediatr Cardiol* 2011;32:1147-1157.
- 74 Wessels MW, Willems PJ. Genetic factors in non-syndromic congenital heart malformations. *Clin Genet* 2010;78:103-123.
- 75 Donofrio MT, Massaro AN. Impact of congenital heart disease on brain development and neurodevelopmental outcome. *Int J Pediatr* 2010;2010.
- 76 Khalil A, Bennet S, Thilaganathan B, Paladini D, Griffiths P, Carvalho JS. Prevalence of Prenatal Brain Abnormalities in Fetuses with Congenital Heart Disease: Systematic Review. *Ultrasound Obstet Gynecol* 2016.

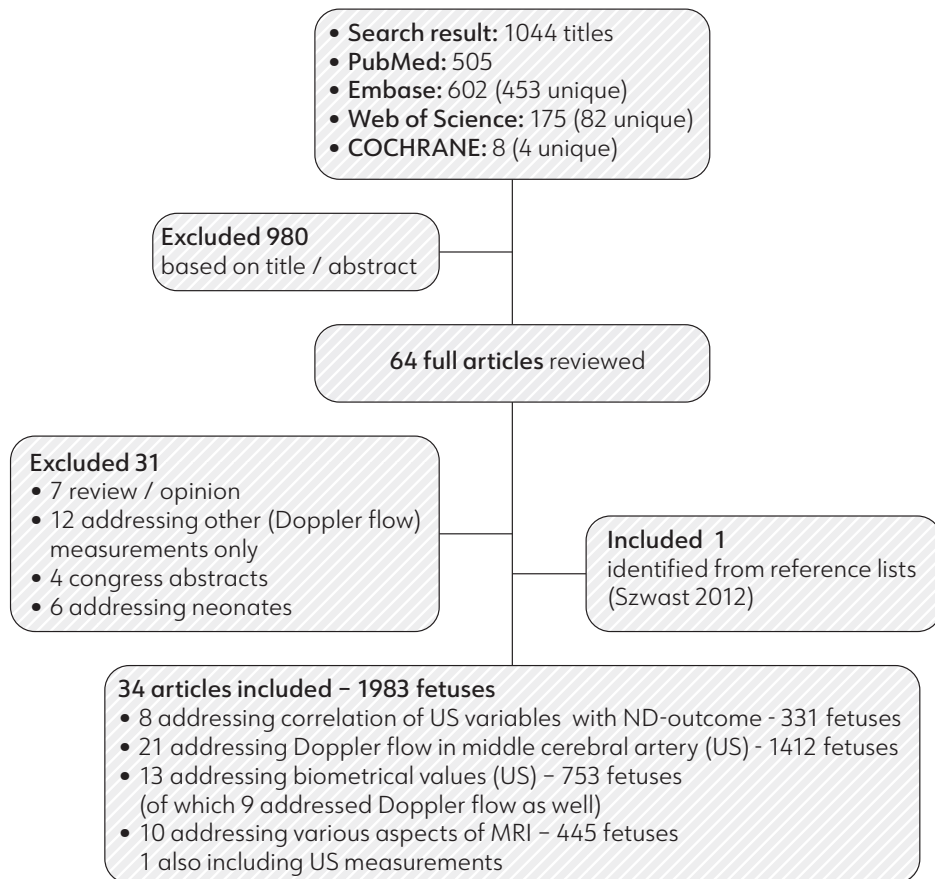


Figure 1: flow diagram of search and inclusion process

Table 1a overview of included MRI studies

Author (year) / country	Design*	Multi-/single center*	Patients	Type of CHD†	GA at MRI (weeks)	Con- trols	Outcome measure ‡	ND assess- ment	Quality score*
Sun (2015) Canada	P	S	30	AS, CoA, DORV, Ebstein, TA, TGA, ToF	36	30	Fetal brain size, oxygen satura- tion in major blood vessels	-	20
Andescavage (2015) USA	P	S	38	CoA, DORV, HLHS, TGA, ToF other	29±6	94	Brain volumes, placental volumes	-	18
Schellen (2015) Austria	R	S	24	ToF	20-34 (mean 25,7)	24	Cerebellar, intracranial, ventricu- lar cavity volumes	-	17
Masoller (2015) Spain	P	S	58	AVSD, AS, CoA, complex CHD, Ebstein, HLHS, PA, TA, TGA, ToF, truncus,	22,1±0,9	58	Brain volume, brain maturation, HC/BPD, MCA PI/CPR, (US) metabolic profile (MRI)	+	20
Brossard (2014) USA	P	M	144	AVSD, DORV, HLHS, PA, TGA, ToF	19-39 (mean 30,6±4,7)	194	No. of brain abnormalities	-	17
al Nafisi (2013) Canada	P	S	22	HLHS+AS/CoA, HLHS, HLHS+restrictive FO	30-39 (mean 35)	12	Brain weight (MRI), CMR blood flow, MCA RI (US)	-	17
Mlczoch (2012) Austria	R	S	53	RSOL, LSOL, other (incl TGA)	20-37 (mean 24)	-	Acquired, cerebral spinal fluid spaces, no. of brain abnormali- ties, malformations	+	17
Clouchoux (2012) USA/Canada/France	P	M	18	HLHS	25-37 (mean 30.8±3,8)	30	Brain volume, cortical surface area and dept, CSF volume, gyrfication index	-	16
Berman (2011) USA/ Canada	case reports	S	3	HLHS, TGA,	32-35	33	diffusion weighted imaging	-	n/a
Limperopoulos (2010) USA/Canada	P	S	55	AS, DORV, Ebstein, HLHS, PA, PS, TA, ToF, TGA, truncus other	25-37 (median 30)	50	Anatomical abnormalities, spec- troscopy, Brain volumes: intracra- nial cavity, total brain, fluid.	-	17

Table 1b: overview of included Ultrasound studies

Author (year) / country	Design*	Multi-/single-center*	Cases	Type of CHD†	GA at US(weeks)	Con-trols	Outcome measures ‡	ND assessment	Quality score	Meta-analysis**	Used normal values
Williams (2015) USA/ Canada	P	S	66	HLHS, TGA, ToF	F1 (mean 23,6±2), F2 (mean 30,6±1,6), F3 (mean 36,4±1)	41	BPD, HC	+	15	HC	Hadlock 1984
Hahn (2015) USA	R	M	133	single ventricle	20-34 (mean 27,2±5,3)	-	Biometry (n=133), MCA PI (n=119)	+	18	mix; HC	Arduini 1990; Hadlock 1984
Masoller (2015) Spain	P	S	58	AS, AVSD, CoA, complex CHD, Ebstein, HLHS, PA, TA, TGA, ToF, truncus	20-24 (mean 22.3±0.9)	58	BPD, CPR, composite score, correlation with MRI, HC, MCA PI,	+	19	mix (n);	Arduini 1990; Kurmanavicius 1999
Zeng 3d Flow (2015) China	P	S	112	HLHS, LSOL, RSOL, TGA	19+6-30+3 (mean 25,7±2,74)	112	3D flow, MCA PI	+	20	mix; Isol; rsol; tga	Arduini 1990
Zeng 3d Volume (2015) China	P	S	73	Ao hypoplasia, AVSD, HLHS, PA, PS, TA, TGA, ToF, truncus	20+4-36+4 (mean 28,2 ± 4,4)	168	cerebral volume (VO-CAL), HC, MCA PI	-	18	mix (n)	n/a
Miller (2014) USA	R	S	43	AS, HLHS	mean 33+5	-	Biometry	-	19	n/a	Olsen 2010

Masoller (2014) Spain	P	S	95	Group 1: AS, CoA, HLHS, TGA Group 2: AVSD, complex CHD, DORV, ToF, truncus arteriosus Group 3: Ebstein, PA, PS, TA	20-23+5 (mean 22+3)	95	Biometry, CPR, fractional moving blood volume, MCA PI	-	19	mix; isol; HC	Arduini 1990; Kurmanavicius 1999
Williams (2013) USA/ Canada	R	M	119	single ventricle (79% HLHS)	18-38 (mean 27)	-	MCA PI, neonatal HC	+	18	mix (n); Isol (n)	Arduini 1990
Hangge (2013) USA	R	S	38	HLHS	mean 26,6±5	-	Biometry, MCA PI, neonatal HC	+	19	Isol (n); HC (n)	Olsen 2010
Cnotta (2013) USA	R	S	33	HLHS	19-37 (median 27)	-	Biometry, UA flow, neonatal HC	-	17	n/a	Olsen 2010+Hadlock 1984
Yamamoto (2013) Canada	R	S	89	CoA, HLHS, HLHS + CoA, PA, TGA	closest to term (mean 32±5)	89	CPR, MCA PI, neonatal HC	-	17	mix; isol; rsol; tga	Ebbing 2007
Szwast (2012) USA	R	S	131	single ventricle (RSOL/LSOL)	LSOL mean 28,0±5,4; RSOL mean 24,4±4,0	92	CPR, MCA PI	-	15	mix (n); Isol; rsol	Arduini 1990
Williams (2012) USA	4 pilot	S	16	HLHS, TGA, TOF	18-24 (mean 22,8±2,8)	-	CPR, MCA PI	+	16	mix; isol; tga	Arduini 1990
Arduini (2011) Italy	R	S	60	AS, AVSD, CoA, HLHS, PA, PS, TGA, ToF, other	30-35 (mean 34,1±1,9)	65	Biometry, CPR, MCA PI	-	15	mix; HC	n/a

Itsukaichi (2011) Japan	R	S	44	CoA, DORV, Ebstein, HLHS, HRHS, PA, PS, single ventricle, TA, TGA, ToF, tumor, truncus, VSD	28-34	140	Biometry(AC, BPD, FL), CPR, MCA PI	-	18	n/a	n/a
McElhinney (2010) USA	P	S	46	HLHS + valvu- loplasty	20-31 (mean 24,3 ±3)	-	Biometry, MCA PI	-	17	Isol; HC	Arduini 1990; Kurmanana- vicius 1999
Guorong (2009) China	P	S	45	AS, CoA, completed endocardial cushion defect, DORV, Ebstein, HLHS, PA, PS, single ventricle, TA, TGA, ToF, truncus,	20-40	275	CPR, MCA PI	-	15	mix; Isol; rsol	not reported
Chen (2009) China	R	S	11	Ebstein	23-37	44	MCA PI	-	16	rsol (n)	n/a
Berg (2009) Germany	R	S	113	AS, HLHS, PA, TGA, ToF	19-41 'closest to term'	1378	CPR, HC postnatal, MCA PI	-	18	mix; Isol; rsol; tga	Ebbing 2007
Hinton (2008) USA/Canada	R	S	28	HLHS/AS	17-36	-	HC pre -and postnatal	-	15	HC (n)	Hadlock 1984
Modena (2006) USA	R	S	71	AS, AVSD, CoA, DORV, HLHS, HRHS, PA, TA, TGA, ToF, Truncus, tumor, VSD	'closest to mid second trimester'	71	CPR, MCA PI	-	16	mix	Arduini 1990

Kaltman (2005) USA	P	S	58	arch interrup- tion, AS, CoA, Ebstein, PA, PS, TA, ToF	20-39	114	CPR, MCA PI	-	19	mix; Isol; rsol	Arduini 1990
Donofrio (2003) USA	P	M	36	HLHS, HRHS, TGA, LVOTO, ToF	23-29 (mean 26,5±3,8)	21	CPR, HC, MCA RI	-	20	n/a	n/a
Jouannic (2002) France	P	S	23	TGA (+/- VSD)	36-38 (mean 36,7)	40	MCA PI, UA PI	-	15	tga	n/a
Meise (2001) Germany	P	S	115	AS, ASD, AVSD, CoA, DORV, Ebstein, HLHS, PA, PS, TA, ToF, truncus, VSD, other	19-41 (mean 30,8)	100	MCA PI, UA PI	-	14	mix	not reported

Table 2: Overview of MRI anomalies

Author / year	other findings	total reported anomalies (CHD)	structural anomalies	cystiform abnormalities	ventricular abnormalities	hemodynamic changes	lesions/delay possibly caused by	total reported anomalies (controls)
Sun 2015	CHD: lower umbilical vein oxygen content and lower cerebral oxygen delivery. Reduced fetal brain size correlated with these findings	1 in 30	1	n/a	n/a	n/a	n/a	n/a in 30
Andescavage 2015	CHD: smaller brain volume and cerebral volume but larger brain-stem volumes, than control fetuses. Placental volumes were not associated with the differences in brain volumes.	4 in 38*	0*	1*	1*	2*		0 in 94
Schellen 2015	TOF: abnormally low total brain volumes and enlarged CSF spaces as early as 20 weeks of gestation	5 in 24**	0**	n/a	5**	n/a		0 in 24
Masoller 2015	CHD: smaller brain volumes, also decreased depths for several fissures and metabolic changes, when compared with controls	0 in 58†	0†	n/a	n/a	n/a		0 in 58
Brossard 2013	CHD: Brain abnormalities in 23% versus 1,5% of normal controls. Subgroup analyses comparing the type and frequency of brain abnormalities based on cardiac physiology did not reveal significant associations, suggesting that the brain abnormalities were not limited to those with the most severe CHD	33 in 144*	3*	2	13	15		3 in 194
al Nafisi 2013	CHD: 6/22 fetuses showed brain weights at or below the 5th centile for gestational age (controls 0/12). No correlation found between brain weight and flow in the SVC, AAo or CVO. No correlation found between SVC flow or brain weight with Doppler flows or aortic isthmus size or Doppler gradient.	n/a	n/a	n/a	n/a	n/a		n/a in 12
Mcllzoich 2012	'Congenital brain disease' was found in 39% of fetuses with CHD	21 in 53**	7**	4	9**	1		n/a

Clouchoux 2012	HLHS fetuses demonstrate diminishing brain volumes in third trimester, as well as delay in cortical gyrification as early as 25 weeks.	5 in 18*	0*	n/a	5*	n/a	0 in 30
Berman 2011	3 fetuses with CHD demonstrated abnormally high water diffusion in the thalamus and periventricular white matter	1 in 3	1	n/a	n/a	n/a	n/a in 33
Limperopoulos 2010	Third-trimester fetuses with some forms of CHD have smaller total brain volumes than normal fetuses and display impaired neuroaxonal development and metabolism.	6 in 52*	2*	2*	4*	n/a	0 in 55
Total (without overlapping cohorts; without articles not assessing / reporting particular focus of interest)							
Prevalence (95%CI)							
		0,18 (-0,06; 0,42)	0,03 (-0,01; 0,08)	0,04 (-0,03; 0,10)	0,12 (0,04; 0,19)	0,06 (-0,03; 0,16)	0,01 (-0,01; 0,03)
*	overlapping publications Andescavage / Brossard / Clouchoux / Limperopoulos						
**	overlapping publications Mlczoch / Schellen						
‡	overlapping publications Masoller 2015 and 2016						
†	includes cerebellar hypoplasia; corpus callosum agenesis; holoprosencephaly; other cerebral malformations; microcephaly; macrocephaly						
n/a	not applicable/or stated						

Table 3: Articles assessing neurodevelopmental outcome

author (year) / country	type of CHD†	fetal data	ND assessment at age	n assessed of total cohort	correlation of ND outcome with fetal data
Williams (2015) USA/Canada	HLHS, TGA, ToF	Biometry	BSID-III at 18 months	46 of 68	After multivariate correction: Low BSID-III cognitive score correlated with low HC/AC ratio at midgestation. Low BSID-III language score was predicted by FL/BPD at beginning 3rd trimester
Hahn (2015) USA *	single ventricle	Biometry	BSID-II at 14 months	82 of 133	Low BSID-II mental score fetal correlated with low AC z-score at > 34 weeks. Low BSID-II psychomotor score correlated with high mean HC/AC ratio, low EFW z-score and low AC z-score at 24-29 weeks.
Hangge (2013) USA	HLHS	Biometry	Adverse neurologic outcomes included clinical seizure activity ischemia, hemorrhage, other injury	38 of 104	Early adverse ND outcome trended with fetal HC < 3rd percentile (p=0.06).
Masoller (2015) Spain	mixed CHD, not requiring surgery in the first 6 months of life	MRI	BSID-III at 4-6 months	17 of 58	BSID-III average score correlated with fetal MRI brain volume, fissure depth and metabolic aspects. "Abnormal brain development" (MRI composite score) correlated with HC and MCA PI at midgestation
Zeng 3d Flow (2015) China	HLHS, LSOL, RSOL, TGA	Flows	BSID-II at 12 months	41 of 112	No significant correlation between MCA-PI and BSID-II score. Low BSID mental and psychomotor score fetal correlated with several aspects of low 3D intracranial flow.
Williams (2013) USA/Canada *	single ventricle (79% HLHS)	Flows	BSID-II at 14 months	72 of 119	High BSID-II psychomotor score was associated with low MCA PI z-score
Williams (2012) USA	HLHS, TGA, ToF	Flows	BSID-III at 18 months and neonatal EEG	13 of 16	Low BSID-III cognitive score correlated with low MCA PI z-score and CPR z score <-1 at midgestation (but not in a multivariate model)
Miczoch (2012) Austria	LSOL, RSOL, other (incl TGA)		developmental status questionnaire	22 of 53	3/8 (37,5%) children with fetal brain abnormalities and 3/14 (21,4%) children with no fetal brain abnormality exhibited developmental problems. Because of the small groups, no statistics were performed.

Figure 2a Quality of included MRI studies

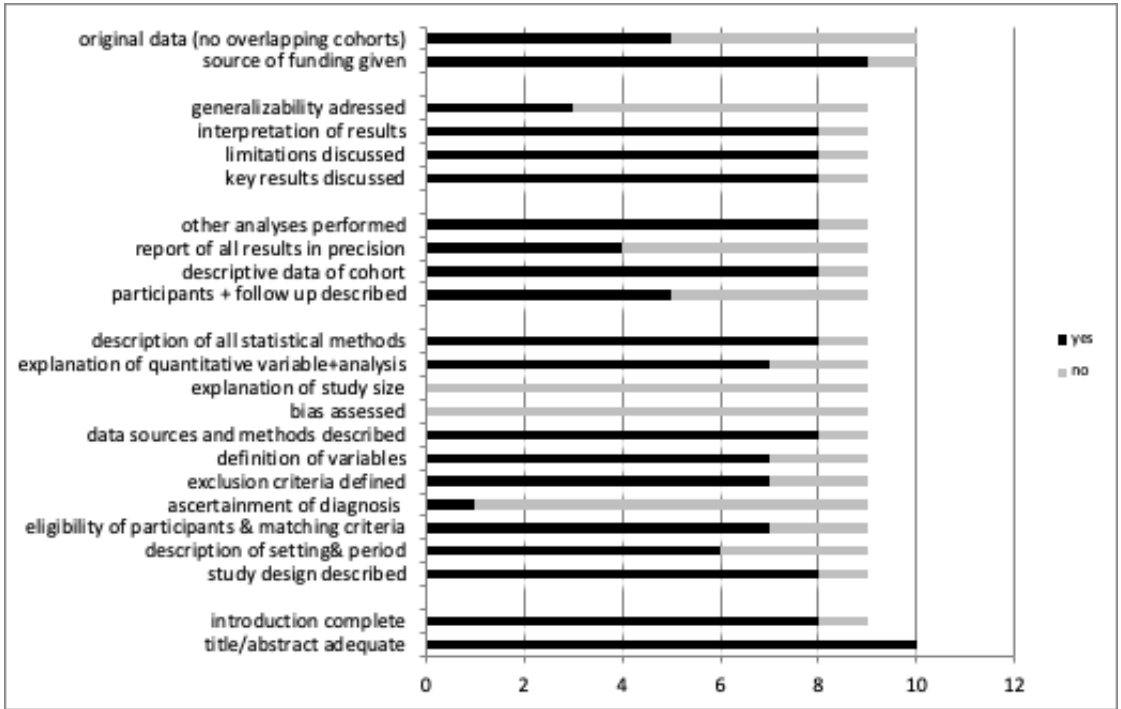


Figure 2b Quality of included ultrasound studies

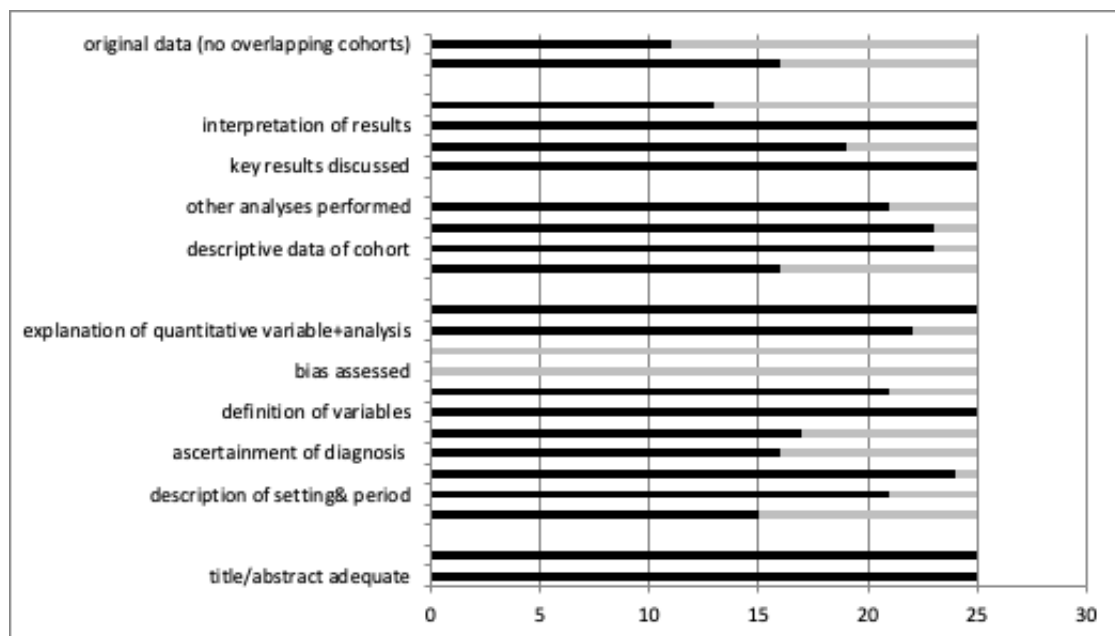


Figure 3 Pooled head circumference z-score – fetuses with mixed types of CHD

Suspected duplicate cohorts are excluded; the effect sizes are corrected for an included control group.

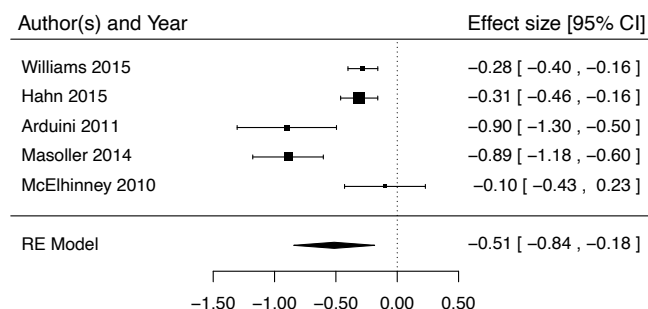


Figure 4a Pooled middle cerebral artery pulsatility index z-score - fetuses with mixed types of CHD

Suspected duplicate cohorts are excluded; the effect sizes are corrected for an included control group.

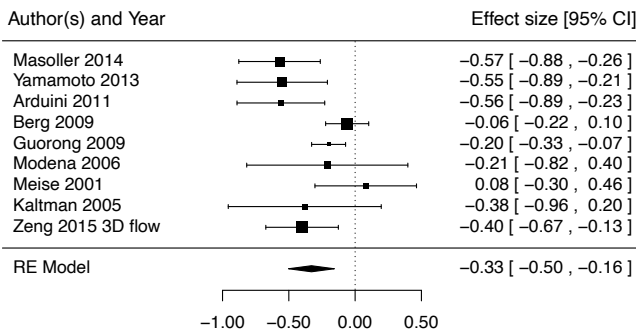


Figure 4b Pooled middle cerebral artery pulsatility index z-score - fetuses with left sided obstructive lesions

Suspected duplicate cohorts are excluded; the effect sizes are corrected for an included control group.

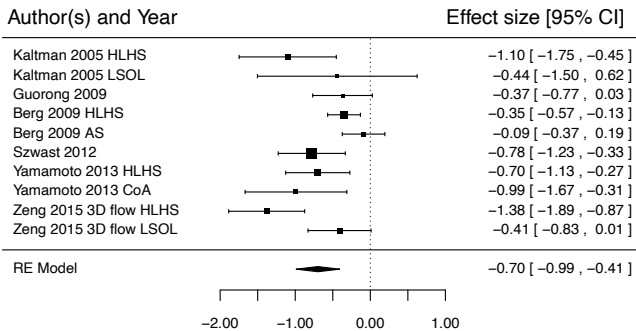


Figure 4c Pooled middle cerebral artery pulsatility index z-score – fetuses with right sided obstructive lesions

Suspected duplicate cohorts are excluded; the effect sizes are corrected for an included control group.

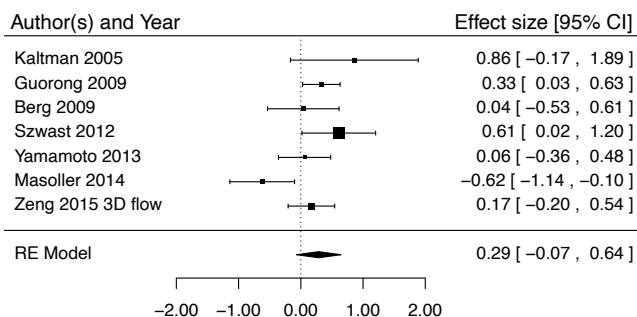
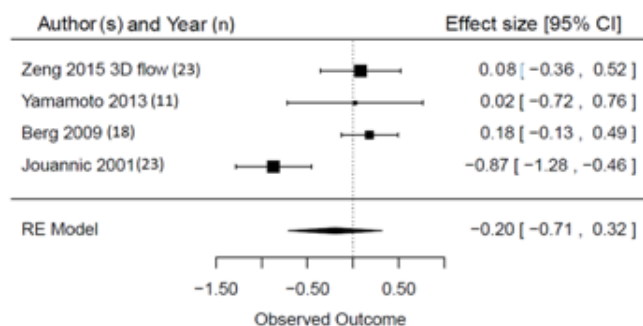


Figure 4d Pooled middle cerebral artery pulsatility index z-score – fetuses with transposition of the great arteries

Suspected duplicate cohorts are excluded; the effect sizes are corrected for an included control group.



Abbreviations:

* P, prospective;

R, retrospective;

S, single center;

M, multicenter

† **Ao hypoplasia**, aortic arch hypoplasia;

AS, Aorta Stenose;

AVSD, Atrioventricular Septum Defect;

CoA, Coarctatio Aortae;

DORV, Double Outlet Right Ventricle;

Ebstein, Eb-stein's anomaly;

FO, Foramen Ovale;

tumor, intracardiac tumor;

HLHS, hypoplastic left heart syndrome ;

other, other non-chromosomal
extracardiac malformations;

PA, Pul-monary Atresia;

PS, Pulmonary Stenosis;

TA, Tricuspidalis atresia;

TI, Tricuspidalis Insufficiency;

TGA, Transposition of the Great Arteries;

ToF, Tetralogy of Fallot;

Truncus, Truncus Arteriosus;

RSOL, Right Sided Obstructive Lesions;

‡ AC, Abdominal Circumference;

BPD, Biparietal Diameter;

CMR, Cardiac Magnetic Resonance;

CPR, Cerebral-Placental Ratio;

CSF, Cerebro-spinal fluid;

FL, Femur Length;

HC, Head Circumference;

MCA, Middle Cerebral Artery;

PI, Pulsatility Index;

RI, Resistance Index;

UA, Umbilical Artery;

VOCAL, Virtual Organ Computer-aided Analysis;

n/a, not applicable

** in which meta-analyses are data included:

mix, all/mixed types of CHD combined (MCA);

lsol, left sided obstructive defects (MCA);

rsol, rightsided obstructive defects (MCA);

tga, transposition of the great arteries (MCA);

HC, head circumference;

(n) not included in the final model,

overlapping publication